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Short communication

Correlation between intracoronary physiology and myocardial perfusion imaging in patients with severe aortic stenosis

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ABSTRACT

Background: Aortic stenosis (AS) is frequently associated with coronary artery disease (CAD). However, the best tool to functionally assess CAD in AS remains undetermined. Fractional flow reserve (FFR) and instantaneous wave-free ratio (iFR) have never been validated in AS.

Methods: FFR, iFR and stress single photon emission computed tomography (SPECT) were performed in a consecutive series of 28 patients with severe AS and 41 borderline coronary lesions during the work-up for valve replacement.

Results: Both FFR and iFR were correlated with an abnormal SPECT. At ROC analysis, FFR yielded an AUC = 0.91 with negative predictive value (NPV) = 95% in detecting ischemia according to SPECT.
iFR showed significant worse agreement with myocardial perfusion imaging compared to FFR (59% vs 85%, p = 0.014). Specifically, a significant larger proportion of false positive measurements (negative SPECT and iFR < 0.89) was observed using iFR vs FFR: 39% vs 12%, p = 0.011. Using a pre-specified 0.82 cut-off, the iFR agreement with SPECT increased to 73%.

Conclusions: FFR yielded a good correlation with SPECT and a high NPV in detecting ischemia-provoking lesions. iFR diagnostic metrics were inferior compared with FFR and improved adopting a lower ischemic threshold.

1. Introduction

The role of coronary physiology in patients with aortic stenosis (AS) undergoing transcatheter aortic valve implantation (TAVI) is not well defined. In fact, although measurements of both FFR and iFR are feasible and safe in patients with severe AS [1–4], on the other hand, little is known about the reliability of physiological indices in this setting.

Recently, different FFR and iFR ischemic thresholds have been identified in severe AS, highlighting the peculiar pathophysiology of coronary flow in these patients [5,6].

The aim of the study was to verify the agreement between intracoronary physiological indices and non-invasive myocardial perfusion imaging (MPI) in patients with severe AS before aortic valve replacement, in order to identify coronary lesions causing myocardial ischemia.

Moreover, we sought to test the ischemic FFR and iFR cut-offs recently proposed by Yamanaka et al. in this clinical setting [5].

2. Methods

Patients with severe AS and bystander coronary artery disease (CAD) undergoing aortic valve replacement (TAVI or surgery) were prospectively enrolled in this observational study (see Appendix). CAD was defined as the presence of a coronary lesion with diameter stenosis >50% in the proximal segment of at least one of the major coronary branches as measured by quantitative coronary analysis (QCA).

The study was approved by the ethical review board of the University of Verona (ID CESC 2015-498).

2.1. Intracoronary physiological measurements

A pressure-monitoring guide-wire (PrimeWire, Volcano Therapeutics, Rancho Cordova, California, USA) was advanced distally to the coronary artery stenosis after

Abbreviations: AS, aortic stenosis; CAD, coronary artery disease; DS, diameter stenosis; FFR, fractional flow reserve; iFR, instantaneous wave-free ratio; MPI, myocardial perfusion imaging; QCA, quantitative coronary analysis; SPECT, single photon emission computed tomography; TAVI, transcatheter aortic valve implantation.

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accurate normalization. FFR and iFR were calculated on-line in a standard fashion. Hyperemia was obtained after administration of intra-coronary bolus of adenosine (150 to 250 μg).

2.2. Myocardial perfusion imaging

Stress-rest myocardial perfusion single photon emission computed tomography (SPECT) was performed using a stress-rest protocol with 900 MBq (25 mCi) of technetium-99m sestamibi. Adenosine was administered as a 6-min infusion at 140 μg/kg/min. Scintigraphic imaging interpretation was performed using a standard 17-segments-model. All the images were evaluated independently by two experienced nuclear specialists unaware of any other study data. In case of discordance, a third operator reviewed the images and decisions were taken accordingly.

2.3. Statistical analysis

Descriptive statistics are reported as median (interquartile range) or proportions. Comparisons between variables were performed using the Mann-Whitney test or the Pearson's chi-square test, as appropriate.

The diagnostic performance of physiological indices, including diagnostic accuracy, negative predictive value (NPV) and positive predictive value (PPV) was tested against the results of MPI. Receiver operator characteristic curves analysis and logistic regression for predictors of abnormal MPI were performed. All the analyses have been performed using SPSS 25.0 (IBM Inc., NY USA). A p-value < 0.05 was considered statistically significant.

3. Results

Twenty-eight patients with severe AS and 41 coronary lesions were enrolled in this prospective observational study between January 2017 and February 2018. Clinical and angiographic characteristics are shown in Table 1.

Inducible perfusion defects reflecting myocardial ischemia at MPI were identified in 15 out of 41(37%) vascular territories supplied by the stenotic vessels in 15 out of 28 (53%) patients.

Hemodynamic conditions were similar and stable during non-invasive MPI and invasive pressure-wire assessment in terms of systolic pressure (130 [115–140] vs 130 [110–140], p = 0.42), diastolic pressure (70 [70–80] vs 70 [60–80], p = 0.38) and heart rate (67 [62–70] vs 70 [62–74], p = 0.23).

Median FFR was 0.81 [0.74–0.89]. Median iFR was 0.82 [0.67–0.89]. Abnormal FFR values (≤0.8) were observed in 19 out of 41 (46.3%) coronary lesions, whereas abnormal iFR (<0.89) values were observed in 30/41(73%).

Notably, markers of AS severity were not significantly associated with the presence of myocardial ischemia at MPI (Table A1) or with the intracoronary physiological assessment (Tables A2–A3).

3.1. Agreement between FFR and stress myocardial SPECT

At ROC curve analysis, FFR showed an AUC of 0.91 (CI: 0.81–1) in detecting the presence of ischemia at MPI. FFR ≤ 0.8 presented a sensitivity of 93.3% (68–99.8%), a specificity of 80.8% (60.6–93.4%), a NPV of 95.4% (CI: 77.2–99.9) and a PPV of 73.7% (CI: 48.8–90.8) in detecting perfusion defects reflecting ischemia at MPI.

Discordances between FFR and SPECT were observed in 6 (15%) coronary lesions (Fig. 1B). Only 1 (2%) coronary lesion with positive MPI was negative at FFR assessment (>0.8). Conversely, 5 (13%) lesions with negative MPI were FFR positive (≤0.8).

ROC-derived FFR < 0.78 cut-off yielded the highest degree of agreement with MPI (88%), with a sensitivity of 87% (CI: 59.5–98.3%), a specificity of 88% (CI: 69.8–97.5), a NPV of 92% (74–99%) and a PPV of 81 (54.3–95.9%) (Appendix).

Using the prespecified FFR < 0.83 [5], the overall agreement with MPI was 78%, with a sensitivity of 93% (CI: 68–100%), a specificity of 69% (CI: 48–86), a NPV of 95% (74–100%) and a PPV of 64% (41–83%) (Fig. A1).

The accuracy of angiography alone in detecting ischemia according to MPI was lower compared with FFR (Appendix).

Table 1
Clinical, echocardiographic and angiographic data.

Variable	Overall	No ischemia at MPI	Ischemia at MPI	p-Value
Patients n.	28(100)	13(46)	15(54)	
Age, years	82(79–88)	82(80–87)	79(76–89)	0.85
Sex female, %	14(50)	5(38)	9(60)	0.045
BMI, kg/m^2	27(24–30)	28(25–30)	25(24–28)	0.079
Hypertension, %	25(89)	10(77)	15(100)	0.085
Diabetes, %	13(46)	7(54)	6(40)	0.23
Dyslipidemia, %	17(61)	7(54)	10(67)	0.75
CKD, %	14(50)	8(62)	6(40)	0.69
AF, %	9(32)	6(46)	3(20)	0.4
Angina (CCS > 1)	6(21)	2(15)	4(27)	0.56
Medical therapy				
Beta-blockers	14(50)	5(38)	9(60)	0.39
Ca channels blocker	16(57)	6(46)	10(67)	0.55
ACEi/ARB	6(21)	3(23)	3(20)	0.64
Statin	15(54)	5(38)	10(67)	0.09
Echocardiographic data				
LVEF%	63(53–67)	64(54–66)	61(45–69)	0.68
EDV, ml	62(54–68)	62(57–68)	55(53–69)	0.13
IVST, mm	13(12–15)	14(13–16)	13(11−13)	0.25
AVMG, mm Hg	43(33–47)	45(42–48)	37(26–42)	0.11
AVPG, mm Hg	68(48–73)	69(64–72)	61(41–66)	0.02
AVA, cm^2	0.70 (0.58–0.82)	0.71 (0.64–0.83)	0.65 (0.52–0.82)	0.24
LA, ml	44(37–60)	44(40–58)	40(31–61)	0.26
Angiographic data				
Lesions n.	41(100)	26(64)	15(36)	
LAD, %	21(51)	10(39)	11(73)	0.16
DS%	55(47–68)	51(45–51)	70(58–76)	0.001
Lesion length, mm	14.1 (10.0–18.9)	13.5 (8.9–17.2)	16.0 (10.0–24.0)	0.16
Reference diameter, mm	3.10 (2.80–3.50)	3.00 (2.78–3.48)	3.12 (2.80–3.60)	0.89
MLD, mm	1.36 (1.05–1.78)	1.57 (1.31–1.83)	1.13 (0.68–1.49)	0.14
FFR	0.81 (0.74–0.88)	0.86 (0.81–0.94)	0.74 (0.60–0.76)	<0.001
iFR	0.82 (0.68–0.91)	0.86 (0.80–0.93)	0.63 (0.53–0.81)	0.001

AF, atrial fibrillation; AVA, aortic valve area; AVMG, aortic valve mean gradient; AVPG, aortic valve peak gradient; BMI, body mass index; EDV, end-diastolic volume; IVST, interventricular septum thickness; LA, left atrium; LAD, left anterior descending artery; MLD, minimal lumen diameter. Data are presented as median values and interquartile range for continuous variables and as numbers and proportions for dichotomous variables.

3.2. Agreement between iFR and stress myocardial SPECT

At ROC curve analysis, iFR showed an AUC of 0.84 (CI: 0.72–0.97) in detecting ischemia at MPI. iFR < 0.89 presented a sensitivity of 93% (68–99%), a specificity of 38% (20–59%), a NPV of 91% (CI: 59–100) and a PPV of 47% (CI: 28–66%) in detecting significant perfusion defects reflecting ischemia at MPI. Discordances between iFR and SPECT were demonstrated in 17/41 (41%) coronary lesions (p-value for comparison with FFR = 0.014). The vast majority of the discordant cases (16/41 = 39%) were false positive (negative SPECT and iFR < 0.89; p-value for comparison with FFR = 0.011), whereas only one lesion (1/41 = 2%) with positive MPI was negative at the iFR assessment (p-value for comparison with FFR = 0.47; Fig. 1C). Using the prespecified iFR < 0.82 [5], the overall agreement with MPI was 73%, with a sensitivity of 80% (CI: 52–96%), a specificity of 69% (CI: 48–86%), a NPV of 86% (64–97%) and a PPV of 60% (36–81%) (Fig. A1).

4. Discussion

The main findings of this study can be summarized as follows:

1) FFR was a better predictor of myocardial ischemia compared with angiography alone, with a high level of agreement with the stress MPI (85%) and AUC_{FFR} of 0.91 (CI: 0.81–1).

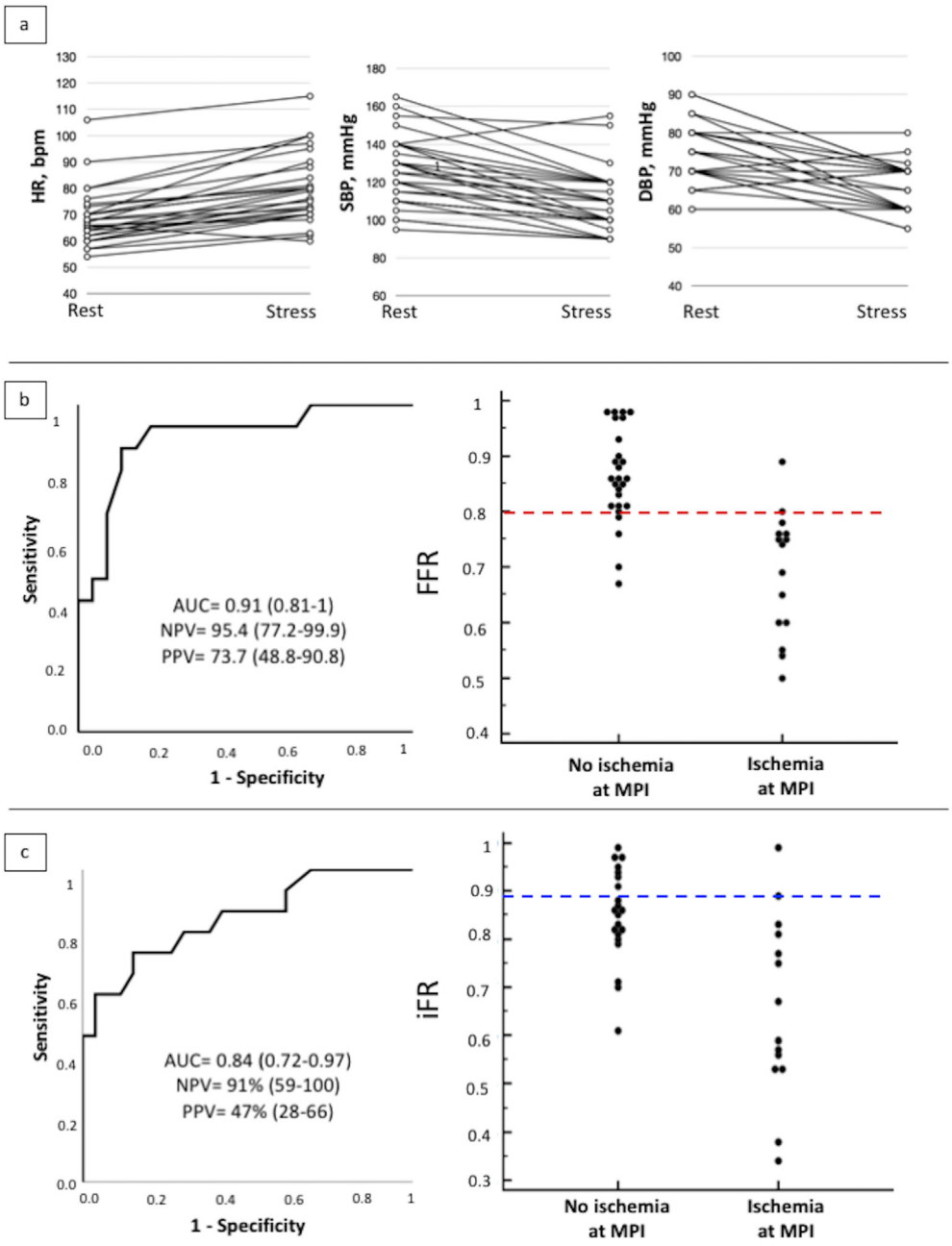

Fig. 1. A) During stress MPI, heart rate increased significantly from 67 [62–70] to 80 [72–90] ($p < 0.001$), systolic blood pressure decreased from 130 [115–140] to 110 [100−120] ($p < 0.001$) and diastolic blood pressure decreased from 70 [70–80] to 60 [60–70] ($p < 0.001$). B) and C) Diagnostic performance of FFR and iFR against stress MPI: ROC curve analysis (left) and coronary distribution according to the FFR/iFR value and stratified by the results of MPI (right).

2) FFR yielded a NPV of 95% in detecting myocardial ischemia in AS patients. In fact, only one (2%) ischemia-provoking coronary stenosis was missed by FFR. Consequently, negative FFR lesions generally do not cause inducible ischemia as assessed by stress MPI.
3) iFR showed a fair performance in detecting myocardial ischemia at MPI, but inferior to FFR using the standard iFR < 0.89 cut-off. Indeed, the agreement with the MPI is low (59%) and the false-positive rate is high (39%; Fig. 1). The agreement between iFR and MPI increased significantly using the pre-specified 0.82 cut-point.

Multiple factors may contribute to coronary flow reserve (CFR) impairment in AS, including increased resting coronary flow, higher than normal zero-flow pressure (Pzf) and reduced maximal hyperemic flow [7]. However, Lumley et al. recently demonstrated that maximal achievable flow during stress is similar between AS patients and controls [8]. Therefore, the augmented resting flow in response to the higher metabolic demand caused by the increased LV afterload and myocardial mass may be the main mechanism responsible for a reduced CFR in AS [9,10]. A significant increase in resting flow implies a higher pressure-gradient across a given coronary stenosis and a lower iFR value. Moreover, being limited to the assessment of the diastolic pressure, iFR may not adequately reflect the physiologic stenosis severity in presence of AS [11].

Notwithstanding the theoretical limitations of measuring FFR in AS, a good correlation between FFR and MPI has been recently reported in a larger cohort of patients with AS [5]. The authors found a fair correlation between iFR and MPI as well, but, consistently with our results, a lower cut-point for iFR was needed to obtain a better association with FFR and

with stress SPECT compared with the standard iFR cut-off. Notably, in our analysis, the ROC-derived optimal FFR cut-off was lower (0.78) compared to what reported by Yamanaka et al. [5].

Recently, Modi et al. suggested 0.75 and 0.86 as optimal cut-points for FFR and iFR respectively in patients without AS, demonstrating a higher diagnostic accuracy and lower discordance rate compared with the standard clinical thresholds [12]. This observation highlights the importance of interpreting physiological assessment as a comprehensive tool rather than as a fixed ischemic cut-off. In our analysis, in fact, iFR presented a fair performance at ROC curve analysis, with an AUC_{iFR} of 0.84, and the NPV of 91% is reassuring about the risk of underestimating a possible ischemic lesion. However, the high rate of false positive results (39%) obtained using the current clinical iFR cut-point (0.89) highlights the inaccuracy of this threshold value and the need for additional investigation on the iFR ischemic cut-off in AS.

4.1. Limitations

The small sample size is a limitation to the conclusions that can be drawn by this analysis, which should be considered hypothesis-generating. In particular, the present study was not powered to determine the best cut-off of physiological indices in the setting of AS.

The accuracy of SPECT has not been validated in AS. However, the significant cardiovascular response observed during adenosine infusion confirmed the efficacy of the stressor (Fig. 1A). Additionally, the presence of balanced ischemia could not be excluded by SPECT in cases of multivessel disease and negative SPECT ($n = 1$).

5. Conclusion

CAD assessment by means of FFR demonstrated substantial agreement with stress-rest MPI and high NPV in identifying coronary lesions with demonstrated ischemic potential in a selected cohort of patients with severe AS and stable CAD. Similarly, iFR showed high NPV in excluding ischemia-provoking coronary lesions but overall agreement with stress-rest MPI was inferior to FFR and does not support its clinical use. A stronger agreement between iFR and MPI was observed using a lower (0.82) threshold.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2019.04.050.

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Disclosures

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References

[1] G. Pesarini, R. Scarsini, C. Zivelonghi, A. Piccoli, A. Gambaro, L. Gottin, et al., Functional assessment of coronary artery disease in patients undergoing transcatheter aortic valve implantation: influence of pressure overload on the evaluation of lesions severity, Circ. Cardiovasc. Interv. 9 (2016), e004088.
[2] Y. Ahmad, M. Götberg, C. Cook, J.P. Howard, I. Malik, G. Mikhail, et al., Coronary hemodynamics in patients with severe aortic stenosis and coronary artery disease undergoing transcatheter aortic valve replacement: implications for clinical indices of coronary stenosis severity, JACC Cardiovasc. Interv. 11 (2018) 2019–2031.
[3] R. Scarsini, G. Pesarini, C. Zivelonghi, A. Piccoli, V. Ferrero, M. Lunardi, et al., Physiologic evaluation of coronary lesions using instantaneous wave-free ratio (iFR) in patients with severe aortic stenosis undergoing trans-catheter aortic valve implantation, EuroIntervention. 13 (2018) 1512–1519.
[4] M. Stoller, S. Gloekler, R. Zbinden, D. Tueller, F. Eberli, S. Windecker, et al., Left ventricular afterload reduction by transcatheter aortic valve implantation in severe aortic stenosis and its prompt effects on comprehensive coronary haemodynamics, EuroIntervention. 14 (2018) 166–173.
[5] F. Yamanaka, K. Shishido, T. Ochiai, N. Moriyama, K. Yamazaki, A. Sugitani, et al., Instantaneous wave-free ratio for the assessment of intermediate coronary artery stenosis in patients with severe aortic valve stenosis: comparison with myocardial perfusion scintigraphy, JACC Cardiovasc. Interv. 11 (2018) 2032–2040.
[6] R. Scarsini, G. Pesarini, C. Zivelonghi, A. Piccoli, V. Ferrero, M. Lunardi, et al., Coronary physiology in patients with severe aortic stenosis: comparison between fractional flow reserve and instantaneous wave-free ratio, Int. J. Cardiol. 243 (2017) 40–46.
[7] J.I. Hoffman, Problems of coronary flow reserve, Ann. Biomed. Eng. 28 (2000) 884–896.
[8] M. Lumley, R. Williams, K.N. Asrress, S. Arri, N. Briceno, H. Ellis, et al., Coronary physiology during exercise and vasodilation in the healthy heart and in severe aortic stenosis, J. Am. Coll. Cardiol. 68 (2016) 688–697.
[9] K. Rajappan, O.E. Rimoldi, D.P. Dutka, B. Ariff, D.J. Pennell, D.J. Sheridan, et al., Mechanisms of coronary microcirculatory dysfunction in patients with aortic stenosis and angiographically normal coronary arteries, Circulation. 105 (2002) 470–476.
[10] K. Rajappan, O.E. Rimoldi, P.G. Camici, N.G. Bellenger, D.J. Pennell, D.J. Sheridan, Functional changes in coronary microcirculation after valve replacement in patients with aortic stenosis, Circulation. 107 (2003) 3170–3175.
[11] M.C. Rolandi, E.M. Wiegerinck, L. Casadonte, Z.Y. Yong, K.T. Koch, M. Vis, et al., Transcatheter replacement of stenotic aortic valve normalizes cardiac-coronary interaction by restoration of systolic coronary flow dynamics as assessed by wave intensity analysis, Circ. Cardiovasc. Interv. 9 (2016), e002356.
[12] B.N. Modi, H. Rahman, T. Kaier, M. Ryan, R. Williams, N. Briceno, et al., Revisiting the optimal fractional flow reserve and instantaneous wave-free ratio thresholds for predicting the physiological significance of coronary artery disease, Circ. Cardiovasc. Interv. 11 (2018), e007041.