Prognostic Value of Simultaneous Analysis with Myocardial Flow Reserve and Right Ventricular Strain by Hybrid 13N-ammonia Positron Emission Tomography/Magnetic Resonance Imaging in Coronary Artery Disease

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Abstract

Myocardial flow reserve (MFR) derived from $^{13}$N-ammonia positron emission tomography (PET) is used to predict adverse cardiac events in the patients with coronary artery disease (CAD). Right ventricular (RV) strain measured by magnetic resonance imaging (MRI) is used to evaluate RV function and predict cardiac events. This study aimed to evaluate the prognostic value of MFR and RV strain measured by hybrid $^{13}$N-ammonia PET/MRI in patients with CAD. Sixty-one patients who underwent $^{13}$N-ammonia PET/MRI were enrolled. The end points were defined as a composite of all-cause death, myocardial infarction, sustained ventricular arrhythmia, hospitalization due to decompensated heart failure, and revascularization. At a follow-up of 2.8 ± 1.9 years, 21 events occurred. Kaplan–Meier analysis showed that the event-free rate was significantly lower in the group with MFR < 1.80 than that with MFR ≥ 1.80 (P < 0.001). Additionally, the event-free rate was significantly lower in the group with RVGLS > −18.22% than that with RVGLS ≤ −18.22% (P = 0.025). After dividing the patients into four groups by the median MFR and the median RVGLS, the event-free rate was lowest in the combined group of MFR < 1.80 and RVGLS > -18.22% than any other groups (P < 0.001). In the Cox proportional hazard analysis, MFR and RVGLS were independent predictors of cardiac adverse events in the patients with CAD. The simultaneous assessment of MFR and RV strain by $^{13}$N-ammonia PET/MRI revealed the feasibility of precise risk stratification for cardiac events in patients with CAD.

Introduction

Myocardial perfusion imaging using positron emission tomography (PET) provides useful diagnostic and prognostic information in patients with coronary artery disease (CAD) (1). $^{13}$N-ammonia PET is essential for assessing precise information on myocardial blood flow (MBF) and coronary flow reserve (CFR). Ventricular dysfunction due to CAD is associated with high morbidity and mortality rates (2). In patients with CAD, the assessment of global myocardial perfusion and function is important for evaluating the diagnosis and prognosis.

Right ventricular (RV) function plays a major role in hemodynamic stability in various cardiovascular diseases (3) (4) (5). Strain is increasingly being used as a marker for contractile deformation, and it may be an early indicator of ventricular dysfunction (6). In an effort to better characterize biventricular function, several imaging techniques have been developed to assess myocardial deformation in the context of its complex process. Cardiac magnetic resonance (CMR) has become the gold standard for the assessment of RV volume and function because of its high spatial resolution (7). CMR feature tracking is a myocardial strain technique used for quantitative evaluation of RV structure and function that does not require additional imaging or tedious postprocessing practices (8). The usefulness of RV strain has been reported in patients with CAD (9), but the clinical validation of additional prognostic evaluation when combined with PET-derived MBF and myocardial flow reserve (MFR) has not been reported.

Hybrid PET/magnetic resonance imaging (MRI) is used as a novel modality for evaluating cardiac diseases, and is able to yield important information regarding various pathologies through molecular and
functional imaging of PET and MRI in a one-stop examination (10). The assessment of RV dysfunction in addition to blood flow analysis may allow the performance of more precise risk classification of CAD. This study aimed to evaluate the prognostic value of a combined analysis of MFR and RV strain by using hybrid $^{13}$N-ammonia PET/MRI in patients with CAD.

**Materials And Methods**

**Materials and Methods**

**Study Population**

We enrolled consecutive 61 patients with coronary artery stenosis >50% as shown by coronary angiography (CAG) from November 2016 to March 2021. All patients underwent $^{13}$N-ammonia PET/MRI within 1 week of CAG. There was no clinical event during the time between CAG and the PET scan. Exclusion criteria were acute coronary syndrome, atrial fibrillation, implanted devices, symptomatic asthma, and pregnancy. We also excluded patients who could not be included in the analysis because of unclear images.

**$^{13}$N-ammonia PET/MRI Protocol**

**Imaging protocol**

PET and MRI were simultaneously conducted using a Biograph mMR (Siemens Healthineers, Erlangen, Germany) with integration of a single scanner (Fig.1). The PET component was built with avalanche photodiodes with lutetium oxyorthosilicate, with detectors that are not affected by strong magnetic fields. The MRI component of this scanner consisted of a 3-T MRI scanner. Several reports have described the performance of this scanner (11) (12).

**PET imaging acquisition and analysis**

The patients were instructed to refrain from any caffeine-containing products for 24 hours and requested to fast for more than 6 hours before the test. For the correction of PET attenuation, an attenuation map was calculated from a two-point Dixon MRI sequence at the beginning of the PET recording (13). All $^{13}$N-ammonia PET images were acquired at rest and during vasodilator stress. We used continuous intravenous infusion of adenosine (140 µg/kg/minute), which was started 3 minutes before the stress scan. A bolus of $^{13}$N-ammonium (370 MBq) was injected with saline flushes at intervals of 1 hour or longer between rest and the stress scan. A 14-minute list-mode dynamic scan was performed. The imaging data were reconstructed using a three-dimensional attenuation-weighted ordered subset expectation maximization iterative reconstruction algorithm with 3 iterations and 21 subsets. The images were smoothed with a 2-mm full width at half maximum Gaussian filter (14). The image data matrix was 172×172, with a pixel size of 3.42 mm and a slice thickness of 2.03 mm. Dynamic data sets were analyzed by Syngo via software (Siemens Healthineers, Erlangen, Germany). A two-compartment model
was used to quantify absolute MBF (ml/g/minute), which was calculated from PET images as previously described (15). The MFR was calculated as the ratio of hyperemic MBF to resting MBF (Fig.2a).

**MRI acquisition and analysis**

The protocol included electrocardiographic-gated balanced steady-state free cine sequences by free-breathing (10) (11). Three standard long-axis views (two-chamber, three-chamber, and four-chamber views) and multiple short axis views were acquired, and the slice thickness was 5 mm. The number of phases obtained in each cardiac cycle was 25. The following parameters were applied: echo time of 1.5 ms, repetition time of 3.4 ms, matrix of 256×256 pixels, flip angle of 50°, and typical field-of-view of 350 mm. The repetition time was automatically adjusted according to the patient’s heart rate.

Left and right volumetric data were determined by quantitative analysis according to the recommendation using Segment CMR software (MEDVISO, Lund, Sweden) (7). Left ventricular global longitudinal strain (LVGLS) was calculated by wall motion tracking techniques as the mean of the global peak systolic strain from each of the three long-axis views. Similarly, right ventricular global longitudinal strain (RVGLS) was measured in four-chamber longitudinal axis images (8) (Fig.2b). Ventricular endocardial contours were drawn manually during the end-diastolic and end-systolic phases. Subsequently, the software automatically traced the cardiac contours during the cardiac cycle. Scans that did not allow for reliable tracking were excluded.

**Clinical Outcomes**

Clinical information on adverse events was obtained via the electronic hospital records. The primary end points were defined as a composite of all-cause death, myocardial infarction, sustained ventricular arrhythmia, hospitalization due to decompensated heart failure, and coronary revascularization. No patients were lost to follow up.

**Statistical Analysis**

Data are presented as the mean ± standard deviation or number and percentage (%). Differences in continuous variables between two groups were compared using Student’s t-test. Categorical variables are expressed as counts and percentages, and were compared by the $\chi^2$ test. The median values of MFR and RVGLS were used as the cut-off points for predicting adverse cardiac events. A Kaplan–Meier analysis was used to assess the survival-free rate of any adverse events, and the log-rank test was used for initial comparisons. The prognostic value was tested by univariate Cox proportional hazard analyses. Statistical analyses were performed using IBM SPSS version 28 (IBM Corp, Armonk, NY, USA). P<0.05 was considered statistically significant.

**Results**

**Patients’ Baseline Characteristics**
This study analyzed 61 patients who underwent \(^{13}\text{N}-\text{ammonia}\) PET/MRI and CAG. The baseline characteristics in patients with (n = 21) and those without (n = 40) cardiac events are shown in Table 1. The mean age of all of the patients was 64.5 ± 13.7 years, and 45 (73.8%) patients were men. Patients with cardiac events were older than those without cardiac events (P = 0.025). Other risk factors and past histories were not significantly different between the two groups.

**Comparison of PET and MRI Parameters**

The comparison of PET and MRI parameters is shown in Table 2. With regard to PET parameters, stress MBF and MFR were significantly lower in patients with cardiac events than in those without cardiac events (P < 0.001, respectively). In the MRI parameters, the end-diastolic volume, end-systolic volume, and ejection fraction of the left and right ventricles were not significantly different between the two groups. LVGLS and RVGLS were significantly higher in patients with cardiac events than in those without cardiac events (P = 0.021 and P = 0.047, respectively).

**Cardiac Adverse Events During Follow-up**

Over a median follow-up of 2.8 ± 1.9 years, there were 21 (35.0%) adverse cardiac events. Of the 21 events, a composite of all-cause death occurred in 3 (14.3%) patients, hospitalization due to decompensated heart failure occurred in 1 (4.7%) patient, and coronary artery revascularization occurred in 17 (81.0%) patients. The patients were divided into groups by the median value of MFR 1.80 and the median value of RVGLS −18.22%. The Kaplan–Meier analysis showed that the event-free rate was significantly lower in the group with MFR ≥ 1.80 than that with MFR < 1.80 (P < 0.001, Fig.3a). Additionally, the event-free rate was significantly lower in the group with RVGLS > −18.22% than that with RVGLS ≤ −18.22% (P = 0.025, Fig.3b). After dividing the patients into four groups of median MFR and median RVGLS, the event-free rate was lowest in the combined group of MFR < 1.80 and RVGLS > 18.22% than any other groups (P < 0.001, Fig.3c). In the Cox proportional hazard analysis (Table 3), MFR (hazard ratio [HR] 0.14, 95% confidence interval [CI] 0.05–0.38; P < 0.001), LVGLS (HR 1.12, 95% CI 1.01–1.23, P = 0.028), and RVGLS (HR 1.08, 95% CI 1.00–1.17, p = 0.041) were independent predictors of cardiac adverse events in patients with CAD.

**Discussion**

In the present study, we revealed the simultaneous assessment for MFR and RVGLS by \(^{13}\text{N}-\text{ammonia}\) PET/MRI was useful in the patients with CAD. The event-free rate was significantly lower in the combined group of below the median MFR and above the median RVGLS than any other groups. The greatest strength of our study is the possibility of the risk stratification for cardiac events using the simultaneous assessment of MFR and RVGLS by \(^{13}\text{N}-\text{ammonia}\) PET/MRI. This is the first study to report the simultaneous assessment of MFR and RVGLS by \(^{13}\text{N}-\text{ammonia}\) PET/MRI, which provides a precise prognosis in patients with CAD.
Recently, RV dysfunction has been shown to predict the development of heart failure and subsequent mortality in several cardiac diseases \( (3) \) \( (4) \) \( (16) \). RV function plays a major role in hemodynamic stability in different cardiovascular diseases. However, estimating RV function remains challenging because of the complex geometry of the RV, the difficulties in defining the endocardial surface because of trabeculated myocardium, and the load dependence of RV systolic function indices \( (6) \). Echocardiographic measurements of RV function, such as the RV area, RV ejection fraction, and tricuspid annular plane systolic excursion, are limited by the dependency on acoustic windows and the operator's experience. CMR is considered the most appropriate modality for quantitative analysis of the myocardium owing to its high contrast, spatial resolution, and wide field-of-view \( (17) \). Several studies have shown that CMR is the reference for non-invasive assessment of structure and function of RV, and its use has been increasing in the diagnosis and assessment of ischemia \( (18) \).

In our study, the RV ejection fraction was not different between patients with adverse events and those without events. However, RVGLS was significantly higher in patients with cardiac events than in those without events. Furthermore, RVGLS was a good predictor of any cardiac event. These findings indicate that the prognosis depends on RV morphological changes rather than function. Longitudinal strain is a sensitive marker for the RV to assess myocardial damage due to ischemia, and it may be an early indicator of ventricular dysfunction \( (19) \) \( (20) \) \( (21) \). Longitudinal strain imaging appears well suited for functional assessment of the heterogeneous and complex anatomy of the RV. Therefore, the analysis of RV longitudinal strain is a measure that can accurately reflect RV systolic function as suggested by its ability to detect even mild abnormalities and to predict a worse prognosis \( (22) \).

RV strain represents morphological and functional changes in several factors, such as contractility, preload, and afterload. RV performance is also affected by the heart rhythm, synchrony of ventricular contraction, RV force interval relationship, and ventricular interdependence \( (6) \). The RV is extremely sensitive to changes in afterload, a major determinant of which is left atrial pressure \( (23) \). Patients with long-standing heart failure often develop pulmonary hypertension as an effect of elevated left-sided pressure. However, whether a low CFR, vascular disease, or diastolic left ventricular dysfunction contributes to RV deformation and dysfunction is unknown. Furthermore, the RV is perfused by several arteries, not only the right coronary artery. Stiermaier et al \( (24) \) reported that the culprit lesion in patients with acute myocardial infarction with RV dysfunction was not located in the right coronary artery in approximately one third of patients. Factors that might prevent RV dysfunction are a lower oxygen demand related to a lower RV mass, diffusion of oxygen from intracameral blood through the thin-walled RV, more extensive collateral flow, and a greater effect of ischemic preconditioning. Furthermore, RV function is not only determined by injury of the free wall. Left ventricular septal contraction can contribute considerably to RV performance, particularly under conditions of severe free wall dysfunction. Therefore, concomitant left ventricular dysfunction can exacerbate the hemodynamic consequences of RV damage.

PET-derived MFR is also regarded as the gold standard method for diagnosing and predicting the prognosis of CAD \( (25) \) \( (26) \). Zidai et al showed that MFR was a strong predictor of major adverse cardiac events in patients with CAD \( (27) \). Their finding was concordant with our result that MFR was an
independent predictor of cardiac events. Recently, Kawakubo et al (28) showed that global strain values were significantly lower in patients with abnormal MFR than in the patients with normal MFR using feature tracking-derived strain values measured by $^{13}$-N-ammonia PET. This study suggested a relationship between MFR and ventricular strain. One of the reasons for a decrease in RV strain may be a lower MFR of the RV area.

With regard to clinical implications, hybrid PET/MRI is a novel modality for evaluating cardiac diseases that can qualify important information regarding various pathologies through molecular and functional imaging of PET and MRI. The combination of molecular imaging with PET and morphological and functional imaging with MRI provides a complementary assessment of left ventricular myocardial perfusion and RV function in a one-stop examination. Furthermore, the total scan time and exposure to radiation can be reduced when a hybrid PET/MRI scanner is used compared with using PET/CT or MRI alone. In our study, the cardiac event rate was the lowest in the groups of below the median MFR value and above the median RVGLS value, which suggested biventricular insufficiency. These patients may have multivessel disease that caused biventricular ischemia and deformation, which then led to the occurrence of cardiac adverse events. Therefore, the evaluation of left ventricular and RV function by hybrid PET/MRI could be more useful for risk stratification than just performing one of these examinations in patients with CAG.

**Study limitations**

This study has some limitations. First, we analyzed a small number of patients from a single center. Further studies with a larger sample size are warranted. Additionally, we used a free-breathing method for MRI. Free-breathing MRI acquisition is useful to reduce motion artifacts because repetitive breath-holding during MRI acquisition impairs PET images in parallel image acquisition. Several previous study have showed the value of the free-breathing method (29) (30), although generally a breath-hold method allows the acquisition of more precise data on MRI.

**Conclusion**

The simultaneous assessment of MFR and RV strain by $^{13}$N-ammonia PET/MRI revealed the feasibility of precise risk stratification for cardiac events in patients with CAD.

**Declarations**

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The authors declare no funds, grants, or other support.

**Competing interests**

The authors declare no conflict of interest
**Author contributions**

All author contributed to the study conception, design. Material preparation, data collection, and analysis were performed by Keiichiro Endo, Takatoyo Kiko, Ryo Yamakuni, Tomofumi Misaka, Takayoshi Yamaki, Kazuhiko Nakazato, Kenji Fukushima, and Yasuchika Takeishi. The first draft of the manuscript was written by Keiichiro Endo and Takatoyo Kiko, and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

**Ethics approval**

The study protocol was approved by the Ethics Committee at Fukushima Medical University (Date 6/1/2016, No.2717) and was conducted in accordance with the Declaration of Helsinki.

**Consent to participate**

All patients provided written informed consent before enrollment.

**Consent to publish**

Patients signed informed consent regarding publishing their data and photographs.

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**Tables**

**Table 1**

| Patients’ baseline characteristics |
| Characteristics                  | All (n = 61) | Event+ (n = 21) | Event− (n = 40) | P     |
|---------------------------------|-------------|----------------|----------------|-------|
| Age, years                      | 64.5 ± 13.7 | 70.3 ± 6.9     | 61.5 ± 15.3    | 0.015 |
| Male sex                        | 45 (73.8)   | 18 (85.7)      | 27 (67.5)      | 0.124 |
| Body mass index, kg/m²          | 24.1 ± 4.5  | 23.4 ± 4.1     | 24.5 ± 4.7     | 0.383 |

### Risk factors and past history

| Risk factors                                  | All (n = 61) | Event+ (n = 21) | Event− (n = 40) | P     |
|-----------------------------------------------|-------------|----------------|----------------|-------|
| Hypertension                                  | 42 (68.9)   | 15 (71.4)      | 27 (67.5)      | 0.753 |
| Diabetes mellitus                             | 21 (34.4)   | 9 (42.9)       | 12 (30.0)      | 0.315 |
| Dyslipidemia                                  | 40 (65.6)   | 14 (66.7)      | 26 (65.0)      | 0.896 |
| Smoking history                               | 36 (59.0)   | 13 (61.9)      | 23 (57.5)      | 0.740 |
| Family history of coronary artery disease     | 7 (11.5)    | 1 (4.8)        | 6 (15.0)       | 0.233 |
| Previous myocardial infarction                | 17 (27.9)   | 6 (28.6)       | 11 (27.5)      | 0.929 |
| Previous percutaneous coronary intervention   | 29 (47.5)   | 10 (47.6)      | 19 (47.5)      | 0.993 |
| Previous coronary artery bypass grafting      | 5 (8.2)     | 0 (0.0)        | 5 (12.5)       | 0.091 |

Data are presented as mean ± standard deviation or n (%).
|                  | All (n = 61) | Event+ (n = 21) | Event− (n = 40) | P     |
|-----------------|--------------|-----------------|-----------------|-------|
| **PET parameters** |              |                 |                 |       |
| Rest MBF, ml/g/minute | 0.72 ± 0.23  | 0.76 ± 0.19    | 0.70 ± 0.25    | 0.32  |
| Stress MBF, ml/g/minute | 1.37 ± 1.25  | 1.06 ± 0.24    | 1.53 ± 0.56    | < 0.001 |
| MFR             | 2.06 ± 0.83  | 1.57 ± 0.12    | 2.36 ± 0.85    | < 0.001 |
| **MRI parameters** |              |                 |                 |       |
| Left ventricle  |              |                 |                 |       |
| EDV, ml         | 145.2 ± 60.4 | 159.9 ± 53.5 | 138.5 ± 62.9 | 0.261 |
| ESV, ml         | 78.7 ± 57.4  | 90.3 ± 46.5    | 73.5 ± 61.7    | 0.353 |
| EF, %           | 50.8 ± 16.5  | 45.9 ± 15.1    | 53.0 ± 16.8    | 0.167 |
| GLS, %          | -13.2 ± 4.6  | -11.3 ± 3.4    | -14.1 ± 4.8    | 0.021 |
| Right ventricle |              |                 |                 |       |
| EDV, ml         | 55.2 ± 24.3  | 57.0 ± 27.3    | 51.1 ± 15.1    | 0.425 |
| ESV, ml         | 48.3 ± 23.4  | 51.0 ± 23.1    | 42.1 ± 23.6    | 0.207 |
| EF, %           | 46.6 ± 12.2  | 46.0 ± 12.0    | 47.9 ± 12.6    | 0.571 |
| GLS, %          | -17.4 ± 5.4  | -15.5 ± 5.7    | -18.4 ± 5.1    | 0.047 |

PET, positron emission tomography; MRI, magnetic resonance imaging; MBF, myocardial blood flow; MFR, myocardial flow reserve; EDV, end-diastolic volume; ESV, end-systolic volume; EF, ejection fraction; GLS, global longitudinal strain.

**Table 3**

Univariate Cox proportional hazards regression analysis of any cardiac event
Cardiac adverse events (n = 21/61)

| PET parameters                | HR    | 95% CI       | P    |
|-------------------------------|-------|--------------|------|
| Rest MBF                      | 8.19  | 0.445–15.96  | 0.157|
| Stress MBF                    | 1.63  | 0.63–1.63    | 0.301|
| MFR                           | 0.14  | 0.05–0.38    | < 0.001|

| MRI parameters                |       |              |      |
|-------------------------------|-------|--------------|------|
| LVEF                          | 0.98  | 0.95–1.01    | 0.229|
| RVEF                          | 1.01  | 0.97–1.04    | 0.690|
| LVGLS                         | 1.12  | 1.01–1.23    | 0.028|
| RVGLS                         | 1.08  | 1.00–1.17    | 0.041|

PET, positron emission tomography; MRI, magnetic resonance imaging; MBF, myocardial blood flow; MFR, myocardial flow reserve; LVEF, left ventricular ejection fraction; RVEF, right ventricular ejection fraction; LVGLS, left ventricular global longitudinal strain; RVGLS, right ventricular global longitudinal strain.

Figures

Fig. 1

Rest scan

PET dynamic acquisition

MRI Localizer MRAC

Cine (free breath) (short axis, 2ch, 4ch)

Stress scan

Vasodilator stress

PET dynamic acquisition

3 min

PET

MRI Localizer MRAC

Cine (free breath) (short axis, 2ch, 4ch)
**Figure 2**

Analysis of perfusion imaging and left and right ventricular global longitudinal strain by $^{13}$N-ammonia PET/MRI

(a) Polar maps and myocardial flow reserve derived from $^{13}$N-Ammonia PET at rest and stress. (b) MRI wall motion tracking of four-chamber longitudinal axis images to quantify LVGLS and RVGLS. Manual trace endo- and epicardial boundaries at the end-diastolic phase (left panels) and end-systolic phase (middle panels). The right panels show the curves of LVGLS and RVGLS.
Kaplan–Meier analysis for survival free of cardiac events

Kaplan–Meier analysis showed that the event-free rate was significantly lower in the group with MFR < 1.80 ml/g/minute (a), RVGLS > −18.22% (b), and the combination of MFR < 1.80 ml/g/minute and RVGLS > −18.22% (c).

MFR, myocardial flow reserve; RVGLS, right ventricular global longitudinal strain