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Differences in coronary microcirculation measurements during regadenoson vs. adenosine — induced hyperemia

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ABSTRACT

Background: *Little is known about the similarity of microcirculation assessment outcomes performed with regadenoson and adenosine. The aim of the current study was to compare coronary flow reserve (CFR) and index of microcirculatory resistance (IMR) assessment using adenosine and regadenoson, and to evaluate predictors regarding the size of differences.*

Methods: *44 patients were enrolled and diagnosed between 2021 and 2023. Fractional flow reserve (FFR), CFR and IMR were measured twice in the circumflex (Cx) (n = 8) or left anterior descending (LAD) (n = 36) artery: once with continuous infusion of adenosine (Adenocor 140 μg/kg/min) and 10 minutes later with regadenoson (Rapiscan 400 μg i.v.).*

Results: *Averaged results were quantified with adenosine and regadenoson for FFR (0.81 [0.75 ÷ 0.89] vs. 0.80 [0.73 ÷ 0.88]), CFR (3.84 [1.67 ÷ 4.08] vs. 3.97 [1.78 ÷ 4.32]) and IMR (20.01 [11 ÷ 24.5] vs. 20.25 [10.75 ÷ 23]), respectively. None of the differences were statistically significant. Among the significant (p < 0.05) predictors of greater ΔCFR, the following can be noted: prior percutaneous transluminal angioplasty/carotid artery stenting (β = 2.35), oral anticoagulant usage (β = 0.89), and prior stroke/transient ischaemic attack (TIA) (β = 1.09), with the latter being also confirmed for greater ΔIMR (β = 8.89). Moreover, patients with New York Heart Association (NYHA) class II/III, as compared to those with NYHA class I, were more likely to have greater ΔIMR (β = 11.89).*

Conclusions: *Regadenoson may be a feasible alternative to adenosine in coronary microcirculation assessment, as it produces similar outcomes. Selected factors were found to be predictors of greater differences in IMR, CFR and FFR values according to the agent used for coronary hyperemia.* (Cardiol J 2025; 32, 1: 19–25)

Keywords: adenosine, coronary flow reserve, fractional flow reserve, index of microcirculation resistance, regadenoson

Introduction

Assessment of coronary microvascular circulation, i.e. coronary flow reserve (CFR) and index of microcirculatory resistance (IMR), are among the most effective indicators for assessing myocardial blood supply and functional abnormalities of the coronary arteries in patients without obstructive coronary artery disease and symptomatic angina or heart failure. In multiple, heretofore published

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studies, the usefulness has been presented of microcirculation testing, as its outcomes are associated with patients' prognosis as well as concomitant diseases and major adverse cardiac event (MACE) occurrence in selected patient subgroups [1–7]. Moreover, such assessment could potentially provide further insight into patients' underlying disease, which regular coronary angiography often omits [8].

It is crucial for measurements to be performed correctly, i.e. under conditions of maximum passive hyperemia. To do so, adenosine infusion is considered as the gold standard. However, it may initiate side effects, such as shortness of breath, bronchospasm, flushing, chest pain and transient atrioventricular conduction block [9]. Hence, in certain subgroups of patients, such as in those with a contraindication to using adenosine, i.e. with reactive airway diseases, it is convenient to introduce regadenoson instead. It works as a more selective agent and can be administrated as a simple bolus via peripheral line. Therefore, it provokes a smaller number of side effects [9]. Importantly, regadenoson was proved to be equivalent to adenosine for FFR assessment [10, 11]. However, there are concerns regarding its feasibility in the CFR and IMR assessments. Studies reported that regadenoson-induced hyperemia is stable, similar to adenosine time-wise, and produces fewer side effects in patients with stable coronary artery disease (CAD) [9, 12]. However, there is a lack of solid data on measurement similarity with adenosine, and overall, the data regarding regadenoson usage during an invasive microcirculatory assessment remains insufficient.

The current study was aimed at identifying whether adenosine and regadenoson used for hyperaemia deliver similar results, and as well other factors, which can influence the difference in FFR, CFR and IMR measurements — using adenosine or regadenoson.

Methods

Population

Coronary microcirculation measurements were analyzed in 44 patients admitted to the invasive cardiology department from 2021 to 2023 with a suspicion of CAD. Patients with indications for physiologically-guided assessment of coronary lesions (with a stenosis of 40 to 80% on visual examination) were eligible for the study. All participants provided their written informed consent. The bioethics committee of the documented university approved the study design (No. 1072.6120.27.2022). The study was conducted in line with the 1964 Declaration of Helsinki.

Physiological examination of coronary arteries with use of adenosine and regadenoson

The examination of the coronary microcirculation was performed during a single angiographic procedure. The FFR, IMR and CRF were measured twice on the same artery. Angiography was performed in the 8 circumflex coronary arteries (Cx) and in the 36 left anterior descending coronary arteries (LAD).

To achieve maximal hyperemia, continuous infusion of adenosine via a peripheral vein was administrated at the dosage of 140 μg/kg/min. Measurements were taken using the dedicated Abbott PressureWire™ X pressure guidewire (Abbott Vascular, Santa Clara, CA). FFR was calculated as the lowest average distal pressure (Pd)/aortic pressure (Pa) from 3 consecutive heartbeats during maximal hyperemia. CFR was calculated as the ratio of mean transit time (Tmn) at rest/hyperemic Tmn, whereas IMR was calculated from the Pd × Tmn equation determined during hyperemia. After the cessation of adenosine, i.e., 10 minutes, a regadenoson test was performed. To achieve maximal hyperemia in this case, 400 μg of regadenoson (Rapiscan 1 amp. 400 mcg, GE Healthcare AS, Nycoveien 1, Norway) was administrated through the peripheral line as a 4-mL bolus (10-second-long infusion) followed by a 10-mL NaCl flush.

Statistical analysis

The analysis of quantitative variables was carried out by calculating the mean, standard deviation, median and quartiles. Analysis of qualitative variables was performed by calculating the number and percentage of occurrences for each value. Univariate analyses of the effect of each potential variable predictor on ΔFFR, ΔCFR and ΔIMR (quantitative variables) were performed using linear regression. The results were presented as regression model parameter values. The normality of variable distribution was checked using the Shapiro–Wilk test. Comparisons regarding the values of quantitative variables in two repeated measures was performed using the Wilcoxon paired t-test. A non-parametric test was used because the differences in the studied parameters were not normally distributed. The analysis assumed a significance level of 0.05. Thus, all p-values

below 0.05 were interpreted as indicating significant relationships. Analysis was performed using the R Core Team (2022). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria (https://www.R-project.org/).

Results

General characteristics

The study included 44 patients (37 males) undergoing coronary angiography, and their general characteristics are shown in Tables 1 and 2. The mean age of the population was 66.82 (± 8.02) years. The majority of patients clinically presented with Canadian Cardiovascular Society (CCS) 1 (54.5%), whereas half of study group had New York Heart Classification (NYHA) class II or above (50%). In terms of cardiovascular risk factors, most patients displayed arterial hypertension (86.4%) and hyperlipidemia (79.6%). Furthermore, prior percutaneous coronary intervention (PCI) (63.6%) and myocardial infarction (MI) in (56.8%) were frequent in the studied population. There were also 16 (36.4%) patients with a history of nicotine dependence in their medical records. Almost one-third of the patients (29.6%) presented symptoms of heart failure and diabetes mellitus. Furthermore, more than half of the patients had evinced hypokinesia during routine echocardiography, while mean left ventricle ejection fraction (LVEF) totalled 46.8 ± 15.2% (Table 3).

Biochemical indices

As is shown in Table 4, there were no abnormalities found in the investigated biochemical indices among the study group.

Pharmacotherapy

By analyzing medical records, almost all patients received acetyl-salicylic acid (ASA; 88.6%) and statins (84.1%) at baseline. As the vast majority of the patients were struggling with arterial hypertension, most of them had taken at least 2 blood-pressure-lowering drugs such as beta-blockers (75.0%), angiotensin-converting enzyme inhibitors (ACEIs; 61.4%), diuretics (31.8%) and calcium channel blockers (CCBs; 25.0%). What is worth mentioning, almost half of the study group had taken proton-pump inhibitors (PPIs; 47.7%). Selected patients received $P2Y_{12}$ inhibitors (18.2%), oral anticoagulants (OACs; 15.9%) and clopidogrel (15.9%). More details are shown in Table 5.

Table 1. Baseline characteristic of patients

Selected indices	Overall group n = 44
Age [years]	66.82 (± 8.02)
Male sex, (n) %	37 (84.09%)
Body mass index [kg/m^2]	27.72 (24.9–30.17)
Hospitalisation time [days]	3 (2.0–5.25)
SBP [mmHg]	139.39 (± 22.2)
DBP [mmHg]	83.55 (± 11.48)
Heart rate	71.27 (± 13.53)
NYHA class	
I	17 (38.64%)
II	9 (20.45%)
II/III	4 (9.09%)
III	9 (20.45%)
CCS class	
I	24 (54.54%)
II	9 (20.45%)
II/III	2 (4.55%)
III	3 (6.82%)
III/IV	1 (2.27%)

All data are expressed as absolute numbers (percentages), means (± SD) or medians (Q1–Q3). CCS — C anadian Cardiovascular Society; DBP — diastolic blood pressure; NYHA — New York Heart Association; SBP — systolic blood pressure

Table 2. Clinical characteristic of patients

Selected indices	Overall group n = 44
CAD	41 (93.18%)
Arterial hypertension	38 (86.36%)
Hyperlipidaemia	35 (79.55%)
Overweight	30 (68.18%)
Prior PCI	28 (63.64%)
Prior MI	25 (56.82%)
Smoking	16 (36.36%)
Diabetes myelitis	13 (29.55%)
Heart failure	13 (29.55%)
Atrial fibrillation	8 (18.18%)
Stroke/TIA	5 (11.36%)
Prior PTA/CAS	4 (9.09%)
Kidney failure	4 (9.09%)
Hypothyroidisms	4 (9.09%)

All data are expressed as absolute numbers (percentages).
CAD — coronary artery disease; MI — myocardial infarction; PCI — percutaneous coronary intervention; PTA/CAS — percutaneous transluminal angioplasty/carotid artery stenting; TIA — transient ischemic attack

Table 3. Echocardiography parameters

Selected indices	Overall group n = 44
LVEF [%]	46.77 (± 15.15)
Akinesia	14 (31.82%)
Hypokinesia	23 (52.27%)

All data are expressed as absolute numbers (percentages) and mean (± SD). LVEF — left ventricle ejection fraction

Table 4. Biochemical indices

Selected indices	Overall group n = 44
Total cholesterol [mmol/L]	3.75 (3.2–4.45)
LDL [mmol/L]	1.9 (1.4–2.55)
HDL [mmol/L]	1.1 (1–1.32)
TG [mmol/L]	1.3 (0.98–2.26)
Creatinine [μmol/L]	94.2 (76.33–110.5)
MDRD eGFR [mL/min/1.73m^2]	68.5 (61–89.25)
TSH [μIU/mL]	1.39 (0.98–2.14)
WBC [10^3/μL]	8.27 (± 2.23)
RBC [10^6/μL]	4.6 (± 0.48)
HGB [g/dL]	14.21 (± 1.4)
HCT [%]	41.75 (38.75–43.42)
PLT [10^3/μL]	219 (193.5–256.25)

All data are expressed as absolute numbers (percentages), means (± SD) or medians (Q1–Q3). eGFR — estimated glomerular filtration rate; HCT — hematocrit; HDL — high-density lipoprotein; HGB — hemoglobin; LDL — low-density lipoprotein; MDRD, RBC — red blood cells; PLT — platelets; TG — triglycerides; TSH — thyroid stimulating hormone; WBC — white blood cells

Table 5. Pharmacotherapy

Selected indices	Overall group n = 44
ASA	39 (88.64%)
Statin	37 (84.09%)
Beta-blocker	33 (75%)
ACEI	27 (61.36%)
PPI	21 (47.73%)
Diuretic	14 (31.82%)
CCB	11 (25%)
P2Y$_{12}$ inhibitor	8 (18.18%)
OACs	7 (15.91%)
Clopidogrel	7 (15.91%)
Insulin	6 (13.64%)
Levothyroxine	2 (4.55%)

All data are expressed as absolute numbers (percentages). ACEI — angiotensin-converting enzyme inhibitors; ASA — acetylsalicylic acid; CCB —calcium channel blockers; OAC — oral anticoagulants; PPI — proton-pump inhibitors

Comparison between regadenoson and adenosine in FFR, CFR and IMR values

Measurements were conducted in the LAD (n = 36) and Cx arteries (n = 8). The median FFR was high in both cases, when using adenosine and regadenoson (0.81 [0.75 ÷ 0.89] and 0.80 [0.73 ÷ 0.88], respectively). No significant differences were noted between FFR, CFR and IMR values in the compared study groups (Fig. 1). The difference between measurements with adenosine and regadenoson proceeded on the same artery were: ΔFFR = 0.02 (0.01 ÷ 0.04), ΔCFR = 0.6 (0.29 ÷ 1.55) and ΔIMR = 3.5 (1.38 ÷ 7.1) (Tab. 6).

Factors related to change between coronary circulation measurements when using adenosine vs. regadenoson — linear regression models

It was revealed that CAD presence and ASA usage were significant predictors of smaller absolute ΔFFR between compared microcirculation methods (β = –0.06, p = 0.006 and β = –0.03, p = 0.046, respectively; Fig. 2). On the other hand, prior percutaneous transluminal angioplasty/ /carotid artery stenting (PTA/CAS) was proved to be a significant predictor of increased ΔFFR (β = 0.046, p = 0.01; Fig. 2).

When considering ΔCFR, the following predictors of its change could be observed: CAD (β = –2.15, p < 0.001), prior PTA/CAS (β = 2.35, p < 0.001), history of stroke/transient ischemic attack (TIA) (β = 1.09, p = 0.03), ASA and OACs usage (β = –1.31, p = 0.009 and β = 0.89, p = 0.04, respectively). Furthermore, on average, for every increase in left ventricle ejection fraction by 1%, the ΔCFR decreased by 0.02 (β = –0.02, p = 0.049, Fig. 2).

Similar to previous results, the use of ASA was related to reduced ΔIMR (β = –8.66, p = 0.03), whereas a history of stroke/TIA predicted an increment in ΔIMR (β = 8.9, p = 0.03). Moreover, as compared to NYHA I class, the presence of II/III class was also related to increased absolute ΔIMR (β = 11.89, p = 0.02; Fig. 2).

Discussion

Contrary to the assessment of FFR, there is limited data regarding regadenoson usage in microcirculation coronary circulation assessments. The present analysis is one of the first to provide insight into this issue. The main findings of the current study are as follows:

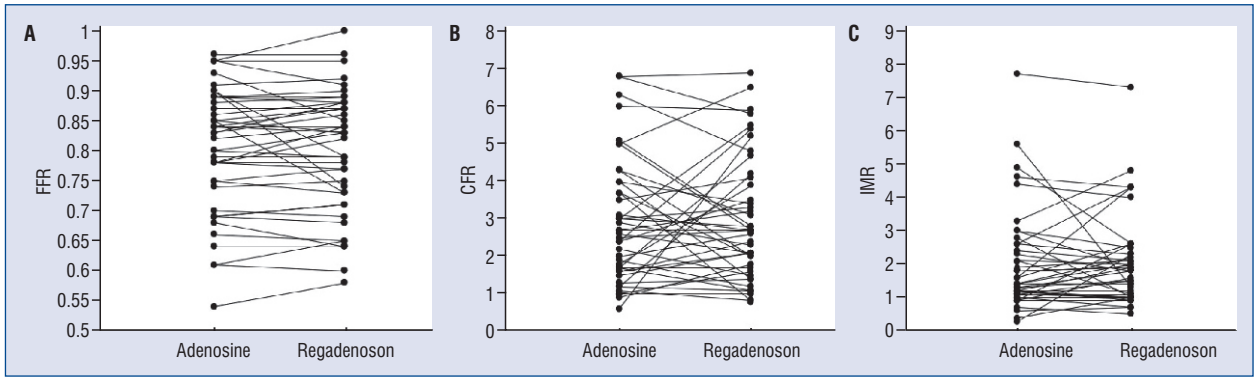

Figure 1. Coronary functional assessment with use of regadenoson and adenosine. Panels **A**, **B**, and **C** show results of measurements (fractional flow reserve [FFR], coronary flow reserve [CFR], and index of microcirculatory resistance [IMR], respectively) in each patient (n = 44) performed with adenosine and regadenoson subsequently. Differences between averaged values obtained using adenosine and regadenoson did not reach statistical significance (p = 0.459 for panel **A**, p = 0.964 for panel **B** and p = 0.745 for panel **C**)

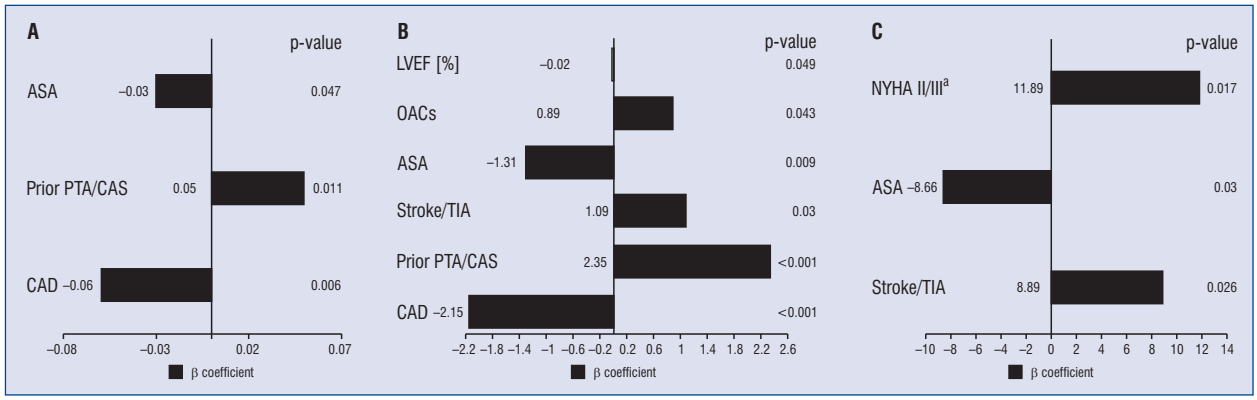

Figure 2. Predictors of change size in coronary circulation measurement values assessed using adenosine vs. regadenoson — linear regression models. **A.** Beta coefficients regarding predictors of ΔFFR; **B.** Beta coefficients regarding predictors of ΔCFR; **C.** Beta coefficients regarding predictors of ΔIMR. [a]As compared to NYHA class I. ASA — acetylsalicylic acid; CAD — coronary artery disease; CAS — carotid artery stenting; CFR — coronary flow reserve; FFR — fractional flow reserve; IMR — index of microcirculatory resistance; LVED — left ventricle ejection disease; NYHA — New York Heart Association; OAC — oral anticoagulants; PTA — peripheral transluminal angioplasty; TIA — transient ischemic attack

Table 6. Quantitative differences in outcomes of coronary functional assessment with use of regadenoson vs. adenosine

Parameter	Overall group (n = 44)
ΔFFR	0.02 (0.01–0.04)
ΔCFR	0.6 (0.29–1.55)
ΔIMR	3.5 (1.38–7.1)

All data are expressed as median (Q1–Q3). CFR — coronary flow reserve; FFR — fractional flow reserve; IMR — index of microcirculatory resistance

1. There were no significant differences in the average FFR, CFR or IMR values in assessments with regadenoson as compared to adenosine;
2. Heightened differences in the microcirculatory measures were predicted by the following: history of stroke/TIAs, prior PTA/CAS, OACs usage, more advanced NYHA class;
3. Treatment with ASA and a diagnosis of CAD at baseline as well as LVEF values were predictors of decreased differences in microcirculatory assessments obtained with regadenoson and adenosine.

In general, regadenoson is a selective agonist of A_{2a} receptors, which along with its reversibility, is associated with a lower risk of adverse effects among patients. This also included those with comorbidities, and overall, contraindications to regular adenosine usage [13]. Moreover, in other studies, it has been

reported that maximal hyperemia can be achieved faster with regadenoson, underscoring further the favorable outcomes of its usage [14]. This, sequentially, in light of the facts that its infusion preparation and administration are simpler than Adenosine infusion, reduces time spent in catheterization laboratory as well [9, 15]. Despite the aforementioned advantages, regadenoson poses several limitations. Firstly, its implementation may produce higher costs [16]. Moreover, the necessity for reliable microcirculatory assessment stability of hyperaemia induced by this agent is still a subject of debate. This is due to the fact that regadenoson was reported to have a varying duration of hyperemic effect, which considering guidelines recommending its single-dose administration, produce uncertainty whether the operator was provided enough time to perform a reliable assessment [17]. Therefore, in patients characterised with complex lesions necessitating multiple coronary flow measurements and additional pullback recordings, adenosine remained superior.

Regarding FFR, the present study confirms a lack of significant differences between the adenosine and regadenoson approach. The reliability of the latter in FFR measurements has been reported in a number of other studies [9–12, 17–20]. For instance, in a study conducted by Nair et al., the authors revealed excellent correlations between regadenoson and adenosine in lesion assessment ($r = 0.99$, $p < 0.001$) [10].

Given the results of the current study, it can be concluded that regadenoson is a valid tool in invasive coronary flow and IMR testing among patients with high FFR (averaged on the whole population). However, as several predictors of larger disparities between two hyperemia-inducing agents were indentified, the reproducibility of our results in other clinical situations are called to question. Since we did not explore the characteristics of these changes regarding the value in measurements between adenosine *vs*. regadenoson testing, the discussion at this point should be extrapolated carefully. It was observed, for example, that a history of stroke/TIA, prior PTA/CAS and higher NYHA class were significant predictors of increased discrepancies between investigated hyperemia-inducing agents. It may be the case that the epicardial and microcirculatory flows among patients characterized by a more serious "clinical burden" were more prone to changes, given the fact that the procedure was prolonged. Overall, to decisively confirm regadenoson feasibility, more focus needs to be placed on specific patient cohorts as well as and specific lesion characteristics, which the present study lacked.

Despite the fact that the means of measurements for IMR and CFR do not significantly differ statistically, insight into the pairs shows that some of the measurements differed dramatically depending on the use of regadenoson or adenosine for the induction of passive hyperemia. There are certainly a number of factors beyond those found to be significant in the statistical analysis, and from present observations, these certainly include hemodynamic conditions that change throughout the study. It should be noted that the regadenoson and adenosine assays were performed at least 10 minutes apart. During this time, some patients' blood pressure changed, some calmed down during the examination, while some began to get nervous, e.g. due to back pain or to other parts of the skeletal system. Another factor that affects the hemodynamic of circulation is the temperature in the laboratory, which in many patients, causes a feeling of cold and the consequences associated with it. Another problem is keeping the guidewire in the same place in both chambers. While waiting for the next measurement, the guidewire often migrates with consecutive heartbeats, and it becomes necessary to correct the guidewire position before subsequent measurements.

To sum up, it is often not possible to create the same hemodynamic conditions for both measurements, which could certainly have influenced the obtained results. This occurs despite the determinations being made by experienced operators.

Limitations

There are some limitations of the present study, including the relatively small group of studied patients, although sufficient statistical power was achieved to draw the discussed conclusions. Furthermore, focus was not put onto differentiating whether the change in differences between adenosine and regadenoson testing was due to the former or latter agent while considering a predicting factor. Nevertheless, the envisaged hope is that there will be a further continuation of the study and enlargement of the study group.

Conclusions

From the preliminary findings, it can be suggested that regadenoson is a feasible alternative to adenosine in microcirculation assessment, as it produces similar outcomes. Selected factors were found to be predictors of greater differences in

IMR, CFR and FFR values according to the agent used for coronary hyperemia.

Data availability statement: Data are available on special request.

Ethics statement: The study was approved by the local bioethics committee and was conducted in line with the 1964 Declaration of Helsinki.

Author contributions: R.J. — conducting the study, gathering data, preparing manuscript, organising statistician, supervising, S.B., R.J — projecting the study, W.S., N.B. — preparing and gathering data, writing draft of the manuscript, A.S., W.W. — editing manuscript, supervising.

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