

Intracoronary Versus Intravenous Adenosine-Induced Maximal Coronary Hyperemia for Fractional Flow Reserve Measurements

Ahmed Khashaba, Ayman Mortada and Azza Omran

Ain Shams University, Cardiology Department Cairo, Egypt.

ABSTRACT

BACKGROUND: Maximal hyperemia is the critical prerequisite for fractional flow reserve (FFR) assessment. Despite intravenous (IV) adenosine currently being the recommended approach, intracoronary (IC) administration of adenosine constitutes a valuable alternative in everyday practice. However, it is surprisingly unclear which IC strategy allows the achievement of FFR values that are comparable to IV adenosine.

OBJECTIVES: This study sought to compare increasing doses of IC adenosine versus IV adenosine for FFR.

METHODS: 30 intermediate coronary stenoses undergoing FFR measurement were prospectively and consecutively enrolled. Hyperemia was sequentially induced by bolus of IC adenosine (ADN; 150 µg) followed by IV adenosine (IVADN) infusion over 3 minutes at dose of (140 µg/kg/min). FFR values, symptoms, and development of atrioventricular block were recorded.

RESULTS: 150 µg doses of IC adenosine were well tolerated and associated with fewer symptoms than IV adenosine. Intracoronary adenosine doses induced a significant decrease of FFR compared with baseline levels ($P < 0.01$). Among the 6 patients with FFR values less than 0.80 identified by IVADN, 4 were correctly identified also by 150 µg bolus IC adenosine. Larger randomized studies with cross-over design are necessary to verify the results.

CONCLUSIONS: This small pilot study suggests that IC adenosine might be an alternative to IV adenosine. Larger randomized studies with a cross-over design are necessary.

KEYWORDS: AVB: atrioventricular- nodal block, CAD: Coronary artery disease, FAME: FFR versus angiography for multi vessel evaluation, FFR: Fractional flow reserve, IC: Intracoronary, ICADN Intracoronary Adenosine, IV: Intravenous, IVADN: intravenous Adenosine, PCI: percutaneous coronary intervention, QCA: quantitative coronary Angiography, CBF: Coronary blood flow

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CORRESPONDENCE: egydr1@gmail.com; aymanmor@hotmail.com; azza_omran@hotmail.com

Introduction

Ischemic heart disease remains a leading cause of morbidity and mortality worldwide.¹ Borderline coronary artery lesions are responsible for about 80% of acute coronary syndromes (ACS).² It is not uncommon during the performance of coronary angiography to identify borderline coronary stenosis (>40 and <80%) in the absence of more severe lesions.³

Percutaneous coronary intervention (PCI) of an intermediate stenosis without evidence of ischemia is often performed, but its benefit is unproven. Coronary pressure-derived fractional flow reserve (FFR) is an index used to identify a

stenosis responsible for reversible ischemia,⁴ which profits from revascularization.⁵

Uncertainty about the significance of these lesions may be augmented by the error associated with visual estimation of the severity of the stenosis. Thus, in a patient with a borderline lesion the results of an FFR can be very useful to evaluate the functional significance of coronary lesions.³

The measurement of fractional flow reserve (FFR) is commonly used in clinical practice to assess the hemodynamic significance of epicardial coronary stenosis and an FFR value of 0.75 is accepted as a physiologically significant stenosis.



However, an FFR between 0.75 and 0.80 is considered to be a borderline and represents a gray zone of functional significance for coronary stenosis.⁶

Achievement of maximal hyperemia of coronary microcirculation is the prerequisite for the exact assessment of FFR in order to minimize the effect of microvascular resistance. With suboptimal coronary hyperemia, FFR will be artificially high, resulting in a potentially significant underestimation of the functional severity of coronary stenosis.⁷

To achieve maximal hyperemia, IV adenosine is considered the standard method, but its use in the catheterization laboratory is time consuming and expensive compared with intracoronary adenosine.⁸ Therefore, this study compared intracoronary adenosine for the potential to achieve a maximal hyperemia equivalent to the standard intravenous route.

Patients and Methods

This study was conducted at the Cardiology Department at Ain Shams University hospital. The study sample was comprised of 22 patients who underwent elective coronary angiography and were found to suffer from 30 borderline lesions in the period from January 2012 to August 2012.

This study is a prospective study designed to compare different strategies to induce coronary vasodilation for FFR measurements. 22 consecutive patients undergoing diagnostic cardiac catheterization for suspected coronary artery disease showing 30 angiographically intermediate lesions (diameter stenosis 50% to 70% at visual estimation) in at least 1 main coronary artery were consecutively and prospectively enrolled. Lesions localized on left and right coronary ostia were excluded. Intermediate lesions in a vessel with thrombus, moderate or severe calcification, angulation, or tortuosity was excluded. PCI may have been performed in such non-target vessels or lesions prior to study enrollment, however, as long as it was successful and uncomplicated.

Clinical exclusion criteria were recent myocardial infarction (within 7 days) or prior myocardial infarction in the territory supplied by the target vessel, severe valvular heart disease, acutely decompensated chronic heart failure, or advanced renal failure (estimated glomerular filtration rate <30 mL/min). Clinical features, cardiovascular risk factors, and left ventricular function were recorded. Cardiovascular medications were not withheld before the study. The study was approved by the local ethical committee and conformed to the Declaration of Helsinki on human research, and informed consent was obtained after complete explanation of the protocol and potential risks.

Coronary angiography. Coronary angiography was performed using standard techniques (Innova 2000 GE, General Electric) along with a quantitative estimation of the coronary artery diameter. Quantitative coronary angiography (QCA) was evaluated and performed with GE QCA software (GE Innova 2000, Fairfield, CT, USA). Heart rate and arterial pressure were continuously monitored throughout the procedure.

Heparin was administered at the beginning of the procedure (60 U/kg).

Pressure measurements were obtained using a Volcano s5i imaging system and Prime Wire™ pressure guide wire. The pressure guide wire was calibrated and introduced into the guiding catheter. The pressure transducer was advanced just outside the tip of the guiding catheter, and the pressure measured by the sensor was then equalized to that of the guiding catheter. The wire was then advanced distally to the target coronary stenosis. Special attention was paid to avoid arterial pressure wave damping, unselective catheterization of coronary ostia and variation in the position of the pressure wire. FFR was calculated as the ratio of distal coronary pressure divided by aortic pressure obtained after achievement of

Table 1. Demographic Data of the study group.

AGE	YRS 65 ± 9
Men	20(90%)
Diabetes,	14(63%)
Hypertension	14(63%)
Smoking Status	
Active smoking	6(27.2%)
Ex smoker	7(31.8%)
Nonsmoker	9(40.9%)
Dyslipidemia	13(59.09%)
Family history of CAD	8(36.3%)
Previous Angina	
CCS I	9(40.9%)
CCS II	7(31.8%)
CCS III	3 (13.6%)
CCS IV	3 (13.6%)
Medications	
ASA	20(90%)
Clopidogrel,	13(59%)
Beta-blockers,	14(63.6%)
RAAS antagonist,	15(68.1%)
Calcium-channel blockers	6(27.2%)
Statins	18(81.8%)
Prior MI—remote area	8(36.3%)
Previous PCI	15(68.1%)
% stenosis visual estimation	58 ± 19
Ejection fraction%	61 ± 12
Target vessel	
LAD	17(56.6%)
LCX	7(23%)
RCA	6(20%)
QCA	64.6 ± 12.5

Note: Values are mean SD or n (%).

Abbreviations: ASA, acetylsalicylic acid; MI, myocardial infarction; PCI, percutaneous coronary intervention.

**Table 2.** Effect of IV Adenosine and IC Adenosine on HR, APB Symptoms and Atrioventricular Blok.

	N	HR	SBP	DBP	MBP	P VALUE
Baseline	30	70 ± 8	144 ± 20	79 ± 9	101 ± 11	
ICADN	30	64 ± 12	144 ± 21	74 ± 9	97 ± 10	0.05
IVADN	30	75 ± 12	137 ± 23	75 ± 12	96 ± 14	

Note: Values are $\bar{A} \pm SD$, or (%). ICADN: intracoronary bolus of Iof adenosine; IVADN 140 $\mu\text{g}/\text{kg}/\text{min}$ intravenous Adenosine.

Abbreviations: DBP, diastolic blood pressure; HR, heart rate, MBP, mean blood pressure.

maximal hyperemia. Femoral or brachial veins were used for systemic drug administration. An FFR value of <0.75 was considered to be a significant ischemic threshold.

Study protocol. After checking the correct position of both the guiding catheter and the pressure wire NTG (200 μg) was administered (in order to reduce vasospasm). The study procedure consisted of 2 sequential steps:

1. IC bolus injection at the dose of 150 μg and rapidly flushed with saline solution then FFR, arterial blood pressure (ABP) and heart rate (HR) readings recorded after 3 seconds. HR and BP were recorded in order to indicate the hyperemic state, evidenced by a 10–20% decrease in BP and a similar increase in HR.
2. The same process was repeated using IV adenosine infusion at the dose of 140 $\mu\text{g}/\text{kg}/\text{min}$. After reaching the steady state of hyperemia, the FFR recording was taken.

Coronary blood flow (CBF) is determined by coronary auto-regulatory mechanisms (causing vasoconstriction) and the systemic blood pressure (driving pressure). So, maximal hyperemia was induced to abolish auto-regulatory mechanisms and CBF became directly related to the driving pressure.

Heart rate, aortic pressure, and distal coronary pressure were continuously recorded and digitally stored throughout all the phases of the study. Patient symptoms (namely an angina-like sensation, dyspnea, or flushing), development of complete atrioventricular-nodal block (AVB), or any other complication were carefully recorded.

Data and statistics management. Data were revised, coded and entered into SPSS version 16. The qualitative data are presented using numbers and percentages while the quantitative data are presented using range and mean $\bar{A} \pm SD$. An independent samples t-test was used to compare two groups with normal distribution, and a with Wilcoxon-rank test was used as a non parametric test.

The confidence interval was set to 95%. The alpha level was 0.05.

Results

Demographic data and risk factors. The baseline characteristics of the study population are summarized in Table 1.

Table 3. mFFR ICADN compared to mFFR IVADN.

	MINIMUM	MAXIMUM	MEAN	SD	P-VALUE
Baseline FFR	0.84	1.00	0.94	0.05	
ICADN FFR	0.65	0.98	0.85	0.08	0.811
IV ADN FFR	0.65	0.98	0.84	0.09	

All incidences of side effects were higher during IV infusion than during all IC infusions.

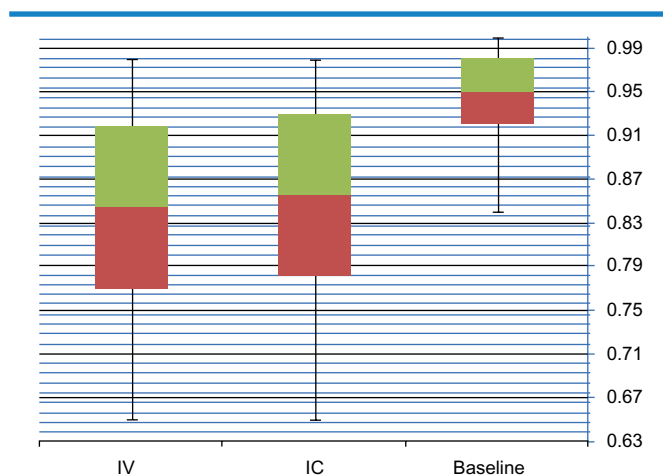
FFR measurements. Mean FFR (mFFR) measurements were recorded only in the vessels with borderline lesion at baseline, after the injection of IV Adenosine, and after IC bolus Adenosine.

IC adenosine dose induced a significant decrease in FFR compared with baseline distal coronary pressure/aortic pressure ($P < 0.05$), (mean baseline FFR 0.94 ± 0.05 , mean IVADN 0.85 ± 0.08 , and Mean ICADN 0.84 ± 0.09) with mean values illustrated in Table 3 and Figure 1.

The primary endpoint of the present study was to test the non-inferiority of ICADN in comparison with IVADN in inducing maximal hyperemia measured as the lowest possible FFR value. We considered the non-inferiority threshold to be a difference of $<0.02 \pm 0.05$ in the FFR value between those calculated inducing maximal hyperemia with IVADN and those with ICADN, assuming the FFR value obtained by IVADN to be the standard reference, and hypothesizing that this value was the lowest possible to detect small differences.⁸

A total of 6 lesions were identified with a positive FFR (FFR <0.75) by IVAND (the standard protocol). 4 of these lesions were correctly diagnosed by ICADN protocol. Notably, as regards to the primary endpoint of the study, ICADN was associated with an FFR value not significantly different from IVADN ($P = 0.811$ for noninferiority).

Safety of IV and IC adenosine. Hemodynamic effect of IV Adenosine protocol and IC Adenosine protocol were recorded, it is summarized in table (2).

**Figure 1.** mFFR recorded values.



During the IC protocol, none of the patients developed nether chest pain or transient A-V block. Meanwhile, during the IV protocol, 6 patients developed chest pain and 4 patients developed transient A-V block. Importantly, AVB was always transient and spontaneously reversible, thus never requiring atropine administration or temporary pacemaker implantation.

Discussion

The induction of maximal coronary hyperemia represents a critical prerequisite to correctly assess FFR.^{9,10} With this aim, although IV adenosine is currently considered the gold standard approach, in everyday practice, IC adenosine administration is frequently used as a cheaper, simpler, and more rapid alternative. In the present study, we thus compared safety and efficacy of high-dose IC adenosine (150 µg). Of note, our data show that IC approaches were feasible and safe in most patients.

IV versus IC adenosine. Intravenous administration of adenosine at a dose of 140 µg/kg/min represents the gold standard for FFR assessment.¹¹ Indeed, the IV route provides several practical advantages, such as an effective and safe protocol, the induction of a prolonged vasodilator stimulus allowing the achievement of a stabilization of pressure traces, and the possibility to perform a pressure wire pullback in cases of multiple lesions or diffusely diseased coronary arteries.¹² However, IV adenosine administration is a time-consuming and costly procedure. Furthermore, patients often experience the typical known side effects related to systemic adenosine infusion. Conversely, IC adenosine administration allows an easy, feasible and rapid procedure that requires a much lower amount of adenosine, thus also reducing costs. Although commonly used in clinical practice in a large number of catheterization laboratories worldwide, IC adenosine administration has the major drawback of a possible suboptimal induction of maximal hyperemia.^{13,14} This is mainly due, on the one hand, to possible nonselective drug administration into the target coronary artery and, by contrast, to the uncertainty regarding the dose needed to achieve maximal coronary vasodilation.¹³⁻¹⁵ The former issue might be addressed by selective IC injection by microcatheter. Using this technique, Yoon et al.⁷ have demonstrated that, compared with IV or IC (in bolus) adenosine at commonly-suggested doses, a dose of 240 µg to 360 µg administered via IC in 1 min (and not in bolus) was more effective at inducing maximal coronary hyperemia. However, this procedure is more invasive than the standard technique and the issue of safety might limit its widespread use. With regard to the second issue, doses lower than 50 µg have been used in several previous studies, although they allow physicians to reliably measure FFR value in less than 1/4 of patients.^{13,14} Casella et al.⁸ have shown that a 150 µg bolus resulted in mean FFR values comparable to those obtained after IV adenosine.¹²

While designing this study, we selected the dose of 150 µg to test the feasibility and the effect of a very high dose of IC adenosine on FFR. Of note, the use of these high IC dose of adenosine is not uncommon in daily practice, especially in the setting of primary PCI for the pharmacological treatment of no-reflow, where even higher doses have been safely administered.^{9,16,17}

Our study demonstrates that high-dose (150 µg) IC adenosine is sufficient to induce maximal hyperemia and was not inferior to IV adenosine. However, the IV approach was associated with the lowest value in most cases, as compared with the IC dose.

Using the cutoff of the FAME study⁵; however, IV adenosine was associated with a lower FFR value in a higher percentage of cases than of those using the IC strategy. Although technical pitfalls due to catheter dislodgement and unselective administration of adenosine might have played a role, this might indicate that the IV approach is superior in inducing maximal hyperemia, and finally, in identifying functionally significant stenosis. In this view, the IV route might represent an alternative to IC administration only in those cases where the FFR value approaches 0.80 (0.81 to 0.83).

Conclusions

On the basis of the results of this study, we suggest using IC adenosine at the tested dose to perform a safe and cost-effective functional evaluation of intermediate stenosis with FFR. PCI can be safely performed if FFR is <0.75. Conversely, if FFR is equivocal, that is, the FFR value is between 0.83 and 0.81, FFR evaluation should be repeated with IV adenosine and then a decision should be made on the basis of the cutoff value of 0.75.

In conclusion, our study clearly demonstrates that high doses of IC adenosine can be relatively safely administered to most patients, and allows for obtainment of the minimum FFR value in a similar proportion of patients to the gold standard IV route. Thus the IV route might be reserved for those cases of equivocal FFR after IC adenosine.

Limitations

The main limitation of the current study is the small sample size. This is a pilot trial, indicating that FFR after IC and IV administration seems to be comparable.

The next step would be a study with extended sample size with a higher proportion of positive FFR <0.75 to increase the negative and positive ICADN protocol specificity and sensitivity.

It is speculated that higher doses of adenosine may be needed to yield a near-maximal hyperemic response in patients with microvascular disorders and other conditions possibly accompanied by decreased sensitivity of the vascular system to adenosine. Arterial hypertension, diabetes mellitus, and myocardial infarction impair vasodilatation of the peripheral microvasculature. These pathologies affect a well-represented



population in the real world, as suggested from the extremely high prevalence of hypertension and diabetes mellitus in this study. In addition, although high intracoronary adenosine bolus could be an acceptable alternative to intravenous adenosine, intracoronary adenosine produces a plateau hyperemic phase of approximately 4 seconds, which corresponds to 3 to 6 beats, but not to a true steady state. This absence of a prolonged hyperemic state is a strong limitation to the IC approach in cases of mild to moderate tandem stenoses or in cases of diffuse disease, when a pullback maneuver of the pressure wire is necessary to detect the exact location of the critical lesion.

Author Contributions

Conceived and designed the experiments: AK. Analyzed the data: AM, AO. Wrote the first draft of the manuscript: AO. Contributed to the writing of the manuscript: AM. Agree with manuscript results and conclusions: AK, AM. Jointly developed the structure and arguments for the paper: AK, AM, AO. Made critical revisions and approved final version: AK, AM. All authors reviewed and approved of the final manuscript.

DISCLOSURES AND ETHICS

As a requirement of publication the authors have provided signed confirmation of their compliance with ethical and legal obligations including but not limited to compliance with ICMJE authorship and competing interests guidelines, that the article is neither under consideration for publication nor published elsewhere, of their compliance with legal and ethical guidelines concerning human and animal research participants (if applicable), and that permission has been obtained for reproduction of any copyrighted material. This article was subject to blind, independent, expert peer review. The reviewers reported no competing interests.

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