The association of $^{18}$F-FDG PET/CT and biomarkers in confirming coronary microvascular dysfunction

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Abstract
Objective: The purpose of this study is to evaluate the association between PET/CT CFR and biomarkers combined in confirming the diagnosis of coronary microvascular dysfunction.

Results: A total of 28 patients (21 males and 7 females) were included in this descriptive observational study (both qualitative and quantitative). The mean patient age was 55.50 ± 10.21 years (range 27–70 years) and the median was 56.5 years (range 49–63 years). All patients underwent Echo, CAG and PET/CT scan. Chest tightness was the most common symptom in our study. Most patients had normal blood pressure ($n = 18$, 64.3%) while only ($n = 10$, 37.5%) had hypertension, and ($n = 1$, 3.6%) had diabetes mellitus. The mean HDL in CMVD ($n = 25$) and non-CMVD ($n = 3$) were 1.30 ± 0.39 and 1.08 ± 0.95, respectively, indicating that the difference between the groups was statistically significant ($p = 0.04$). Similarly, the mean HBA1c- (glycated haemoglobin) in CMVD ($n = 25$) and non-CMVD ($n = 3$) were 5.6 ± 0.53 and 5.0 ± 0.26, respectively, with ($p = 0.03$). Our findings managed to show the association between biomarkers and PET/CT CFR in confirming the diagnosis of coronary microvascular dysfunction.

Keywords: Coronary microvascular dysfunction (CMVD), Brain natriuretic peptide (BNP), Red cell distribution (RDW), Coronary flow reserve (CFR)

Introduction
Chest pain has been a common symptom in both cardiovascular and respiratory diseases or as referred pain in some of the gastrointestinal diseases. Chest pain as a cardiovascular symptom most commonly represents an important early indicator of either acute myocardial infarction or aortic dissection. Thus, early diagnosis and intervention has become particularly important in the management of cardiovascular diseases/emergencies.

Recent studies have shown that both obstructive epicardial coronary arteries and nonobstructive coronary microvascular disease have a similar fate of poor prognosis and a common entity of chest discomfort [1].

Coronary microvascular dysfunction is a clinical syndrome encompassing changes that lead to functional and structural abnormalities in the coronary microvasculature. These changes disrupt the ability of the vessels to vasodilate and augment coronary blood flow in response to increased myocardial demand, causing angina and ischemia [2].

Various studies have also revealed that 49% of patients who are undergoing clinically indicated coronary arteriogram do not have significant stenosis [3, 4]. Furthermore, 60% of these patients may have coronary microvascular dysfunction.

Previous study has indicated that, 59% of patients with anginal symptoms, but with angiographically normal coronary arteries, were found to have an abnormal response to vasodilator agents, adenosine, and acetylcholine, suggestive of coronary microvascular dysfunction [5]. Sade et al. [6], in their study which focused on angina-like
chest pain and angiographically normal coronary arteries observed that 40% of study subjects had reduced CFR (mean, 1.7±0.24) suggestive of microvascular dysfunction.

Hung et al. [7] in their study reported that, in healthy adults, an appropriate CFR cutoff value is over 3. Different biomarkers have been implicated in relation to the pathogenesis of coronary microvascular dysfunction namely CRP, LDL, HDL, BNP, troponin, red cell redistribution width etc. [7]. Inflammation and immune dysregulation play a pivotal role in endothelial dysfunction and CAD pathogenesis. Previous data have also documented the use of biomarkers in coronary microvascular disease [7]. The aim of this current study is to review and assess the value of F-FDG PET/CT combined with biomarkers in the diagnosis of CMVD.

Main text
Methodology
Study population
We assessed 28 patients admitted at department of cardiology, Wuhan union hospital, 26 who presented with typical angina symptoms and had a typical history of chest pain, ST-changes on EKG with normal coronary arteries on coronary angiography. 2 were control without any symptoms, no history of hypertension, diabetes mellitus or coronary artery disease, there ECG and CAG were normal.

Study type
A hospital based observational study.

Study objective
The purpose of this study is to evaluate the association between PET/CT CFR and biomarkers combined in confirming the diagnosis of coronary microvascular dysfunction.

Definition of terms
CMVD Patients with CFR of <2.6 which was considered abnormal.
Non-CMVD Patients with CFR of ≥2.6 which was considered normal.

Statistical analysis
Baseline patient characteristics were summarized. All data are presented as mean ± SD for continuous variables and n (%) for categorical variables. Comparisons between the groups were performed using student T-test for continuous variables and Chi square or Fisher exact test for categorical variables. Statistical analyses were done using IBM SPSS statistical software version 20.0. A p < 0.05 was considered statistically significant.

Positron emission tomography
Image acquisition
All patients fasted for at least 6 h before PET/CT examination. The images were obtained using a dedicated PET/CT scanner (Discovery VCT® , GE medical systems, Milwaukee WI, USA) 40–60 min after intravenous injection of 3.75–5.55 MBq/kg of 18F-FDG. A low dose CT scan was obtained for attenuation correction using: tube voltage 120 kV, 80 mAs, and 3.75 mm slice collimation. PET data were constructed with the ordered subset expectation maximization algorithm. Both CT and PET data were sent to a work station (Xeleris®, GE medical systems) for evaluation.

PET-CT scan was used to measure coronary flow reserve and assess the microvascular coronary perfusion.

Results
A total of 28 patients (21 males and 7 females) were included in this descriptive observational study both qualitative and quantitative. The mean patient age was 55.50±10.21 years (range 27–70 years) and the median was 56.5 years (range 49–63 years). A total of 16 patients had chest tightness, four chest pain and eight had mixed symptoms (chest tightness and chest pain). The characteristics of patients are summarized in Table 1.

| Variables         | Attribute | Frequency | Percentage |
|-------------------|-----------|-----------|------------|
| Gender            | Male      | 21        | 75         |
|                   | Female    | 7         | 25         |
| Symptoms          | Chest tightness | 16 | 57.1       |
|                   | Chest pain | 4         | 14.3       |
|                   | Mixed     | 8         | 28.6       |
| Blood pressure    | < 120/80 mmHg | 14 | 50         |
|                   | 120/80–139/89 mmHg | 8 | 28.6       |
|                   | > 139/89   | 6         | 21.4       |
| Smoking           | Yes       | 6         | 21.4       |
|                   | No        | 22        | 78.6       |
| Alcohol           | Yes       | 1         | 3.6        |
|                   | No        | 27        | 96.4       |
| Hypertension      | Yes       | 10        | 35.7       |
|                   | No        | 18        | 64.3       |
| Diabetes mellitus | Yes       | 1         | 3.6        |
|                   | No        | 27        | 96.4       |
| New York Heart Association (NYHA) | I–II | 24 | 85.7 |
|                   | III–IV    | 4         | 14.3       |
Chest tightness was the most common symptom in our study. Most patients had normal blood pressure (n=18, 64.3%) while only (n=10, 37.5%) had hypertension, and (n=1, 3.6%) had diabetes mellitus. Also, most of the patients in our study were in NYHA class I–II (n=24, 85.7%).

The mean PET/CT CFR (PET/CT coronary flow reserve) was 2.0982±0.55 (range 1.16–3.69). The mean LVEF (left ventricular ejection fraction) was 47.89±12.57 (range 24–72%)

The mean HDL in CMVD (n=25) and non-CMVD (n=3) were 1.30±0.39 and 1.08±0.95, respectively, indicating that the difference between the groups was statistically significant (p=0.04). The mean RDW (red cell distribution) in CMVD (n=25) and non-CMVD (n=3) were 13.9±1.75 and 12.7±0.32, respectively, indicating that the difference between the groups was statistically significant (p=0.06). Similarly, the mean HBA1c- (glycated haemoglobin) in CMVD (n=25) and non-CMVD (n=3) were 5.6±0.53 and 5.0±0.26, respectively, suggesting that the difference between the groups was statistically significant (p=0.03). Also, the mean BNP (Brain natriuretic peptide) in CMVD (n=25) and non-CMVD (n=3) were found to be 316.17±526.35 and 42.17±21.18, respectively, indicating that the difference between the groups was statistically significant (p=0.02). The relationship of different biomarkers in relation to patients with CMVD and those without CMVD, the distribution of patients with different biomarkers in relation to patients with CMVD found to be, low HDL 1.30±0.55 (95% CI −0.08 to 1.23) p=0.03 and high BNP 316.17±526.35 (95% CI −316.2 to 909), p=0.02, which were all statistical significant. For those who had CMVD, n=15 had Type 1 CMVD and n=10 had Type 2 CMVD.

Discussion

The aim of this current study is to assess the association of F-FDG PET/CT combined with biomarkers in confirming the diagnosis of CMVD. Coronary flow reserve (CFR) is a non-invasive measure of coronary vasomotor function that integrates the hemodynamic effects of epicardial coronary stenosis, diffuse atherosclerosis and microvascular dysfunction on myocardial tissue perfusion [10]. CFR can be measured non-invasively by PET, Transthoracic Doppler echocardiography and cardiac MRI. We chose PET because dynamic PET imaging affords robust and reproducible measurements of absolute myocardial blood flow (MBF) in ml/min/g at rest and during pharmacological stress which allows the calculation of CFR (defined as a ratio between MBF at stress and MBF at rest [10, 11].

Our findings show that 57.1% of coronary microvascular dysfunction patients presented with chest tightness and not chest pain which is a typical presenting symptom of ischemic heart disease. We also found that all those patients who are smoking (24.1%) suffered from coronary microvascular dysfunction while 35.7% of the patients had hypertension. In addition, CMVD patients n=25 (89.3%) presented with low HDL (cardio protective in CMVD patients) and high RDW, HBA1c, BNP while non CMVD patients n=3 (10.7%) were found to have low LDL levels which were also like CMVD patients. Most of the patients in our study were male (75%), which is consistent with other previous literature of microvascular dysfunction [12]. Conflicting findings have also been reported regarding female sex and microvascular dysfunction. Recent studies reported an existence of association between female gender and increased microvascular dysfunction [13].

Kobayashi et al. [14] in their study observed that there was no sex difference in IMR (index of microvascular resistance) although CFR was lower in females than males possibly due to shorter resting thermodilution transit times in females, and female gender was an independent predictor in the decrease of CFR. Murthy et al. [15] in their study which used PET and CFR threshold < 2.0 found that microvascular dysfunction was common in both men and women (51% and 54%), respectively.

Most of our study subjects (89%) had reduced CFR < 2.6 with normal CAG findings thus confirming diagnosis of microvascular coronary artery disease and showing high sensitivity to PET imaging. Our findings

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Table 2: Showing the mean and standard deviation of the biomarkers and imaging studies

| Variable | N   | Minimum | Maximum | Mean ± SD |
|----------|-----|---------|---------|-----------|
| Age      | 28  | 27      | 70      | 55.50 ± 10.21 |
| LDL      | 28  | 0.94    | 3.48    | 2.25 ± 0.68   |
| HDL      | 28  | 0.7     | 2.13    | 1.27 ± 0.37   |
| TROPONIN | 28  | 0.3     | 2030    | 164.90 ± 458.74 |
| CRP      | 28  | 0       | 59.3    | 9.55 ± 13.31  |
| RDW      | 28  | 12      | 18      | 13.75 ± 1.70  |
| HBA1C    | 28  | 4.5     | 6.7     | 5.51 ± 0.54   |
| BNP      | 28  | 0       | 2266    | 286.81 ± 503.73 |
| ECHO     | 28  | 24      | 72      | 47.89 ± 12.57 |
| PET-CFR  | 28  | 1.16    | 3.69    | 2.10 ± 0.55   |
above are congruent with previous published literatures which observed that patients with and without coronary artery disease (CAD) have CFR thresholds of 1.5–2.6 [16–22]. PET/CT images of 50 years old patient diagnosed as 1 type CMVD (Coronary microvascular dysfunction) as shown in Fig. 1.

Fig. 1 A 50 years old male patient with chief complain of chest tightness, his Resting + ATP Load Pet myocardial perfusion imaging (a) and relative intake (b) showed left ventricular apical segment myocardial infarction, there were several segmental myocardial ischemias in different degrees between wall, lower wall and inferior wall, and absolute quantification (c) showed the absolute decrease of blood flow in the lower wall of left ventricle in resting state, the total and average blood flow of the left ventricle decreased, the left ventricle systolic function decreased, and the apical and lower wall movements were lower; comprehensive information is diagnosed as 1 type CMVD (coronary microvascular disease). (d) Showed regional and whole CFR.
Also, we found patients with abnormal CAG but with normal CFR indicating that they had no ischemic heart disease while we had patients with normal CAG but with abnormal CFR indicating they have ischemic cardiomyopathy. Hence, a misdiagnosis is likely which will eventually lead to mismanagement and finally resulting to poor prognosis because CMVD patients have almost equal complication like those with obstructive epicardial CAD. Therefore, it is important that we improve our knowledge on diagnosis of CMVD either by exploring more biomarkers especially cytokines and at the same time improve our knowledge on PET/CT CFR, to get an accurate diagnosis of CMVD and understand it more.

There are some limitations within our study. First, the low number of our study subjects and the cross-sectional nature of our study limit the magnitude at which our results can be used in a large clinical setting. Another limitation is the use of data from a single center. Also, symptom review was challenging since chest tightness is usually elucidated from the patients. Therefore, large prospective study with large sample size is required to validate our findings.

Conclusion
PET/CT CFR examination combined with assessment of biomarkers such as, HDL, RDW, HBA1C, and BNP is very important in confirming the diagnosis of CMVD.

Limitations
There are some limitations within our study. First, the low number of our study subjects and the cross-sectional nature of our study limit the magnitude at which our results can be used in a large clinical setting. Another limitation is the use of data from a single center. Also, symptom review was challenging since chest tightness is usually elucidated from the patients. Therefore, large prospective study with large sample size is required to validate our findings.

Abbreviations
CFR: coronary flow reserve; PET: positron emission tomography; CAD: coronary artery disease.

References
1. Loffler AI, Bourque JM. Coronary microvascular dysfunction, microvascular angina, and management. Curr Cardiol Rep. 2016;18(1):1.
2. Chen C, Wei J, AlBadri A, et al. Coronary microvascular dysfunction—epidemiology, pathogenesis, prognosis, diagnosis, risk factors and therapy. Circ J. 2016;81(1):3–11.
3. Farrehi PM, Bernstein SJ, Rasak M, et al. Frequency of negative coronary arteriographic findings in patients with chest pain is related to community practice patterns. Ann J Manag Care. 2002;8(7):643–8.
4. Bradley SM, Maddox TM, Stanislawski MA, et al. Normal coronary rates for elective angiography in the Veterans Affairs Healthcare System: insight from the VA CART program (veterans affair clinical assessment reporting and tracking). J Am Coll Cardiol. 2014;63(5):417–26.
5. Hasdai D, Holmes DR Jr, Higano ST, et al. Prevalence of coronary flow reserve abnormalities among patients with nonobstructive coronary artery disease and chest pain. Mayo Clin Proc. 1998;73(12):1133–40.
6. Sade LE, Eroglu S, Bozbas H, et al. Relation between epicardial fat thickness and coronary flow reserve in women with chest pain angiographically normal coronary arteries. Atherosclerosis. 2009;204(2):380–5.
7. Hung OY, Lee SK, Eshtehardi P, et al. Novel biomarkers of coronary microvascular disease. Future Cardiol. 2016;12(14):497–509.
8. Cholesterol levels. American Heart Association. 2010. http://ahacholesterolksw-gtr.com/publication/?i=435100%23%7B%22issue_id%22%3A435100%22page%22%3A4%7D. 9. What do my cholesterol levels mean? American Heart Association. 2007. https://www.heart.org/en/health-topics/cholesterol/prevention-and-treatment-of-high-cholesterol-hyperlipidemia.
10. Gould KL, Johnson NP, Bateman TM, et al. Anatomic versus physiologic assessment of coronary artery disease. Role of coronary flow reserve, fractional flow reserve, and positron emission tomography imaging in revascularization decision making. J Am Coll Cardiol. 2013;62(18):1639–53.
11. Carinci PG, Rimoldi OE. The clinical value of myocardial blood flow measurement. J Nucl Med. 2009;50(7):1076–87.
12. Corcoran D, Young R, Adlam D, et al. Coronary microvascular dysfunction in patients with stable coronary artery disease: the CE-MARC 2 coronary physiology sub-study. Int J Cardiol. 2018;1(266):7–14.

13. Lee JM, Layland J, Jung JH, et al. Integrated physiologic assessment of ischemic heart disease in real-world practice using index of microcirculatory resistance and fractional flow reserve: insights from International Index of Microcirculatory Resistance Registry. Circ Cardiovasc Interv. 2015;8(11):e002857.

14. Kobayashi Y, Fearon WF, Honda Y, et al. Effect of sex differences on invasive measures of coronary microvascular dysfunction in patients with angina in the absence of obstructive coronary artery disease. JACC Cardiovasc Interv. 2015;8(11):1433–41.

15. Murthy VL, Naya M, Taqueti VR, et al. Effects of sex on coronary microvascular dysfunction and cardiac outcomes. Circulation. 2014;129(24):2518–27.

16. Murthy VL, Naya M, Foster CR, et al. Improved cardiac risk assessment with noninvasive measures of coronary flow reserve. Circulation. 2011;124(20):2215–24.

17. Pepine CJ, Anderson RD, Sharaf BL, et al. Coronary microvascular reactivity to adenosine predicts adverse outcome in women evaluated for suspected ischemia: results from National Heart, Lung and Blood Institute WISE (Women’s Ischemia Syndrome Evaluation) study. J Am Coll Cardiol. 2010;55(25):2825–32.

18. Serruys PW, di Mario C, Piek J, et al. Prognostic value of intracoronary flow velocity and diameter stenosis in assessing the short- and long-term outcomes of coronary balloon angioplasty: the DEBATE study (Doppler end-points balloon angioplasty trial Europe). Circulation. 1997;96(10):3369–77.

19. Suwaidi JA, Hamasaki S, Higano ST, et al. Long-term follow-up of patients with mild coronary artery disease and endothelial dysfunction. Circulation. 2000;101(9):948–54.

20. Fukushima K, Javadi MS, Higuchi T, et al. Prediction of short-term cardiovascular events using quantification of global myocardial flow reserve in patients referred for clinical 82Rb PET perfusion imaging. J Nucl Med. 2011;52(5):726–32.

21. Taqueti VR, Hachamovitch R, Murthy VL, et al. Global coronary flow reserve is associated with adverse cardiovascular events independently of luminal angiographic severity and modifies the effect of early revascularization. Circulation. 2015;131(1):19–27.

22. Camici PG, Crea F. Coronary microvascular dysfunction. N Engl J Med. 2007;356(8):830–40.