Heliyon 10 (2024) e29629

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon

Research article

Going beyond summed stress scores: Correlating global and territorial coronary flow reserve by single photon emission tomography with routine myocardial perfusion imaging

Abigail CC. Chng [a], Bryan MH. Keng [a], Xue Fen Teng [a], Kok Wei Aik [a], Muhammad Khairulnizar Azman [a], Larry R. Natividad [a], Candice SM. Chong [a], Packrisamy N. Neela [a], Ru-San Tan [a,b], Lohendran Baskaran [a,b], Terrance SJ. Chua [a,b], Felix YJ. Keng [a,b], Angela S. Koh [a,b,*]

[a] National Heart Centre Singapore, Singapore
[b] Duke-NUS Medical School, Singapore

ARTICLE INFO

Keywords:
Summed stress scores
Coronary flow reserve
Single photon emission tomography
Myocardial perfusion imaging
Coronary artery disease

ABSTRACT

(a) Background: Technological advancement in the recent years has enabled the application of single photon emission tomography (SPECT) to evaluate myocardial blood flow (MBF). This method offers increased sensitivity in the assessment of coronary health, quantifiable through non-invasive imaging beyond the more conventional methods such as with myocardial perfusion imaging (MPI).
(b) Aims: To correlate MBF, derived by dynamic SPECT, both global and by coronary territories to the summed stress scores (SSS) on conventional MPI.
(c) Methods: Images obtained from dipyridamole-gated SPECT MPI stress and rest studies performed on recruited subjects were examined. We calculated the global and regional coronary flow reserve (CFR) via a standard software package, taken as the ratio of stress MBF to rest MBF, using CFR<2.5 as the cut off.
(d) Results: Amongst the 90 recruited subjects (mean age 67 ± 8 years; of which 76% were males), 49% had MPI within normal limits (summed stress score (SSS) 0–3; Left ventricular ejection fraction (LVEF) > 50%). We observed a progressive reduction in global and regional CFR across the normal SSS category to that of severely abnormal (SSS >13). Reduced global CFR with correspondent lower CFR across the regional arteries were detected in scans within normal limits of MPI scans in subjects who were older (69 ± 7 vs. 62 ± 9 years, p = 0.034). Decreasing CFR was significantly associated with increasing age across the regional arteries.
(e) Conclusion: In our study we depict the global and regional MBF values obtained via SPECT MPI in correlation to the respective SSS categories. Our data proposes that dynamic SPECT has a part in refining cardiac risk stratification, particularly in the older adult population, who are at greater risk.

* Corresponding author. National Heart Centre Singapore, 5 Hospital Drive, Singapore 169609.
E-mail address: angela.koh.s.m@singhealth.com.sg (A.S. Koh).

https://doi.org/10.1016/j.heliyon.2024.e29629
Received 18 December 2023; Received in revised form 21 March 2024; Accepted 11 April 2024
Available online 14 April 2024

List of abbreviations

CAD -	Coronary artery disease
CFR -	Coronary flow reserve
CZT -	Cadmium Zinc Telluride
LAD -	Left anterior descending artery
LCX -	Left circumflex artery
LVEF -	Left ventricular ejection fraction
MACE -	Major adverse cardiovascular events
MBF -	Myocardial blood flow
MPI -	Myocardial perfusion imaging
PET -	Positron emission tomography
RCA -	Right coronary artery
SPECT -	Single photon emission tomography
SD -	Standard deviation
SSS -	Summed stress score

1. Introduction

Coronary flow reserve (CFR) is derived from the ratio of myocardial blood flow (MBF) in a state of maximal hyperaemia to that of a state of rest. This is a representation of the functional capacity of the myocardial circulation, a quantitative measure of the severity and haemodynamic significance of coronary artery disease. It has, in recent years, been incorporated into national guidelines [1,2] as part of ischaemia assessment and risk stratification. CFR can be obtained through various non-invasive and invasive modalities of cardiac testing, however is not yet routine or widely used in clinical practice.

In the recent years, it has become evident that CFR is a valuable tool for prognostication in cardiovascular health. Kelshiker et al.'s meta-analysis underscores that reduced CFR is strongly linked to an elevated risk of all-cause mortality and major adverse cardiovascular events (MACE) [3]. This is supported by multiple studies on CFR derived by positron emission tomography (PET) in patients [4,5], establishing CFR as an independent predictor of cardiac mortality and MACE. Bajaj et al.'s research revealed that CFR is not only independently associated with increased body mass index (BMI) and adverse outcomes, but also serves as a superior discriminator of risk compared to BMI and traditional risk factors such as age, sex, hypertension [6]. Furthermore, the correlation between CFR and cardiovascular health can be observed even in individuals without overt coronary artery disease. Taqueti et al. demonstrated that reduced CFR was independently associated with minimally elevated troponin and MACE [7], diastolic dysfunction and hospitalization of patients with heart failure [8].

Technological advancement in the recent years has enabled the application of single photon emission tomography (SPECT) to evaluate myocardial blood flow (MBF). This method offers increased sensitivity in the assessment of coronary health, quantifiable through non-invasive imaging beyond the more conventional methods such as with myocardial perfusion imaging (MPI), such as through the conventional grading with the summed stress scores (SSS). In this study, we correlate MBF, quantified in absolute numbers by dynamic SPECT, both global and by coronary territory to SSS on conventional MPI.

2. Materials and methods

Images obtained from dipyridamole-gated SPECT MPI stress and rest studies performed on recruited subjects were examined. We calculated the global and regional coronary flow reserve (CFR) via a standard software package, taken as the ratio of stress MBF to rest MBF. The regional territories studied were the left anterior descending (LAD), left circumflex (LCX), right coronary artery (RCA). The threshold of CFR <2.5 was taken to be abnormal [9]. The inclusion criteria included all patients who were referred by cardiologists for clinically indicated SPECT MPI. The exclusion criteria included patients with contraindications to dipyridamole.

SPECT MPI list-mode acquisition was performed on a single dedicated Cadmium Zinc Telluride (CZT SPECT camera (Spectrum Dynamics D-SPECT). An injection of 37 MBq of 99m-Tc-tetrofosmin was used to localize and optimize the position of the patient's heart in the field of view for rest imaging. 333 MBq of 99m-Tc-tetrofosmin was injected at a rate of 1.0 cm3/s using an automatic injector and flushed by 40 ml of saline to deliver a tight bolus. Rest list-mode imaging was performed simultaneously with bolus injection and continued for 6 min. Gated rest images were acquired after dynamic imaging.

Pharmacological stress was induced via dipyridamole perfusion (0.56 mg/kg over 4 min) followed by 925 MBq of 99m-Tc-tetrofosmin bolus injection at a rate of 1.0cm3/s at hyperemia. Stress list-mode imaging was performed in the same manner. Rest and stress dynamic acquisitions were completed within 75 min.

Dynamic imaging data and perfusion information were analysed by Corridor 4DM software (version 2017, INVIA, USA). 4DM uses the Leppo Renkin-Crone equation where $A = 0.874$, $B = 0.443$, and $K1 = MBF \times (1 - A \times \exp(-B/MBF))$ [10].

Manual coutouring of left ventricular endocardial and epicardial surfaces were performed from summed myocardial images after 2 min acquisition time. Global and regional left anterior descending artery (LAD), left circumflex (LCx), right coronary artery (RCA) time activity curves were automatically generated by the software.

2.1. Statistical analysis

Continuous variables are expressed as mean ± standard deviation (SD) and were compared using one-way ANOVA. All tests were two-tailed and a p value less than 0.05 was considered statistically significant.

3. Results

3.1. Baseline characteristics

A total of 90 subjects met the inclusion criteria and were examined in the study. The mean age is 67 years, with range (±8 years), 68 (76%) are males. 44 (49%) had normal MPI (summed stress score (SSS 0–3); Left ventricular ejection fraction (LVEF) > 50%).

3.2. Global and territorial CFR and summed stress scores

44 subjects had normal MPI studies (SSS 0–3), and the remaining 49 subjects had abnormal MPI studies, consisting 26 subjects with mildly abnormal studies (SSS 4–8), 9 subjects with moderately abnormal studies (SSS 9–13) and 11 subjects with severely abnormal studies (SSS >13). We observed a progressive reduction in global and regional CFR from normal (SSS 0–3), mildly (SSS 4–8) to moderately (SSS 9–13) to severely (SSS >13) abnormal SSS categories on MPI shown in Fig. 1.

Table 1 shows mean CFR values in correspondence to SSS category. We stratified CFR for each coronary artery by SSS categories, depicting mean, standard deviation and 95% confidence intervals for each territory. We observed significant differences in LAD CFR (p-value <0.0001), LCX CFR (p-value = 0.0020), RCA CFR (p-value 0.0300) and global CFR (p-value <0.0001) measurements according to summed stress score category. Again we demonstrate the overall gradual reduction in global and regional CFR across SSS categories. The mean global CFR was 2.585 for normal studies, 2.114 for mildly abnormal studies, 2.209 for moderately abnormal studies and 1.430 for severely abnormal studies.

3.3. CFR and age

We proceeded to assess relationships between age and CFR, particularly among normal MPI scans with LVEF >50%. We observed that patients who had abnormal global CFR had lower LAD CFR (1.94 ± 0.27 vs 2.96 ± 0.59, $p < 0.0001$), LCX CFR (1.92 ± 0.46 vs 3.19 ± 0.47, $p < 0.0001$), RCA CFR (2.14 ± 0.37 vs 3.52 ± 0.51, $p < 0.0001$) and were older in age (69 ± 7 vs 62 ± 9 years, $p = 0.034$). Correlation of CFR with age was significant with global CFR ($p = 0.006$) and LAD CFR ($p = 0.008$), LCX CFR ($p = 0.031$) and RCA CFR ($p = 0.014$) shown in Fig. 2.

4. Discussion

We correlate MBF, quantified in absolute numbers by dynamic SPECT, both globally and according to the coronary territories, to the summed stress scores (SSS) on conventional MPI. The correlation between global, LAD, LCX and RCA CFR across SSS categories is a useful depiction of CFR values studied alongside SSS categories. That is, with each SSS category, one may then extrapolate the expected

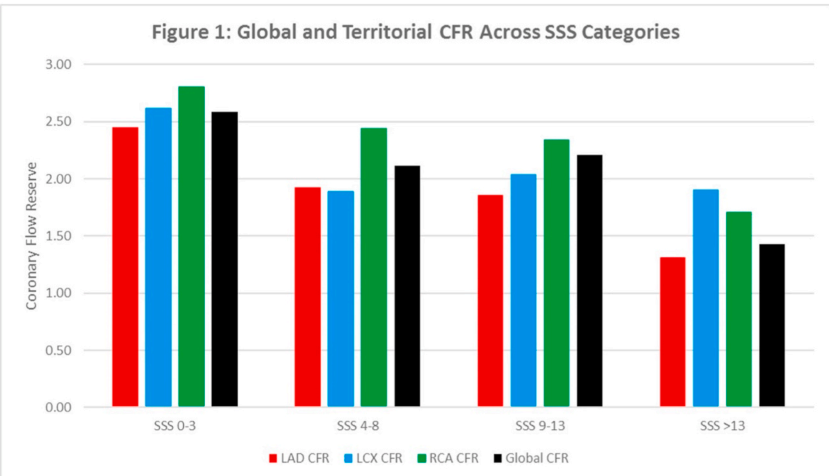

Fig. 1. Global and territorial CFR across SSS Categories
Abbreviations: CFR-coronary flow reserve, SSS-summed stress scores, LAD-Left anterior descending artery, LCX-Left circumflex artery, RCA-Right coronary artery.

Table 1
Mean CFR values for each SSS category.

Table 1		N	Mean	Std. Deviation	Std. Error	95% Confidence Interval for Mean		p value
						Lower Bound	Upper Bound	
LAD CFR	SSS 0-3	44	2.454	0.691	0.104	2.244	2.664	
	SSS 4-8	26	1.925	0.820	0.161	1.594	2.256	
	SSS 9-13	9	1.859	0.330	0.110	1.605	2.113	
	SSS>13	11	1.314	0.446	0.135	1.014	1.613	
								<0.0001
LCX CFR	SSS 0-3	44	2.616	0.838	0.126	2.361	2.870	
	SSS 4-8	26	1.895	0.797	0.156	1.574	2.217	
	SSS 9-13	9	2.038	0.636	0.212	1.549	2.527	
	SSS>13	11	1.904	0.834	0.251	1.343	2.464	
								0.0020
RCA CFR	SSS 0-3	44	2.807	0.891	0.134	2.536	3.078	
	SSS 4-8	26	2.441	1.427	0.280	1.865	3.018	
	SSS 9-13	9	2.346	1.422	0.474	1.253	3.438	
	SSS>13	11	1.711	0.505	0.152	1.371	2.050	
								0.0300
Global CFR	SSS 0-3	44	2.585	0.705	0.106	2.370	2.799	
	SSS 4-8	26	2.114	1.068	0.209	1.683	2.545	
	SSS 9-13	9	2.209	0.673	0.224	1.692	2.726	
	SSS>13	11	1.430	0.507	0.153	1.089	1.771	
								<0.0001

Abbreviations: CFR-Coronary Flow Reserve, SSS-Summed Stress Scores, LAD-Left Anterior Descending Artery, LCX-Left Circumflex Artery, RCA-Right Coronary Artery.

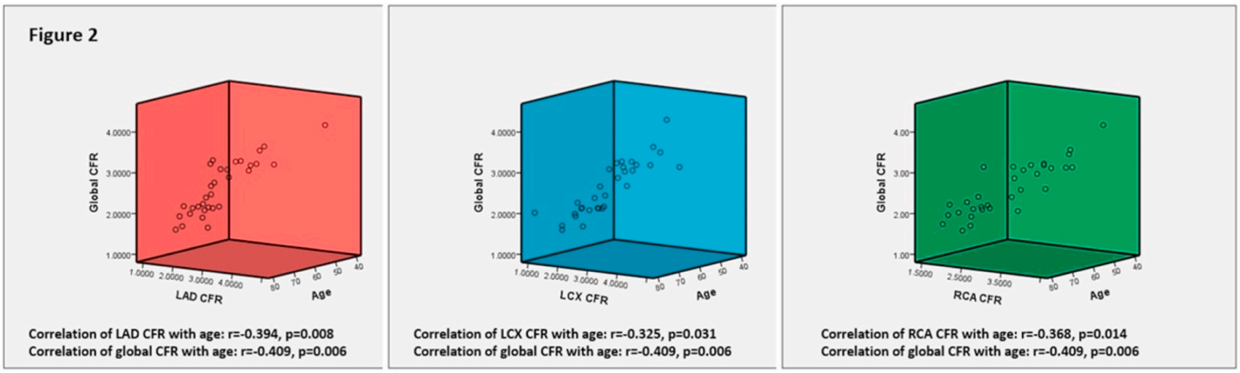

Fig. 2. Correlation of global and territorial CFR with age
Abbreviations: CFR-Coronary Flow Reserve, LAD-Left Anterior Descending Artery, LCX-Left Circumflex Artery, RCA-Right Coronary Artery.

CFR, thereby adding greater risk stratification and prognostication, as a potential application of dynamic SPECT technology. A systematic review by Motwani et al. on the benefits and limitations of CFR and FFR, derived by the various investigative modalities, inclusive of SPECT MPI, identified that the key advantages of quantification of CFR are greater risk stratification and prognostication, and these were demonstrated in several studies [11]. Ziadi et al. evaluated the prognostic value of CFR using PET and found that CFR predicts hard cardiac events (cardiac death and myocardial infarction) and MACE independent of the SSS [12]. In another study by Murthy et al., CFR <1.5 was associated with a 5.6-fold increase in the risk of cardiac death compared to CFR >2, furthermore the incorporation of CFR correctly reclassified 34.8% of patients into the intermediate-risk category [13]. This suggests that CFR, even derived through non-invasive imaging could further improve risk stratification for CAD.

Pang et al. demonstrated greater diagnostic efficacy for coronary artery disease by CZT SPECT quantitative myocardial blood flow parameters, compared with traditional SPECT MPI derived semi-quantitative parameters. The results compared the sensitivity and specificity for diagnosis of coronary artery disease (CAD) based on the two measurements, as defined in their study by ≥ 50% or ≥75% coronary artery stenosis on coronary angiography, and showed that the myocardial quantitative blood flow parameters were superior [14]. In another study by Liu et al., patients with suspected CAD were evaluated with both SPECT MPI and coronary angiography. They measured and compared SSS with CFR across global and regional CAD and similarly found that increased SSS and impaired CFR were significantly corresponded with degree of CAD [15]. The correlation between the different grades SSS and CFR is as demonstrated in our results. A key difference between the studies of Pang et al. and Liu et al. is in the study populations – they have selected patients with suspected or diagnosed CAD, whereas we have also included the full risk range of patients. This has enabled us to also demonstrate that even amongst normal MPI scans (SSS 0–3), we can detect abnormal CFR (<2.5) – making it more sensitive to the early detection of underlying CAD. However, in the absence of invasive coronary angiography data, these observations may be limited by false negatives among those MPI graded as normal. Despite the lack of anatomical confirmation of flow-limiting coronary stenoses, the measurement of CFR, an indication of haemodynamic significance of the stenoses, would be useful to guide treatment. For instance, in the evaluation of atypical chest pain in the setting of normal MPI scan, preserved myocardial blood flow values adds diagnostic confidence to clinicians, possibly averting more downstream cardiac testing. Merhige and Breen demonstrated in their study with PET MPI, a significant number of >50% of cases avoided needing invasive coronary evaluation and surgery resulting in not only great cost savings but also great clinical outcomes, what we also hope to achieve with our data on SPECT MPI [16].

The observation that age is negatively associated with myocardial blood flow across all three coronary territories is in agreement with other observations. However, age-related observations regarding coronary flow patterns that occur with aging remain enigmatic. Several hypotheses include age-dependent variable responses to vasodilator stress [17], increases in systolic blood pressure that increases cardiac work with age [18] and declines in compliance of the vascular system [19]. Individual patient differences in heart rate at rest or stress may also influence cardiac work and coronary blood flow, which we did not account for in this analysis. Nevertheless, age has been shown to be an important determinant of CFR. In a study assessing CFR in patients with vasospastic angina compared to controls with normal coronaries, there was no significant difference in CFR between spasm-positive and spasm-negative vessels, instead they found that age was the most importance factor determining CFR [20]. Similarly in Stegehuis et al.'s study of CFR and the factors that impact it, increasing age and female gender were found to be associated with a lower CFR [21]. Thus we aimed to further delineate this relationship through our analysis and our findings demonstrate that age may be important factor for all three coronary arterial territories (not just overall MBF). Future work would need to be undertaken to explore whether age-related changes in CFR are pathological or physiological or age-based cut-offs in MBF estimations are necessary for clinical management.

4.1. Limitations

Finally, we acknowledge limitations in our study which include small sample size and lack of clinical and medication data that would impact estimations of myocardial blood flow. Future work involving larger sample size and adjustments for confounders would be warranted.

5. Conclusions

In our study we depict the global and regional MBF values obtained via SPECT MPI in correlation to the respective SSS categories. Our data proposes that dynamic SPECT has a part in refining cardiac risk stratification, particularly in the older adult population, who are at greater risk. Its clinical application in guiding treatment via a non-invasive means will also reduce exposure to unnecessary procedural risks.

Ethical considerations

The use of human studies presented in this manuscript was approved by the SingHealth Institutional Review Board and was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki. Written informed consent was obtained from all recruited clinical subjects.

Funding

The project is supported by funding from the National Medical Research Council of Singapore (MOH-000153, MOH-000739 and MOH-001193-00) to A.S.K.

Data availability

All data to support the conclusions have been either provided or are otherwise publicly available.

CRediT authorship contribution statement

Abigail CC. Chng: Writing – review & editing, Writing – original draft. **Bryan MH. Keng:** Writing – review & editing, Conceptualization. **Xue Fen Teng:** Writing – review & editing. **Kok Wei Aik:** Writing – review & editing. **Muhammad Khairulnizar Azman:** Writing – review & editing. **Larry R. Natividad:** Writing – review & editing. **Candice SM. Chong:** Writing – review & editing. **Packrisamy N. Neela:** Conceptualization, Writing – review & editing. **Ru-San Tan:** Writing – review & editing. **Lohendran Baskaran:** Conceptualization, Writing – review & editing. **Terrance SJ. Chua:** Writing – review & editing. **Felix YJ. Keng:** Writing – review & editing. **Angela S. Koh:** Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

We thank the staff of the imaging laboratories for participating in the conduct of the study.

References

[1] J. Knuuti, et al., 2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes, Eur. Heart J. 41 (3) (2020) 407–477.
[2] M. Gulati, et al., 2021 AHA/ACC/ASE/CHEST/SAEM/SCCT/SCMR guideline for the evaluation and diagnosis of chest pain: a report of the American college of cardiology/American heart association joint committee on clinical practice guidelines, Circulation 144 (22) (2021) e368–e454.
[3] M.A. Kelshiker, et al., Coronary flow reserve and cardiovascular outcomes: a systematic review and meta-analysis, Eur. Heart J. 43 (16) (2021) 1582–1593.
[4] M.C. Ziadi, et al., Impaired myocardial flow reserve on rubidium-82 positron emission tomography imaging predicts adverse outcomes in patients assessed for myocardial ischemia, J. Am. Coll. Cardiol. 58 (7) (2011) 740–748.
[5] V.L. Murthy, et al., Improved cardiac risk assessment with noninvasive measures of coronary flow reserve, Circulation 124 (20) (2011) 2215–2224.
[6] N.S. Bajaj, et al., Coronary microvascular dysfunction and cardiovascular risk in obese patients, J. Am. Coll. Cardiol. 72 (7) (2018) 707–717.
[7] V.R. Taqueti, et al., Interaction of impaired coronary flow reserve and cardiomyocyte injury on adverse cardiovascular outcomes in patients without overt coronary artery disease, Circulation 131 (6) (2015) 528–535.
[8] V.R. Taqueti, et al., Coronary microvascular dysfunction and future risk of heart failure with preserved ejection fraction, Eur. Heart J. 39 (10) (2018) 840–849.
[9] A.I. Löffler, J.M. Bourque, Coronary microvascular dysfunction, microvascular angina, and management, Curr. Cardiol. Rep. 18 (1) (2016) 1.
[10] D. Agostini, et al., First validation of myocardial flow reserve assessed by dynamic (99m)Tc-sestamibi CZT-SPECT camera: head to head comparison with (15)O-water PET and fractional flow reserve in patients with suspected coronary artery disease. The WATERDAY study, Eur J Nucl Med Mol Imaging 45 (7) (2018) 1079–1090.
[11] M. Motwani, et al., Reasons and implications of agreements and disagreements between coronary flow reserve, fractional flow reserve, and myocardial perfusion imaging, J. Nucl. Cardiol. 25 (1) (2018) 104–119.
[12] M.C. Ziadi, et al., Impaired myocardial flow reserve on rubidium-82 positron emission tomography imaging predicts adverse outcomes in patients assessed for myocardial ischemia, J. Am. Coll. Cardiol. 58 (7) (2011) 740–748.
[13] V.L. Murthy, et al., Improved cardiac risk assessment with noninvasive measures of coronary flow reserve, Circulation 124 (20) (2011) 2215–2224.
[14] Z.K. Pang, et al., [Diagnostic efficiency and incremental value of myocardial blood flow quantification by CZT SPECT for patients with coronary artery disease], Zhonghua Xinxueguanbing Zazhi 50 (5) (2022) 494–500.
[15] F.S. Liu, S.Y. Wang, Y.C. Shiau, Y.W. Wu, Integration of quantitative absolute myocardial blood flow estimates from dynamic CZT-SPECT improves the detection of coronary artery disease, J. Nucl. Cardiol. 29 (5) (2022) 2311–2321.
[16] M.E. Merhige, et al., Impact of myocardial perfusion imaging with PET and (82)Rb on downstream invasive procedure utilization, costs, and outcomes in coronary disease management, J. Nucl. Med. 48 (7) (2007) 1069–1076.
[17] M.J. Senneff, E.M. Geltman, S.R. Bergmann, Noninvasive delineation of the effects of moderate aging on myocardial perfusion, J. Nucl. Med. 32 (11) (1991) 2037–2042.
[18] M. Brandfonbrener, M. Landowne, N.W. Shock, Changes in cardiac output with age, Circulation 12 (4) (1955) 557–566.
[19] J.I. Hoffman, Maximal coronary flow and the concept of coronary vascular reserve, Circulation 70 (2) (1984) 153–159.
[20] S. Sueda, H. Kohno, H. Fukuda, T. Uraoka, Coronary flow reserve in patients with vasospastic angina: correlation between coronary flow reserve and age or duration of angina, Coron. Artery Dis. 14 (6) (2003) 423–429.
[21] V.E. Stegehuis, et al., Impact of clinical and haemodynamic factors on coronary flow reserve and invasive coronary flow capacity in non-obstructed coronary arteries: a patient-level pooled analysis of the DEBATE and ILIAS studies, EuroIntervention 16 (18) (2021) e1503–e1510.