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Published in:
Circulation. Cardiovascular interventions

DOI:
10.1161/CIRCINTERVENTIONS.119.007893

Published: 01/01/2020

Document Version
Publisher's PDF, also known as Version of record

Citation for pulished version (APA):
Wijntjens, G. W. M., van Uffelen, E. L., Echavarría-Pinto, M., Casadonte, L., Stegehuis, V. E., Murai, T., Marques, K. M. J., Yoon, M.-H., Tahk, S.-J., Casella, G., Leone, A. M., López Palop, R., Schlundt, C., Rivero, F., Petraco, R., Fearon, W. F., Johnson, N. P., Jeremias, A., Koo, B.-K., ... van de Hoef, T. P. (2020). Individual Lesion-Level Meta-Analysis Comparing Various Doses of Intracoronary Bolus Injection of Adenosine With Intravenous Administration of Adenosine for Fractional Flow Reserve Assessment. *Circulation. Cardiovascular interventions*, *13*(1), Article e007893. https://doi.org/10.1161/CIRCINTERVENTIONS.119.007893

Circulation: Cardiovascular Interventions

ORIGINAL ARTICLE

Individual Lesion-Level Meta-Analysis Comparing Various Doses of Intracoronary Bolus Injection of Adenosine With Intravenous Administration of Adenosine for Fractional Flow Reserve Assessment

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BACKGROUND: Intravenous infusion of adenosine is considered standard practice for fractional flow reserve (FFR) assessment but is associated with adverse side-effects and is time-consuming. Intracoronary bolus injection of adenosine is better tolerated by patients, cheaper, and less time-consuming. However, current literature remains fragmented and modestly sized regarding the equivalence of intracoronary versus intravenous adenosine. We aim to investigate the relationship between intracoronary adenosine and intravenous adenosine to determine FFR.

METHODS: We performed a lesion-level meta-analysis to compare intracoronary adenosine with intravenous adenosine (140 µg/kg per minute) for FFR assessment. The search was conducted in accordance to the Preferred Reporting for Systematic Reviews and Meta-Analysis statement. Lesion-level data were obtained by contacting the respective authors or by digitization of scatterplots using custom-made software. Intracoronary adenosine dose was defined as; low: <40 µg, intermediate: 40 to 99 µg, and high: ≥100 µg.

RESULTS: We collected 1972 FFR measurements (1413 lesions) comparing intracoronary with intravenous adenosine from 16 studies. There was a strong correlation (correlation coefficient =0.915; $P<0.001$) between intracoronary-FFR and intravenous-FFR. Mean FFR was 0.81±0.11 for intracoronary adenosine and 0.81±0.11 for intravenous adenosine ($P<0.001$). We documented a nonclinically relevant mean difference of 0.006 (limits of agreement: −0.066 to 0.078) between the methods. When stratified by the intracoronary adenosine dose, mean differences between intracoronary and intravenous-FFR amounted to 0.004, 0.011, or 0.000 FFR units for low-dose, intermediate-dose, and high-dose intracoronary adenosine, respectively.

CONCLUSIONS: The present study documents clinically irrelevant differences in FFR values obtained with intracoronary versus intravenous adenosine. Intracoronary adenosine hence confers a practical and patient-friendly alternative for intravenous adenosine for FFR assessment.

VISUAL OVERVIEW: A visual overview is available for this article.

Key Words: adenosine ■ hyperemia ■ meta-analysis ■ software ■ vasodilatation

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The Data Supplement is available at https://www.ahajournals.org/doi/suppl/10.1161/CIRCINTERVENTIONS.119.007893.

For Sources of Funding and Disclosures, see page 8.

Circulation: Cardiovascular Interventions is available at www.ahajournals.org/journal/circinterventions

WHAT IS KNOWN

- While either intravenous infusion or intracoronary bolus adenosine can be used for fractional flow reserve assessment, the fragmented literature has not been pooled for a definitive answer regarding their numerical equivalence.

WHAT THE STUDY ADDS

- Intracoronary adenosine confers a feasible and highly accurate alternative for intravenous adenosine for the purpose of fractional flow reserve assessment, regardless of the intracoronary adenosine dosage used.

Nonstandard Abbreviations and Acronyms

CFR	coronary flow reserve
FFR	fractional flow reserve
QUADAS-2	Quality Assessment of Diagnostic Accuracy Studies-2

Maximal vasodilatation of the coronary resistance vessels (hyperemia) is essential for reliable stenosis severity assessment by fractional flow reserve (FFR) or coronary flow reserve (CFR). Suboptimal levels of hyperemia may result in misclassification of stenosis functional severity, thus leading to substantial under-treatment of patients. Hyperemia is generally induced by administration of potent vasodilatory agents, of which continuous infusion of adenosine into a central or peripheral vein at a rate of 140 mg/kg per minute (intravenous adenosine) is considered standard clinical practice.[1,2] Intravenous adenosine, however, is frequently associated with the occurrence of patient discomfort, distinct hypotension,[3] and prolonged procedural times. This may obscure stenoses assessment or impede multiple testing in the on-growing setting of multivessel disease. Bolus injection of adenosine directly into the coronary artery (intracoronary adenosine) may confer a feasible alternative for intravenous adenosine, which results in similar FFR values.[4] Moreover, it is better tolerated by patients, more cost-effective and less time-consuming. However, current literature remains fragmented and modestly sized regarding the equivalence of intracoronary bolus and intravenous infusion of adenosine and the dose of intracoronary adenosine required for this purpose. The present individual lesion-level meta-analysis was designed to overcome this limitation of the literature and provide a definitive result for clinical practice.

METHODS

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Study Design

The present study design encompasses an individual lesion-level meta-analysis, comparing intracoronary adenosine with intravenous adenosine for determination of FFR. It followed the Preferred Reporting for Systematic Reviews and Meta-Analysis statement.[5]

Search Strategy

A systematic search was performed in MEDLINE/Pubmed, Cochrane Library, Embase, and Web of Science from inception to April 2018 to identify relevant studies comparing intracoronary adenosine with intravenous adenosine for determination of FFR. The search query combined terms for FFR, intracoronary adenosine, and intravenous adenosine as follows: ("fractional flow reserve *OR* FFR *OR* 'Fractional Flow Reserve, Myocardial' [Mesh]") *AND* ("intracoronary adenosine *OR* IC adenosine") *AND* ("intravenous adenosine *OR* intravenous adenosine"). Reference lists of all retrieved articles were screened to identify potential eligible studies missed by the respective search. The systematic search was restricted for peer-review articles in human subjects, no other restrictions, including language restrictions, were applied. Conference abstracts were deferred from inclusion.

Study Selection and Quality Assessment

Articles were considered eligible for inclusion if they compared intracoronary adenosine with intravenous adenosine at a rate of 140 µg/kg per minute for invasive FFR assessment using sensor-equipped guide wires for the same lesion. No specific exclusion criteria other than the search restrictions were applied. Two reviewers (Dr Wijntjens and E.L. van Uffelen) independently screened the titles and abstracts of potential eligible studies resulting from the search and performed data extraction from eligible studies. Moreover, the methodological quality of the included studies was examined using the QUADAS (Quality Assessment of Diagnostic Accuracy Studies)-2 tool. Disagreements between the reviewers were resolved by discussion.

Data Extraction

Lesion-level FFR values were obtained by contacting the respective authors for lesion-level data, or, in the absence of a response from the respective authors, by digitization of reported scatterplots using custom-made semiautomatic bitmap-to-digital software written by Imperial College London, United Kingdom, in MatLab (Mathworks Inc, Natick, MA).[6]

Statistical Analysis

One-stage and 2-stage meta-analytic methods were used to analyze individual patient data.[7] For 1-stage meta-analytic methods, correlation coefficients adjusted for repeated measurements were calculated using linear mixed-effect model to assess the correlation between FFR measured with intracoronary and intravenous adenosine as the primary analysis. As a secondary analysis, systematic differences in FFR values between intracoronary adenosine and intravenous adenosine measurements were assessed using parametric (Bland-Altman) and nonparametric (Passing-Bablok) methods. For

2-stage (random effect-analysis) meta-analytic methods, FFR values were summarized as mean±SD, and statistical differences were tested by paired Student *t* test. Between trial heterogeneity was assessed using the I^2 statistic, and publication bias was assessed using funnel plot asymmetry. We also performed subgroup analysis for measurements performed with low-dose (<40 µg), intermediate-dose (40–99 µg), and high-dose intracoronary adenosine (≥100 µg) versus intravenous adenosine. $P<0.05$ were considered statistically significant. FFR values ≤0.80 were considered hemodynamically significant. The STATA 14.1 (StataCorp, College Station, TX) and Review Manager 5.3 (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark) statistical and software package were used for all calculations.

RESULTS

Selection of the Studies

Figure 1 depicts the flow diagram of the study selection process. We identified 107 citations (Table I in the Data Supplement), excluding duplicates and abstracts, from our initial systematic search from large electronic databases, which were screened based on their title and abstract. We identified 80 citations that warranted assessment in full text. Of these, 60 did not meet the predefined inclusion criteria, whereas in 20 citations intracoronary adenosine was compared with intravenous adenosine for FFR assessment in the same coronary artery using sensor-equipped guide wires. Two citation did not display study outcome in scatterplots nor responded to repeated requests for study data and 2 citations reported pooled-data from previous reports. Hence, we were able to obtain lesion-level data from 16 studies (Table II in the Data Supplement), of which the authors delivered data on a lesion-level basis from 14 citations[8–21] and data were extracted by digitization of scatterplots using custom-made semiautomatic bitmap-to-digital software from 2 citations[22,23] (Figure 1).

Quality of the Selected Studies

Figure 2 shows the risk of bias and applicability concerns of the included studies. Overall, risk of bias for the included studies was considerable low (Figure 2; specified in Figure I in the Data Supplement). Publication bias was low as heterogeneity among study results was insignificant ($I^2=0$, $P=0.84$), and funnel plot analysis did not show asymmetry (Table; Figure 3).

Relationship Between Intracoronary Bolus Injection of Adenosine and Intravenous Administration of Adenosine

We included a total of 1972 FFR measurements from 1413 lesions. Overall, there was a strong correlation between intracoronary and intravenous adenosine (correlation coefficient=0.915 [95% CI, 0.900–0.931], $P<0.001$; intercept=0.074 [95% CI, 0.061–0.087], $P<0.001$). FFR was higher for intracoronary adenosine as compared to intravenous adenosine (intracoronary: 0.81±0.11 versus intravenous: 0.81±0.11, $P<0.001$). Passing-Bablok

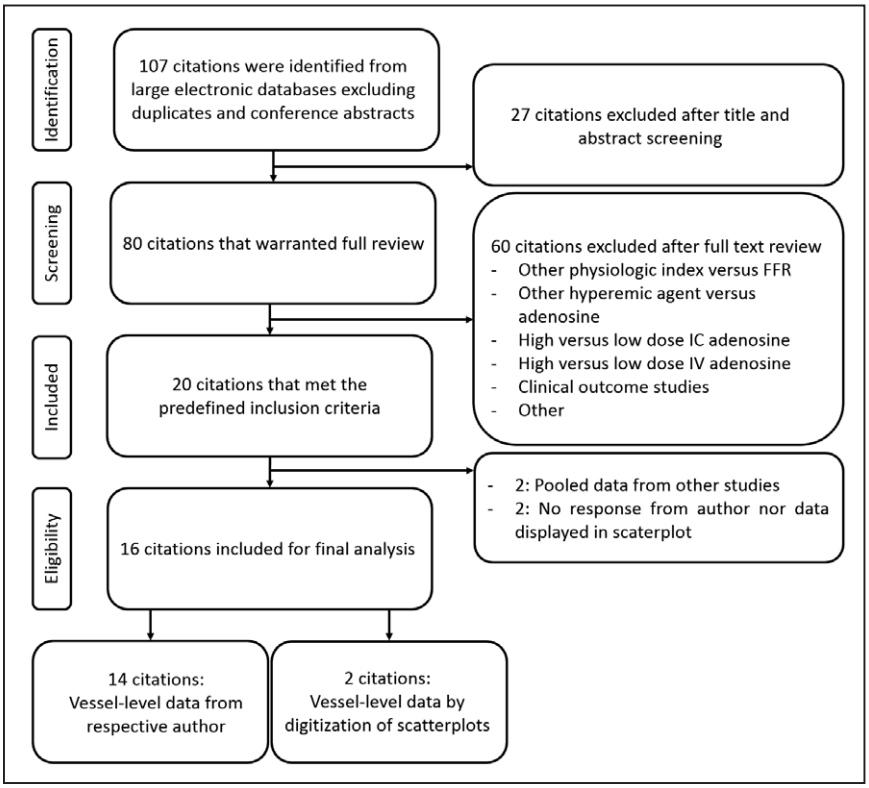

Figure 1. Study flow diagram of the study selection process.
FFR indicates fractional flow reserve; IC, intracoronary; and IV, intravenous.

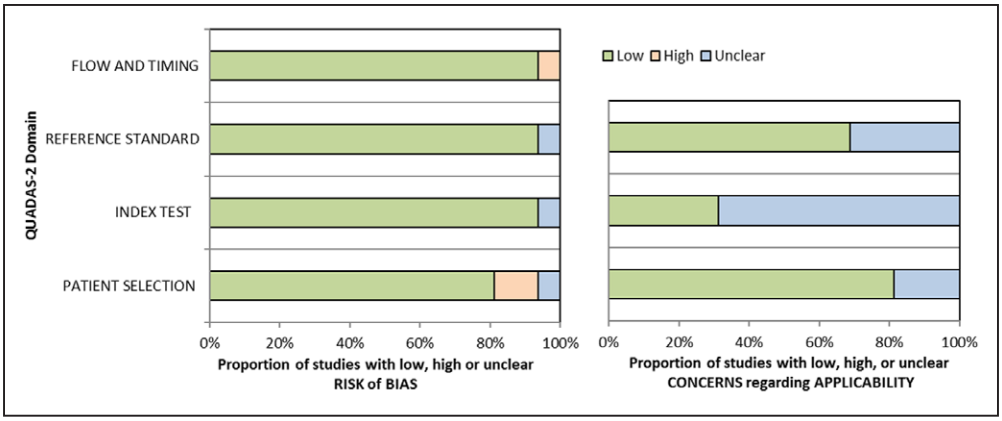

Figure 2. Risk of bias and applicability concerns analysis for the selected studies.
QUADAS-2 indicates Quality Assessment of Diagnostic Accuracy Studies-2.

regression did reveal a nonclinically relevant systematic difference (intercept A: 0.009 [95% CI, 0.009–0.021]) and a nonsignificant proportional difference between the administration routes (slope B: 1.000 [95% CI, 0.983–1.000]). Bland-Altman analysis documented a mean difference of 0.006±0.037 (limits of agreement: −0.066 to 0.078; Figure 4A and 4B) between the administration routes. Visual inspection of the Bland-Altman plots revealed that large between-routes differences could be due to either lower intracoronary or intravenous values.

Taken into consideration the clinically adopted 0.80 FFR cutoff, intracoronary-FFR disagreed with intravenous-FFR in 7.8% of cases (154 out of 1972), of which intracoronary-FFR was abnormal and intravenous-FFR normal in 2.9% of cases (58 out of 1972), and intracoronary-FFR was normal and intravenous-FFR abnormal in 4.9% of cases (96 out of 1972). In 0.7% of measurement (14 out of 1972) intracoronary-FFR was <0.75 and intravenous-FFR was >0.80, and in 0.7% of measurements (13 out of 11972) intravenous-FFR was <0.75 and intracoronary-FFR was >0.80.

Two-step meta-analytic outcome data are summarized in the Table.

Low-dose intracoronary adenosine (<40 µg) was compared with intravenous adenosine in 91 measurements (91 lesions). There was a strong correlation between intracoronary and intravenous adenosine (correlation coefficient=0.981 [95% CI, 0.938–1.024], *P*<0.001; intercept=0.018 [95% CI, −0.015 to 0.052], *P*=0.282). FFR was similar between low-dose intracoronary and intravenous adenosine (intracoronary: 0.76±0.17 versus intravenous 0.76±0.17, *P*=0.302). Passing-Bablok regression did not reveal a significant systematic difference (intercept A: 0.001 [95% CI, −0.039 to 0.033]) nor a significant proportional difference between the administration routes (slope B: 1.007 [95% CI, 0.966–1.058]). Bland-Altman analysis documented a mean difference of 0.004±0.035 (limits of agreement: −0.064 to 0.072; Figure 4C and 4D). Low-dose intracoronary-FFR disagreed with intravenous-FFR in 7.7% of cases (7 out of 91), of which low-dose intracoronary-FFR was abnormal and intravenous-FFR normal in 4.4% of cases (4 out of 91), and low-dose intracoronary-FFR was normal and intravenous-FFR abnormal in 3.3% of cases (3 out of 91).

Intermediate-dose intracoronary adenosine (40–99 µg) was compared with intravenous adenosine in 1082 measurements (1.037 lesions) for FFR assessment. There was a strong correlation between intracoronary and intravenous adenosine (correlation coefficient=0.906 [95% CI, 0.888–0.924], *P*<0.001; intercept=0.086 [95% CI, 0.071–1.008], *P*<0.001). FFR was higher for intermediate-dose intracoronary adenosine as compared to intravenous adenosine (intracoronary: 0.82±0.10 versus intravenous: 0.81±0.11, *P*<0.001). Passing-Bablok analysis revealed a significant systematic difference (intercept A: 0.016 [95% CI, 0.010–0.043]) but a nonsignificant proportional difference between the administration routes (slope B: 0.993 [95% CI, 0.958–1.000]). Bland-Altman analysis documented a mean difference of 0.011±0.035 (limits of agreement: −0.059 to 0.080; Figure 4E and 4F). Intermediate-dose intracoronary-FFR disagreed with intravenous-FFR in 7.9% of cases (85 out of 1082), of which intermediate-dose intracoronary-FFR was abnormal and intravenous-FFR normal in 2.3% of cases (25 out of 1082) and intermediate-dose intracoronary-FFR was normal and intravenous-FFR abnormal in 5.5% of cases (60 out of 1082).

High-dose intracoronary adenosine (≥ 100 µg) was compared with intravenous adenosine in 799 measurements (506 lesions) for FFR assessment. There was a strong correlation between intracoronary and intravenous adenosine (correlation coefficient=0.894 [95% CI, 0.864–0.923], *P*<0.001; intercept=0.088 [95% CI, 0.063–0.111], *P*<0.001). FFR was equal between high-dose intracoronary adenosine and intravenous adenosine (intracoronary: 0.81±0.10 versus intravenous: 0.81±0.10, *P*=0.984). Passing-Bablok analysis did not reveal a significant systematic difference (intercept A: 0.000 [95% CI, 0.000–0.016]) nor a significant proportional difference between the administration routes (slope B: 1.000

Table. Physiological Outcome Data and 2-Step (Random Effect) Meta-Analytic Differences

Study or IC Adenosine Subgroup	IC Adenosine, µg		Lesions	IC-FFR	IV-FFR		Weight	Weighted Difference
	RCA	LCA	N	Mean±SD	Mean±SD	*P* Value*	%	Mean (95% CI)
Low-dose (<40 µg)								
Jeremias et al[8]	15–20	18–24	60	0.78±0.15	0.79±0.15	0.809	1.2	−0.01 (−0.06 to 0.04)
Casadonte et al[9]	20	40	12	0.86±0.07	0.85±0.05	0.082	1.3	0.01 (−0.04 to 0.06)
De Bruyne et al[22]	20	20	19	0.63±0.20	0.61±0.19	0.047	0.1	0.02 (−0.14 to 0.18)
Subtotal			91	0.76±0.17	0.76±0.17	0.302	2.6	0.00 (−0.04 to 0.04)
Heterogeneity: I^2=0%, P=0.85								
Intermediate-dose (40–99 µg)								
de Bruyne et al[22]	40	40	17	0.62±0.18	0.62±0.18	0.631	4.2	0.00 (−0.12 to 0.12)
Koo et al[10]	40–80	80	20	0.83±0.06	0.78±0.09	<0.001	1.5	0.05 (0.00 to 0.10)
Seo et al[11]	40–80	80	68	0.80±0.10	0.80±0.10	0.109	3.0	0.00 (−0.03 to 0.03)
Park et al[12]	40–80	80	238	0.82±0.10	0.81±0.10	<0.001	11.7	0.01 (−0.01 to 0.03)
Jang et al[13]	40–80	80	193	0.83±0.09	0.82±0.10	<0.001	9.5	0.01 (−0.01 to 0.03)
Schlundt et al[14]	40–80	80	114	0.84±0.11	0.84±0.11	0.931	4.2	0.00 (−0.03 to 0.03)
Yoon et al[15]	36–60	48–80	44	0.80±0.08	0.77±0.10	<0.001	2.4	0.03 (−0.01 to 0.07)
Johnson et al[16]	40–99	40–99	45	0.78±0.12	0.77±0.12	0.002	1.4	0.01 (−0.04 to 0.06)
Casella et al[17]	60	60	47	0.78±0.11	0.75±0.12	<0.001	1.6	0.03 (−0.02 to 0.08)
Casella et al[17]	90	90	48	0.78±0.12	0.75±0.11	0.002	1.6	0.04 (−0.01 to 0.09)
López-Palop et al[18]	60	60	108	0.85±0.07	0.83±0.09	<0.001	7.4	0.02 (−0.00 to 0.04)
Leone et al[19]	60	60	50	0.88±0.07	0.87±0.07	<0.001	4.6	0.01 (−0.02 to 0.04)
Rivero et al[20]	60	60	90	0.83±0.09	0.82±0.10	0.837	4.4	0.01 (−0.02 to 0.04)
Subtotal			1082	0.82±0.10	0.81±0.11	<0.001	53.7	0.01 (0.01 to 0.02)
Heterogeneity: I^2=0%, P=0.85								
High-dose (≥100 µg)								
Casella et al[17]	120	120	46	0.78±0.12	0.76±0.12	0.015	1.4	0.02 (−0.03 to 0.07)
Casella et al[17]	150	150	46	0.76±0.13	0.75±0.11	0.070	1.4	0.01 (−0.04 to 0.06)
Sandhu et al[23]	120	120	45	0.83±0.08	0.83±0.08	0.802	2.8	0.00 (−0.04 to 0.04)
Johnson et al[16]	100–200	100–200	136	0.78±0.11	0.76±0.11	<0.001	5.0	0.02 (−0.01 to 0.05)
López-Palop et al[18]	180	180	108	0.83±0.09	0.83±0.09	0.285	5.9	0.00 (−0.02 to 0.02)
López-Palop et al[18]	300	300	105	0.82±0.09	0.83±0.09	0.005	5.8	−0.01 (−0.03 to 0.01)
López-Palop et al[18]	600	600	101	0.81±0.09	0.83±0.09	<0.001	5.5	−0.01 (−0.03 to 0.01)
Leone et al[19]	300	300	48	0.87±0.07	0.86±0.07	0.026	4.3	0.01 (−0.02 to 0.04)
Leone et al[19]	600	600	43	0.87±0.07	0.87±0.07	0.566	3.9	0.00 (−0.03 to 0.03)
Rivero et al[21]	600	600	121	0.82±0.08	0.83±0.09	0.025	7.4	−0.01 (−0.03 to 0.01)
Subtotal			799	0.81±0.10	0.81±0.10	0.984	43.4	−0.00 (−0.01 to 0.01)
Heterogeneity: I^2=0%, P=0.78								
Total			1791	0.81±0.11	0.81±0.11	<0.001	100	0.01 (0.00 to 0.01)
Heterogeneity: I^2=0%, P=0.84								

FFR indicates fractional flow reserve; IC, intracoronary; IV, intravenous; LCA, left coronary arteries; and RCA, right coronary artery.
*Paired Student *t* test.

[95% CI, 0.981–1.000]). Bland-Altman analysis documented a mean difference of −0.000±0.038 (limits of agreement: −0.074 to 0.074; Figure 4G and 4H). High-dose intracoronary-FFR disagreed with intravenous-FFR in 7.0% of cases (56 out of 799), of which high-dose intracoronary-FFR was abnormal and intravenous-FFR normal in 2.9% of cases (23 out of 799) and high-dose intracoronary-FFR was normal and intravenous-FFR abnormal in 4.1% of cases (33 out of 799).

DISCUSSION

The present individual lesion-level meta-analysis compared intracoronary adenosine with intravenous adenosine for

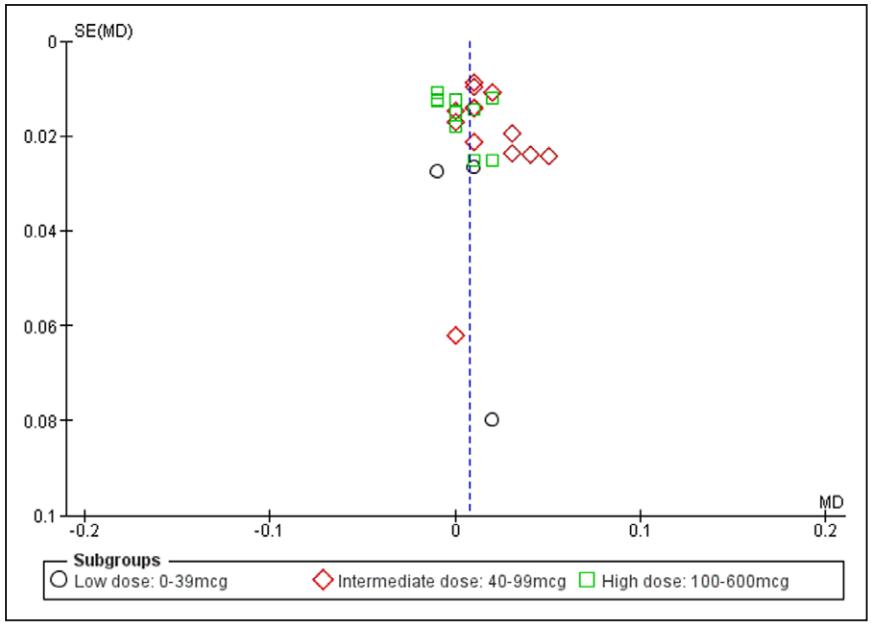

Figure 3. Funnel plot displaying symmetry of the study results.

determining FFR. We documented that the difference in FFR values obtained with intracoronary and intravenous adenosine routes is very small and falls within the reported FFR variability. Consequently, we may conclude that intracoronary-FFR-intracoronary is equivalent to intravenous-FFR, regardless of the dose of adenosine used for intracoronary administration in our cohorts.

Induction of Maximal Hyperemia by Adenosine

Correct classification of stenoses severity by FFR and CFR mandates maximal vasodilation of the coronary resistance vessels, which is generally induced by administration of pharmacological vasodilatory agents. In contemporary clinical practice, continuous administration of adenosine at a rate of 140 µg/kg per minute is advocated as the clinical standard[1,2] as intravenous adenosine was the standard means to induce hyperemia in FFR-validation trials as well as clinical outcome trials that documented the clinical benefit of FFR-guided revascularization.[2,24,25] However, intravenous adenosine administration is associated with various clinical as well as practical ambiguities. First of all, it is recommended that hyperemia is induced by intravenous adenosine infusion for at least 2 minutes or until a steady state is achieved. This impedes multiple testing, especially in patients with multivessel disease, or post-percutaneous coronary intervention assessment. Second, intravenous adenosine induces systemic vasodilation and is therefore inevitable associated with adverse systemic side-effects, including chest pain, respiratory disorders, hypotension, and tachycardia. Third, taken into consideration the time-consuming aspect of intravenous adenosine and the relatively high amount of adenosine, intravenous adenosine is relative costs-ineffective. In comparison, intracoronary adenosine induces regional myocardial hyperemia for ≈20 seconds, hence it is better tolerated by patients, less-time consuming and more cost-effective compared to intravenous adenosine.

Initial studies documented equivalence in coronary vasodilation between low-dose intracoronary and intravenous adenosine.[1,8,22] Nevertheless, these results have been opposed by studies that suggested higher doses of adenosine required to achieve maximal coronary vasodilatation.[17,26–28] Therefore, current literature remains fragmented on the diagnostic accuracy of intracoronary adenosine and its optimal dosage required to achieve hyperemia equivalent to intravenous adenosine administration.[8,14,18,19] Nevertheless, most of these studies are underpowered due to a relatively limited sample size. A recent meta-analysis on the subject documented similar diagnostic accuracy for intracoronary adenosine as compared to intravenous adenosine for the calculation of FFR. Nonetheless, this study compared intracoronary with intravenous adenosine at a study-level, thus presenting weighted data more prone to bias associated with the use of aggregate data in meta-regression.[29] The present lesion-level meta-analyses are the largest effort on the subject and compared intracoronary adenosine with intravenous adenosine on a lesion-level basis, which allows a more accurate comparison of intracoronary adenosine with intravenous adenosine for determination of FFR.

Interpretation of Study Results

We document strong correlation between intracoronary and intracoronary adenosine, regardless of the dosage of intracoronary adenosine. Moreover, the mean difference between FFR derived from intracoronary adenosine and intravenous adenosine-derived FFR is only 0.006 FFR units on average. The difference between administration routes amounted only to 0.004, 0.011, or 0.000 FFR units

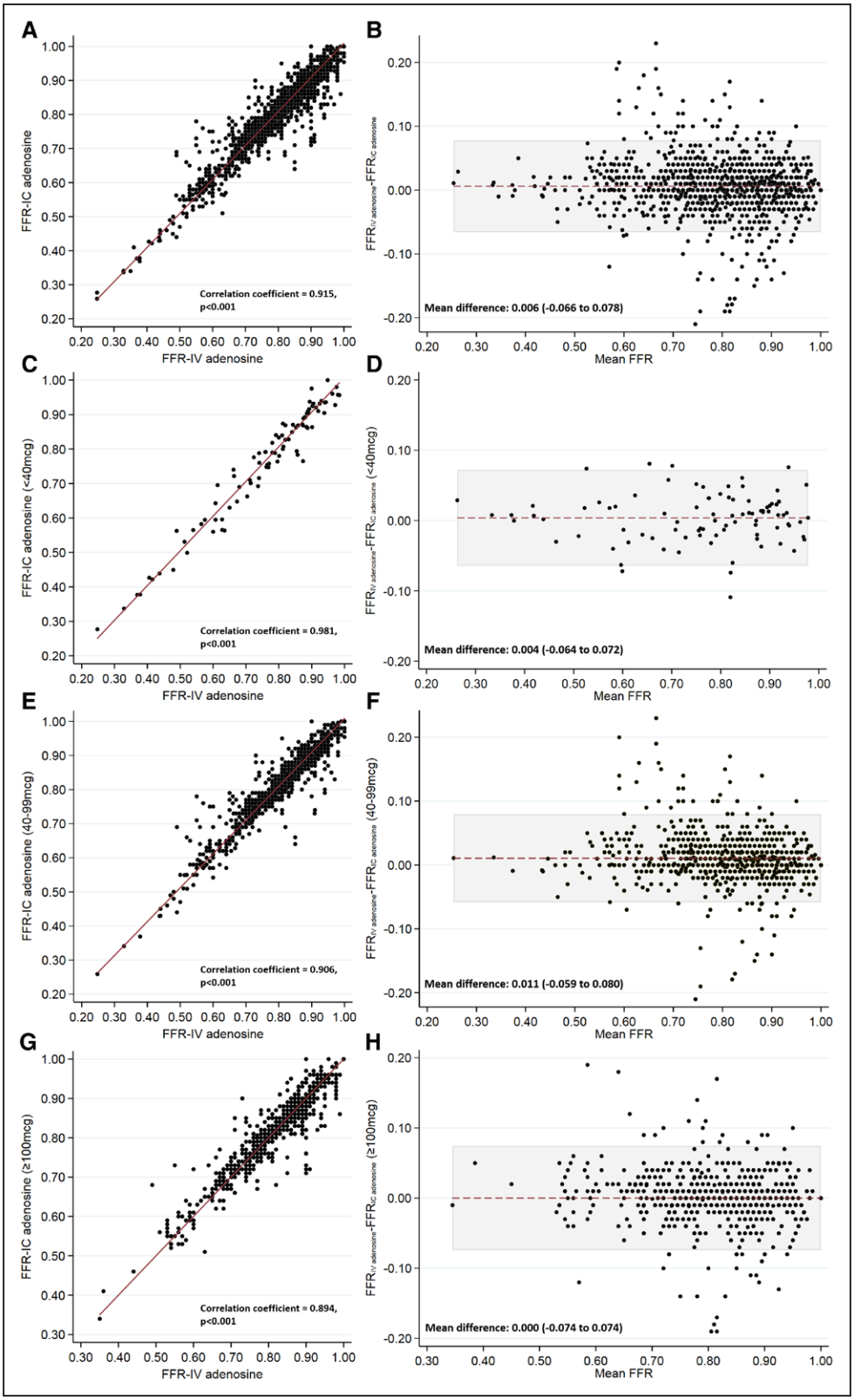

Figure 4. Passing-Bablok regression and Bland-Altman analyses of agreement comparing intracoronary (IC) adenosine with intravenous (IV) adenosine using a one step meta-analytic method.
Passing-Bablok fit and correlation coefficient for (**A**) the overall population, (**C**) low-dose IC adenosine, (**E**) intermediate-dose IC adenosine, (**G**) high-dose IC adenosine; and Bland-Altman analysis for (**B**) the overall population, (**D**) low-dose IC adenosine, (**F**) intermediate-dose IC adenosine, and (**H**) high-dose IC adenosine. FFR indicates fractional flow reserve.

for low-dose, intermediate-dose, and high-dose intracoronary adenosine, respectively. Taken into consideration that the minimal reported test/retest repeatability of FFR itself a SD of 0.019,[16] FFR differences <0.019 units are smaller than the variability of the FFR measurements itself and can, therefore, be considered clinically irrelevant.[27]

Some considerations need to be taken into account when interpreting our results. First, although a maximal difference of 0.011 FFR units in the present study may still affect decision-making for treatment when FFR values lie close to the clinical threshold (7.8% of patients in the present study), a propensity matched-cohort previously documented no difference in clinical outcome of nonrevascularized lesions with normal FFR values (FFR>0.75) whether measured using intravenous adenosine or intracoronary adenosine of ≥40 µg.[30] This would indicate that around the 4.9% of lesions included in the present meta-analysis deemed significant by intravenous-FFR, but insignificant by intracoronary-FFR, may have undergone unnecessary percutaneous coronary intervention in contemporary clinical practice. The large size of our work allows us to conclude that intravenous adenosine leads to clinical irrelevant lower FFR values compared with intracoronary administration. This is clearly depicted in our Bland-Altman plots that show that large between-routes discrepancies can go either way (−0.066 to 0.078) as demonstrated in Figure 4. Second, most studies compared intracoronary adenosine with intravenous adenosine in nonrandomized order. Only the study by Schlundt et al[14] randomized the order of intravenous adenosine and intracoronary adenosine and demonstrated no significant difference in FFR values between intravenous adenosine and intermediate-dose intracoronary denosine. Moreover, the dominant number of studies do not report a drift check post-assessment, a flush of saline following bolus injection of adenosine, nor the presence of stable hyperemia for FFR determination (Figure II in the Data Supplement). This may have affected adequate comparison between the various doses of intracoronary adenosine and intravenous adenosine. Third, the present study is not designed to demonstrate a dose-response relationship between FFR and incremental intracoronary-dose adenosine. Yet, we document that intracoronary adenosine, regardless of its dose result in similar FFR values than intravenous adenosine, which is considered the golden standard for FFR assessment and has been the standard means of FFR-validation studies as well as the landmark FAME studies (Fractional Flow Reserve versus Angiography for Multivessel Evaluation). Most importantly, it is a general misconception that pharmacological vasodilatory agents, including adenosine, are able to achieve true maximal hyperemia. Instead, multiple α-adrenergic and endothelin-1-induced vasoconstrictors interfere with the capability of adenosine to completely eliminate all active coronary vasomotor tone.[31] Moreover, the interaction between adenosine-induced vasodilation and coronary vasoconstrictors remains to be elucidated.[32] Therefore, it is important to realize that the present study merely investigates the capacity of intracoronary adenosine to induce exhausted adenosine-dependent vasodilation defined by that achieved by intravenous adenosine and which may differ between various patient populations.

Clinical Implications

Despite the proven clinical benefit of physiology-guided revascularization, the clinical adoption of FFR remains limited worldwide. Part of which may be explained by the assumed requisite of intravenous adenosine to induce hyperemia. As a corollary, physiological parameters obtained in the resting state increasingly gained ground in our catheterization laboratories. Nonetheless, a comprehensive evaluation of ischemic heart disease can only be obtained by combined hyperemia-dependent FFR and CFR measurements.[33] We demonstrate that intracoronary adenosine may confer a feasible alternative for intravenous adenosine to determine FFR/CFR, which, therefore, may stimulate global physiology-guided revascularization using FFR/CFR.

Limitations

The present individual lesion-level meta-analyses has some limitations. First of all, we extracted FFR values in 2 out of 16 studies (81 out of 1920 lesions) using custom-made software. The derived mean±SD for FFR, however, are comparable to those shown in the original articles (Table), and digitization of scatterplots was documented to have excellent test-retest reproducibility.[6] Moreover, a sensitivity analysis excluding these 2 studies did not result in significant differences (data not shown). Second, we were not able to retrieve all data as the authors of 2 articles did not reply to our request for lesion-level data. Nevertheless, the present study encompasses the largest dataset of measurements that compared intracoronary adenosine with intravenous adenosine for FFR assessment on a lesion-level basis. Third, the low-dose adenosine group encompasses 91 measurement (91 lesions), of which 60 were derived from one study. This precludes definitive conclusions regarding equivalence between low-dose intracoronary adenosine and intravenous adenosine. Fourth, the present analysis does not shows which vessels were interrogated to study differences in correlation between intracoronary and intravenous adenosine for left anterior descending versus non-left anterior descending territories. Fifth, the study by Casadonte et al[9] was classified as low-dose despite having measurements with intracoronary bolus injection of 40 µg adenosine for the LCA, which conflicted with the intermediate group. The study by Yoon et al[15] was classified as intermediate-dose intracoronary adenosine despite having measurements with intracoronary bolus injection of 36 to 60 µg for the RCA, which conflicted with the low-dose group. The study by Sandhu et al,[23] compared intracoronary adenosine with

intravenous adenosine at a rate of 180 µg/kg per minute. These inconsistencies were taken for granted with the intention to do a more detailed analysis. Sixth, Bland-Altman analyses do not correct for repeated measures. Nevertheless, the correlation coefficient corrected by mixed-effect models largely agree with Spearman ρ correlations (Materials in the Data Supplement). It is, therefore, unlikely that correction for repeated measures would affect the results of Bland-Altman analysis. The Passing-Bablok method assumes an offset/slope linear relationship between intracoronary and intravenous adenosine, nevertheless such relationship remains unproven.

Conclusions

The present individual lesion-level meta-analyses demonstrates a clinically irrelevant difference in FFR between intracoronary adenosine and intravenous adenosine regardless of the dose of adenosine used.

ARTICLE INFORMATION

Received February 9, 2019; accepted October 15, 2019.

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Disclosures

Dr Wijntjens is partly supported by a research grant from Philips-Volcano. Drs Echavarría-Pinto, Leone, López Palop, Jeremias, Koo, Johnson, Fearon, Piek, and van de Hoef received research grants or have served as speaker at educational events organized by St Jude Medical, Boston Scientific, or Volcano Corporation, manufactures of sensor-equipped guide wires. The other authors report no conflicts.

REFERENCES

1. Wilson RF, Wyche K, Christensen BV, Zimmer S, Laxson DD. Effects of adenosine on human coronary arterial circulation. *Circulation*. 1990;82:1595–1606. doi: 10.1161/01.cir.82.5.1595
2. Pijls NH, De Bruyne B, Peels K, Van Der Voort PH, Bonnier HJ, Bartunek J Koolen JJ, Koolen JJ. Measurement of fractional flow reserve to assess the functional severity of coronary-artery stenoses. *N Engl J Med*. 1996;334:1703–1708. doi: 10.1056/NEJM199606273342604
3. Echavarría-Pinto M, Gonzalo N, Ibañez B, Petraco R, Jimenez-Quevedo P, Sen S, Nijjer S, Tarkin J, Alfonso F, Núñez-Gil IJ, et al. Low coronary microcirculatory resistance associated with profound hypotension during intravenous adenosine infusion: implications for the functional assessment of coronary stenoses. *Circ Cardiovasc Interv*. 2014;7:35–42. doi: 10.1161/CIRCINTERVENTIONS.113.000659
4. Toth GG, Johnson NP, Jeremias A, Pellicano M, Vranckx P, Fearon WF, Barbato E, Kern MJ, Pijls NH, De Bruyne B. Standardization of fractional flow reserve measurements. *J Am Coll Cardiol*. 2016;68:742–753. doi: 10.1016/j.jacc.2016.05.067
5. McInnes MDF, Moher D, Thombs BD, McGrath TA, Bossuyt PM, Clifford T, Cohen JF, Deeks JJ, Gatsonis C, Hooft L, et al; the PRISMA-DTA Group. Preferred reporting items for a systematic review and meta-analysis of diagnostic test accuracy studies: the PRISMA-DTA statement. *JAMA*. 2018;319:388–396. doi: 10.1001/jama.2017.19163
6. Cook CM, Petraco R, Shun-Shin MJ, Ahmad Y, Nijjer S, Al-Lamee R, Kikuta Y, Shiono Y, Mayet J, Francis DP, et al. Diagnostic accuracy of computed tomography-derived fractional flow reserve: a systematic review. *JAMA Cardiol*. 2017;2:803–810. doi: 10.1001/jamacardio.2017.1314
7. Simmonds MC, Higgins JP, Stewart LA, Tierney JF, Clarke MJ, Thompson SG. Meta-analysis of individual patient data from randomized trials: a review of methods used in practice. *Clin Trials*. 2005;2:209–217. doi: 10.1191/1740774505cn087oa
8. Jeremias A, Whitbourn RJ, Filardo SD, Fitzgerald PJ, Cohen DJ, Tuzcu EM, Anderson WD, Abizaid AA, Mintz GS, Yeung AC, et al. Adequacy of intracoronary versus intravenous adenosine-induced maximal coronary hyperemia for fractional flow reserve measurements. *Am Heart J*. 2000;140:651–657. doi: 10.1067/mhj.2000.109920
9. Casadonte L, Marques KM, Spaan JAE, Siebes M. Temporal dissociation between the minimal distal-to-aortic pressure ratio and peak hyperemia during intravenous adenosine infusion. *Am J Physiol Heart Circ Physiol*. 2017;312:H992–H1001. doi: 10.1152/ajpheart.00632.2016
10. Koo BK, Kim CH, Na SH, Youn TJ, Chae IH, Choi DJ, Kim HS, Lee MM, Oh BH, Park YB, et al. Intracoronary continuous adenosine infusion. *Circ J*. 2005;69:908–912. doi: 10.1253/circj.69.908
11. Seo MK, Koo BK, Kim JH, Shin DH, Yang HM, Park KW, Lee HY, Kang HJ, Kim HS, Oh BH, et al. Comparison of hyperemic efficacy between central and peripheral venous adenosine infusion for fractional flow reserve measurement. *Circ Cardiovasc Interv*. 2012;5:401–405. doi: 10.1161/CIRCINTERVENTIONS.111.965392
12. Park JJ, Petraco R, Nam CW, Doh JH, Davies J, Escaned J, Koo BK. Clinical validation of the resting pressure parameters in the assessment of functionally significant coronary stenosis; results of an independent, blinded comparison with fractional flow reserve. *Int J Cardiol*. 2013;168:4070–4075. doi: 10.1016/j.ijcard.2013.07.030
13. Jang HJ, Koo BK, Lee HS, Park JB, Kim JH, Seo MK, Yang HM, Park KW, Nam CW, Doh JH, et al. Safety and efficacy of a novel hyperaemic agent, intracoronary nicorandil, for invasive physiological assessments in the cardiac catheterization laboratory. *Eur Heart J*. 2013;34:2055–2062. doi: 10.1093/eurheartj/eht040
14. Schlundt C, Bietau C, Klinghammer L, Wiedemann R, Rittger H, Ludwig J, Achenbach S. Comparison of intracoronary versus intravenous administration of adenosine for measurement of coronary fractional flow reserve. *Circ Cardiovasc Interv*. 2015;8:e001781. doi: 10.1161/CIRCINTERVENTIONS.114.001781
15. Yoon MH, Tahk SJ, Yang HM, Park JS, Zheng M, Lim HS, Choi BJ, Choi SY, Choi UJ, Hwang JW, et al. Comparison of the intracoronary continuous infusion method using a microcatheter and the intravenous continuous adenosine infusion method for inducing maximal hyperemia for fractional flow reserve measurement. *Am Heart J*. 2009;157:1050–1056. doi: 10.1016/j.ahj.2009.03.012
16. Johnson NP, Jeremias A, Zimmermann FM, Adjedj J, Witt N, Hennigan B, Koo BK, Maehara A, Matsumura M, Barbato E, et al. Continuum of vasodilator stress from rest to contrast medium to adenosine hyperemia for fractional flow reserve assessment. *JACC Cardiovasc Interv*. 2016;9:757–767. doi: 10.1016/j.jcin.2015.12.273
17. Casella G, Leibig M, Schiele TM, Schrepf R, Seelig V, Stempfle HU, Erdin P, Rieber J, König A, Siebert U, et al. Are high doses of intracoronary adenosine an alternative to standard intravenous adenosine for the assessment of fractional flow reserve? *Am Heart J*. 2004;148:590–595. doi: 10.1016/j.ahj.2004.04.008
18. López-Palop R, Carrillo P, Frutos A, Cordero A, Agudo P, Mashlab S, Bertomeu-Martínez V. Comparison of effectiveness of high-dose intracoronary adenosine versus intravenous administration on the assessment of fractional flow reserve in patients with coronary heart disease. *Am J Cardiol*. 2013;111:1277–1283. doi: 10.1016/j.amjcard.2013.01.270
19. Leone AM, Porto I, De Caterina AR, Basile E, Aurelio A, Gardi A, Russo D, Laezza D, Niccoli G, Burzotta F, et al. Maximal hyperemia in the assessment of fractional flow reserve: intracoronary adenosine versus intracoronary sodium nitroprusside versus intravenous adenosine: the NASCI (Nitroprussiato

versus Adenosina nelle Stenosi Coronariche Intermedie) study. *JACC Cardiovasc Interv*. 2012;5:402–408. doi: 10.1016/j.jcin.2011.12.014
20. Rivero F, Cuesta J, Bastante T, Benedicto A, Fernández-Pérez C, Antuña P, García-Guimaraes M, Alfonso F. Reliability of physiological assessment of coronary stenosis severity using intracoronary pressure techniques: a comprehensive analysis from a large cohort of consecutive intermediate coronary lesions. *EuroIntervention*. 2017;13:e193–e200. doi: 10.4244/EIJ-D-16-00574
21. Rivero F, Cuesta J, Bastante T, Benedicto A, García-Guimaraes M, Fuentes-Ferrer M, Alvarado T, Alfonso F. Diagnostic accuracy of a hybrid approach of instantaneous wave-free ratio and fractional flow reserve using high-dose intracoronary adenosine to characterize intermediate coronary lesions: Results of the PALS (Practical Assessment of Lesion Severity) prospective study. *Catheter Cardiovasc Interv*. 2017;90:1070–1076. doi: 10.1002/ccd.27038
22. De Bruyne B, Pijls NH, Barbato E, Bartunek J, Bech JW, Wijns W, Heyndrickx GR. Intracoronary and intravenous adenosine 5'-triphosphate, adenosine, papaverine, and contrast medium to assess fractional flow reserve in humans. *Circulation*. 2003;107:1877–1883. doi: 10.1161/01.CIR.0000061950.24940.88
23. Sandhu PS, Kaul U, Gupta RK, Ghose T. Fractional flow reserve: intracoronary versus intravenous adenosine induced maximal coronary hyperemia. *Indian Heart J*. 2013;65:147–151. doi: 10.1016/j.ihj.2013.02.006
24. Tonino PA, De Bruyne B, Pijls NH, Siebert U, Ikeno F, van' t Veer M, Klauss V, Manoharan G, Engstrøm T, Oldroyd KG, et al; FAME Study Investigators. Fractional flow reserve versus angiography for guiding percutaneous coronary intervention. *N Engl J Med*. 2009;360:213–224. doi: 10.1056/NEJMoa0807611
25. De Bruyne B, Pijls NH, Kalesan B, Barbato E, Tonino PA, Piroth Z, Jagic N, Möbius-Winkler S, Mobius-Winckler S, Rioufol G, et al; FAME 2 Trial Investigators. Fractional flow reserve-guided PCI versus medical therapy in stable coronary disease. *N Engl J Med*. 2012;367:991–1001. doi: 10.1056/NEJMoa1205361
26. Jeremias A, Filardo SD, Whitbourn RJ, Kernoff RS, Yeung AC, Fitzgerald PJ, Yock PG. Effects of intravenous and intracoronary adenosine 5'-triphosphate as compared with adenosine on coronary flow and pressure dynamics. *Circulation*. 2000;101:318–323. doi: 10.1161/01.cir.101.3.318
27. Adjedj J, Toth GG, Johnson NP, Pellicano M, Ferrara A, Floré V, Di Gioia G, Barbato E, Muller O, De Bruyne B. Intracoronary adenosine: dose-response relationship with hyperemia. *JACC Cardiovasc Interv*. 2015;8:1422–1430. doi: 10.1016/j.jcin.2015.04.028
28. De Luca G, Venegoni L, Iorio S, Giuliani L, Marino P. Effects of increasing doses of intracoronary adenosine on the assessment of fractional flow reserve. *JACC Cardiovasc Interv*. 2011;4:1079–1084. doi: 10.1016/j.jcin.2011.08.004
29. Rigattieri S, Biondi Zoccai G, Sciahbasi A, Di Russo C, Cera M, Patrizi R, Fedele S, Berni A, Pugliese FR. Meta-analysis of head-to-head comparison of intracoronary versus intravenous adenosine for the assessment of fractional flow reserve. *Am J Cardiol*. 2017;120:563–568. doi: 10.1016/j.amjcard.2017.05.024
30. Pothineni NVK, Edupuganti MM, Almomani A, Payne J, Raina S, Fnu S, Abualsuod A, Wong J, Uretsky BF, Hakeem A. Comparison of the prognostic value of non-ischaemic fractional flow reserve using intracoronary versus intravenous adenosine. *EuroIntervention*. 2018;13:1680–1687. doi: 10.4244/EIJ-D-16-00375
31. Loghin C, Sdringola S, Gould KL. Does coronary vasodilation after adenosine override endothelin-1-induced coronary vasoconstriction? *Am J Physiol Heart Circ Physiol*. 2007;292:H496–H502. doi: 10.1152/ajpheart.00818.2006
32. Heusch G. Adenosine and maximum coronary vasodilation in humans: myth and misconceptions in the assessment of coronary reserve. *Basic Res Cardiol*. 2010;105:1–5. doi: 10.1007/s00395-009-0074-7
33. Wijntjens GWM, van Lavieren MA, van de Hoef TP, Piek JJ. Physiological assessment of coronary stenosis: a view from the coronary microcirculation. *Interv Cardiol*. 2015;7:401–413.