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Impact of increasing dose of intracoronary adenosine on peak hyperemia duration during fractional flow reserve assessment

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Background: Fractional Flow Reserve (FFR) is currently indicated as a first line strategy for the functional assessment of intermediate coronary stenoses. However, the protocol for inducing hyperemia still lacks standardization. Intracoronary adenosine boli, with a progressive increase to high-dosage, have been proposed as a sensitive and accurate strategy for the classification of coronary stenoses, although being potentially affected by the achievement of plateau of the effect and by a less prolonged and stable hyperemia as compared to intravenous administration. Therefore, the aim of the present study was to define the conditioning parameters and assess the impact of increasing-dose intracoronary adenosine on peak hyperemia duration in patients undergoing FFR for intermediate coronary stenoses.

Methods: FFR was assessed in patients with intermediate (40 to 70%) lesions by pressure-recording guidewire (Prime Wire, Volcano), after induction of hyperemia with intracoronary boli of adenosine (from 60 to 1440 μg, with dose doubling at each step). Hyperemic duration was defined as the time for the variation form minimum FFR $\pm$ 0.02 and time to recovery till baseline values.

Results: We included 87 patients, undergoing FFR evaluation of 101 lesions. Mean peak hyperemia duration and time to recovery significantly increased with adenosine doses escalation ($p = 0.02$ and $p < 0.001$). Peak hyperemia duration and time to recovery with 1440 μg adenosine were 14.5 $\pm$ 12.6 s and 45.2 $\pm$ 30.7 s, respectively. Hyperemia duration was not related to Quantitative Coronary Angiography (QCA) parameters or FFR values. In fact, a similar increase in the time of hyperemic peak was noted when comparing patients with positive or negative FFR ($p_{between} = 0.87$) or patients with lesions < or ≥20 mm ($p_{between} = 0.92$) and lesions involving left main coronary or proximal left anterior descending artery (LAD) ($p_{between} = 0.07$). A linear relationship was observed between time to recovery and FFR variations, with a greater time to baseline required in patients with FFR ≤ 0.80 ($p = 0.003$) and in lesions ≥ 20 mm ($p = 0.006$), but not in LAD/LM lesions ($p = 0.55$).

Conclusions: The present study shows a progressive raise in the duration of peak hyperemia and time to recovery, after the administration of increasing doses of intracoronary adenosine for the assessment of FFR. Therefore, considering the potential advantages of a high-dose adenosine protocol, allowing a more prolonged hyperemia and a more precise and reliable measurement of FFR, further larger studies with such FFR strategy should certainly be advocated to confirm its safety and benefits, before its routinely use recommendation.

1. Background

Functional assessment of coronary stenoses represents a valid complement to the traditional anatomic evaluation of coronary angiography and, in particular, in patients with intermediate lesions, allowing to identify and lead to revascularization only those significant lesions, with ischemic potential [1]. The Fractional Flow Reserve (FFR), measuring physiologic parameters, as the fall in coronary pressure across a stenosis, after the achievement of maximal hyperemia, has emerged as an accurate and reliable method for the assessment of hemodynamically relevant coronary stenoses [2,3]. However, despite several trials pointing at the prognostic benefits of limiting coronary revascularization only to

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those lesions with a FFR ≤ 0.80, [4,5], the strategy for achieving maximum hyperemia is still debated.

Although intravenous infusion of adenosine is considered the gold standard [6], the use of intracoronary (IC) boli of adenosine can offer several practical advantages, being faster, needing a lower amount of adenosine, reduced costs [7], a lower risk of systemic adverse effects and not requiring a central vein for the infusion. Nevertheless, inadequate achievement of hyperemia and shorter duration of effect have been reported with intracoronary adenosine, risking diminishing the stability and accuracy of the measurements [6,8]. The dosing of adenosine used for IC boli has emerged as a critical parameter for the correct performing of FFR, with certain studies reporting a dose-response relationship [9,10], whereas other ones documenting the achievement of a plateau of the effect even at lower dosages of adenosine [11–13]. However, in the latter studies, in contrast, a progressive raise in the duration of hyperemic peak was observed, suggesting the possibility of a further recruiting of the coronary vasodilating potential. Therefore, in absence of a univocal consensus on the protocol for the measurement of FFR and of a complete comprehension of the physiological effects of adenosine on coronary circulation, we aimed to assess the impact of increasing-dose intracoronary adenosine and the parameters conditioning hyperemia duration in patients undergoing FFR for intermediate coronary stenoses.

2. Methods

We included patients undergoing coronary angiography at our Division of Cardiology, "Maggiore della Carità" Hospital, Eastern Piedmont University in Novara, Italy, from August 2014 to January 2017 for elective indication or acute coronary syndrome and receiving fractional flow reserve assessment for intermediate coronary stenoses (angiographic 40 to 70% stenosis).

Exclusion criteria were: 1) allergy to adenosine (patients' self-reported in case of previous exposure to the drug); 2) baseline bradycardia (Heart Rate < 50 bpm); hypotension (blood pressure < 90 mm Hg); 4) refusal to provide signed informed consent. All patients signed the informed consent to participate in the study. The study was approved by our local Ethical Committee.

Main demographic, clinical and angiographic data were recorded in a dedicated database, protected by password. Hypertension was defined as systolic pressure > 140 mm Hg and/or diastolic pressure > 90 mm Hg or if the individual was taking antihypertensive medications. Diabetes mellitus was defined as previous diagnosis, specific treatment administration (oral drug or insulin), fasting glycemia > 126 mg/dl or HbA1c > 6.5%. Chronic renal failure was considered for history of renal failure or an admission glomerular filtrate (GFR) < 60 mol/min/1.73 m^2 by MDRD (Modification of Diet in renal Disease) formula.

Main chemistry parameters were assessed at admission, following a fasting period of 12 h, as previously described [14].

3. Study protocol

Coronary angiography was performed preferentially from a left transradial approach, using standard Judkins 6-French right and left catheters. Heart rate and arterial pressure were continuously monitored throughout the procedure. Heparin was administered at the beginning of the procedure (60 units/kg) and non-ionic contrast material was used for all patients. Angiographic visual assessment of coronary lesions was followed by an off-line analysis of quantitative parameters of the stenosis.

Quantitative coronary angiography was performed by an automatic edge-detection system (Siemens Acom Quantcor QCA, Erlangen, Germany). After the visual inspection of the coronary artery, the frame of optimal clarity was selected, showing lesion at maximal narrowing and arterial silhouette in sharpest focus. After the calibration of guiding catheter, analysed arterial segment with coronary lesion was defined by moving the cursor from the proximal to the distal part of coronary artery to ensure adequate determination of reference diameter. We have measured minimal luminal diameter, reference diameter, percent diameter stenosis, and length of the lesion. A stenosis was considered significant if >70%, intermediate between 40 and 70%.

In patients displaying intermediate coronary stenoses, fractional flow reserve (FFR) was performed immediately after coronary angiography, as previously described [9].

All patients received multiple intracoronary adenosine boli with a progressive increase to high dose adenosine, if tolerated (60, 120, 180, 360,720 and 1440 μg). Each bolus was followed by a flush with saline. Measurement of FFR was started 3 s after bolus administration. Each bolus was administrated at least 1 min after the previous one (in all cases until pressure curves returned to baseline values). In order to minimize and standardize fluid volume infusion, we prepared the drug with a special dilution of 60 μg/ml and 360 μg/ml (the last one used for 360, 720 and 1440 μg doses).

For each adenosine dose, we measured the absolute values of the arterial and distal post-stenotic pressure (P_a and P_d, respectively) and the value of the FFR, that was defined by the formula FFR $= P_d/P_a$. FFR was considered pathological for values ≤ 0.80. Delta P_d/P_a was defined as the difference of post-adenosine FFR from baseline.

Hyperemic peak duration was calculated as the range of time (seconds) comprised from the minimum FFR ± 0.02, whereas time to recovery was defined as the period required to return to baseline FFR from the hyperemic peak (minimum FFR value), reported in seconds.

4. Statistical analysis

All statistical analyses were performed by SPSS Statistics Software 23.0. (SPSS Inc., Chicago, Illinois) Continue variables were represented as mean ± SD, while categorical variables as percentage. Chi-Square and ANOVA test were appropriately used to compare clinical and

Table 1
Main clinical and demographic features in overall population.

Clinical features	*N* = 87
Age (mean ± SD)	67.2 ± 10.7
Male sex (%)	79.3
Weight (mean ± SD)	80.4 ± 17
Hypertension (%)	78.2
Active smokers (%)	13.8
Diabetes mellitus (%)	29.6
Hypercholesterolemia (%)	63.2
Previous MI (%)	23
Previous PCI (%)	62.8
Previous CABG (%)	4.6
Renal failure (%)	18.4
Indication to angiography (%)	
Stable angina/silent ischemia	57.9
ACS	16.1
DCM/arrhythmias	15.8
Concomitant therapy	
ACE inhibitors (%)	26.4
ARBs (%)	33.3
Statins (%)	65.5
Beta blockers (%)	35.6
Nitrates (%)	61.3
Ca-antagonists (%)	27.8
Diuretics (%)	33.3
ASA (%)	69
Clopidogrel (%)	21.8
Multivessel CAD	47.4
Main chemistry parameters (mean ± SD)	
White Blood cells ($*10^3$/dl)	8.1 ± 2.2
Haemoglobin (g/dl)	13.5 ± 1.6
Platelet count ($*10^3$/dl)	236.8 ± 75.5
Creatinine (mg/dl)	1.02 ± 0.39
Glycaemia (mg/dl)	119.2 ± 40.2
Glycosylated Haemoglobin (%)	6.3 ± 1
Total Cholesterol (mg/dl)	154.8 ± 35
HDL-Cholesterol (%)	43.5 ± 13.2
Triglycerides (%)	124.3 ± 73.4
C-reactive protein (mg/dl)	0.9 ± 4
Baseline haemodinamics	
Systolic Blood Pressure (mm Hg ± SD)	133.8 ± 18.3
Diastolic Blood Pressure (mm Hg ± SD)	77.9 ± 11
Heart rate (bpm)	67.3 ± 11.4

angiographic features according to FFR results. Repeated measure ANOVA was performed to compare the duration of peak hyperemia and time to recovery according to the adenosine dose and for different subgroups (defined for positive FFR results, lesion length, left main/proximal-LAD lesions). Linear regression analysis was performed to assess the relationship between hyperemic duration and FFR values or QCA parameters. A p value < 0.05 was considered statistically significant.

5. Results

We included in our study 87 patients, undergoing FFR evaluation on 101 lesions. Baseline characteristics of the included patients are reported in Table 1. High-dose intracoronary adenosine was well tolerated in the majority of patients, with only 6 cases of bradycardia, 10 patients with transient sinus block and 2 cases of transient AV block, spontaneously solved. In case of symptomatic bradycardia or prolonged AV block, with high-dose adenosine, lasting more than the hyperemic peak duration, and therefore potentially interfering with the FFR assessment, the measurement of FFR was interrupted. A positive FFR (≤0.80) was observed in 25 lesions (24.8%). Table 2 displays main angiographic and QCA parameters.

Peak hyperemia duration significantly increased with increasing doses of adenosine (8.4 ± 6.4 vs 10.9 ± 10.6 vs 10.9 ± 6.5 vs 12.4 ± 10.1 vs 13.5 ± 10.3 vs 14.5 ± 12.6 s, $p < 0.001$), as shown in Fig. 1A. No change in major hemodynamic parameters was induced by adenosine at the moment of FFR measurement (Table 1-Supplementary).

Time to recovery significantly increased with increasing doses of adenosine (18.3 ± 7.2 vs 22.3 ± 10 vs 25.7 ± 13.7 vs 28.9 ± 15.4 vs 33.6 ± 20.7 vs 45.2 ± 30.7 s, $p < 0.001$), as shown in Fig. 1B. In addition, the rate of lesions displaying a positive FFR increased with adenosine dose escalation (10.9% vs 13.9% vs 16.8% vs 19.8% vs 21.8% vs 24.8%, $p < 0.001$), as shown in Fig. 2 (Supplementary).

Mean values of hyperemic peak duration, time to recovery and in the measurement of FFR (delta Pd/Pa) were not significantly affected by major clinical factors (Table 2 Supplementary), with the only exception for female gender, that tended to be associated with a reduced hyperemia, in terms of both peak effect and especially for the duration.

The duration of hyperemic peak was not related to QCA parameters or delta P_d/P_a values, as shown in Table 3, on the contrary time to recovery was higher for longer lesions and inversely related with delta P_d/P_a values and reference diameter (Table 3).

Moreover, a similar increase in the maximal hyperemia duration was noted when comparing patients with positive or negative FFR ($p_{between} = 0.87$) or patients with lesions < or ≥20 mm ($p_{between} = 0.92$) and lesions involving left main coronary or proximal left anterior descending artery (LAD) ($p_{between} = 0.07$, Fig. 3A-Supplementary).

Time to recovery, instead, was enhanced in patients with a positive FFR ($p_{between} = 0.003$), and in longer lesions ($p_{between} = 0.006$), but not in the case of proximal disease ($p_{between} = 0.55$; Fig. 3B-Supplementary).

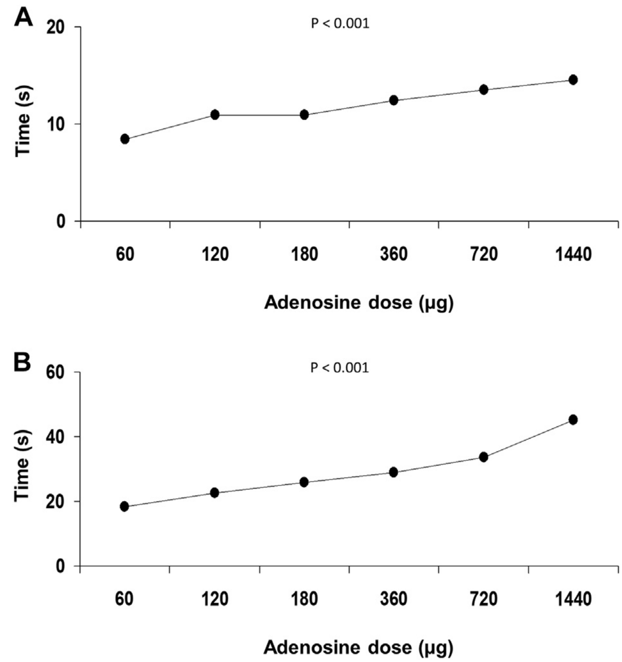

Fig. 1. Mean values of peak hyperemia duration (1A, upper graph) and time to recovery (1B lower graph) with increasing doses of intracoronary adenosine in overall population.

Table 2
Angiographic characteristics in overall population.

Variable	$N = 101$
N of diseased vessels	
1	52.9
2	25.3
≥3	21.8
Target vessel FFR	
LAD (%)	48
Circumflex (%)	14
RCA (%)	25
RI (%)	4
LM (%)	8
RD (mm ± SD)	3.1 ± 0.67
MLD (mm)	1.7 ± 0.42
Percent stenosis (%)	66.4 ± 13.9
Length (mm)	18.3 ± 12.6
ACC/AHA classification	
Type B1 (%)	25
Type B2 (%)	30
Type C (%)	45
Lesion location	
Proximal (%)	45
Mid (%)	42
Distal (%)	13
Calcifications (%)	9
In-stent restenosis (%)	7
Bifurcation (%)	11.2

6. Discussion

The present study represents the first assessment of the impact of high-dose intracoronary adenosine on hyperemia duration in patients undergoing FFR for intermediate coronary stenoses. We identified the increase of the adenosine dose as the only parameter conditioning the duration of the hyperemic peak, that was not, in fact, conditioned by the significance of the coronary stenoses or by quantitative parameters of the lesion. Opposite findings, instead, were observed for the total duration of hyperemia (time to recovery), that was increased by longer lesions, smaller vessels and the amplitude of FFR variation, in addition to adenosine doses.

Even though coronary angiography still represents the gold standard in the diagnosis and treatment of coronary artery disease (CAD), recent evidence has emerged for the importance of assessing the ischemic potential of coronary lesions to better define their prognostic impact. Fractional flow-reserve (FFR) is currently indicated in guidelines as the reference method for the functional assessment of coronary stenoses. In fact, an FFR value below/equal to 0.80 identifies lesions associated with ischemia, with an accuracy of >93% [2,15], therefore impacting on the outcome. In fact, in the large randomized, multicenter FAME trial (Fractional Flow Reserve Versus Angiography for Multivessel Evaluation) [5,16] all types of adverse events were decreased by 30% in the 1st year after PCI, when treatment was guided by FFR rather than by the conventional angiographic assessment of the lesion.

The FFR is defined as the ratio of maximum blood flow in a stenotic artery to maximum blood flow if the same artery is normal assuming

Table 3
Correlation between hyperemia duration and angiographic parameters or fractional flow reserve (FFR) values.

Variable	Peak hyperemia duration		Time to recovery	
	Regression coefficient	*p* Value	Regression coefficient	*p* Value
Adenosine 60 μg				
Lesion length (mm)	−0.05	0.64	0.32	0.05
RD (mm)	0.11	0.32	−0.17	0.31
MLD (mm)	0.02	0.86	−0.27	0.14
delta P_d/P_a	0.15	0.15	- 0.32	0.001
Adenosine 120 μg				
Lesion length (mm)	0.06	0.73	0.15	0.34
RD (mm)	0.07	0.69	−0.41	0.01
MLD (mm)	0.19	0.30	−0.13	0.47
delta P_d/P_a	−0.06	0.58	−0.48	<0.001
Adenosine 180 μg				
Lesion length (mm)	0.08	0.64	0.28	0.08
RD (mm)	−0.09	0.60	−0.26	0.12
MLD (mm)	−0.16	0.38	−0.003	0.89
delta P_d/P_a	−0.09	0.73	−0.40	<0.001
Adenosine 360 μg				
Lesion length (mm)	0.04	0.81	0.34	0.03
RD (mm)	−0.18	0.28	−0.34	0.04
MLD (mm)	−0.26	0.16	−0.09	0.64
delta P_d/P_a	0.09	0.41	−0.41	<0.001
Adenosine 720 μg				
Lesion length (mm)	0.34	0.05	0.31	0.06
RD (mm)	−0.27	0.10	−0.40	0.01
MLD (mm)	−0.30	0.69	−0.09	0.64
delta P_d/P_a	0.09	0.41	−0.33	0.003
Adenosine 1440 μg				
Lesion length (mm)	0.06	0.74	0.17	0.30
RD (mm)	−0.04	0.83	−0.31	0.05
MLD (mm)	−0.08	0.67	−0.03	0.85
delta P_d/P_a	0.01	0.92	−0.24	0.04

that these measurements are obtained when the microvasculature resistance is minimal and constant (maximal hyperemia) [2,16,17]. This ratio is defined by the two pressures, measured by a pressure wire proximally and distally to the stenosis. To measure FFR, however, it is mandatory to achieve maximal hyperemia of the epicardial arteries and microvascular system, as inadequate vasodilatation can result in falsely high FFR values and underestimation of the significance of the lesion.

Adenosine represents the first-choice agent for the induction of hyperemia during FFR, although controversies still exist on the best strategy and dosing for its administration.

Intravenous infusion has been reported to achieve an adequate and prolonged hyperemia, thus allowing a stable and accurate measurement of FFR. Nevertheless, intracoronary adenosine, with increasing dose boli, has demonstrated a similar effectiveness in the induction of hyperemia, offering in addition several practical advantages, therefore now representing the most diffuse strategy in the majority of catheterization laboratories [6,7].

In fact, IC adenosine does not imply the use of a central vein for the infusion and requires much lower amounts of adenosine, thus translating into economic advantages and a reduced risk of systemic effects. In fact, a transient reduction of heart rate and blood pressure or atrioventricular blocks have been reported more frequently with intravenous adenosine, resulting in the need of stopping the protocol and unreliable assessment of the FFR [8,18,19].

Moreover, IC adenosine has been shown to induce faster onset and recovery of hyperemia, that represents the ideal kinetics for rapid and repeated measurements of FFR. Nevertheless, an extremely short duration of hyperemia has been suggested to potentially prevent the correct identification of significant stenoses, additionally not allowing to perform a pullback of the pressure wire in case of multiple tandem stenoses [9,13].

Furthermore, the exact dose of IC adenosine required to induce an adequate maximal hyperemia is still debated. In the first study applying adenosine to human coronary circulation, Wilson et al. reported that very low dose adenosine (2 to 16 μg) allowed to achieve a minimal hyperemia in the majority of patients, reaching about 10% of the vasodilating effect of papaverine, administered as a comparator [6].

A subsequent study, in 457 patients [20] found a significant increase in Doppler flow velocity when increasing adenosine dose from 24 to 35–36 μg, a result that was similarly observed in a canine model [8]. Oppositely, Murtagh et al. [12] documented that a single high dose of 42 μg of adenosine for both the right and left coronary arteries was sufficient to achieve maximum hyperemia and accurate FFR in most patients. More recently, Roether et al. [11] confirmed in 130 lesions undergoing FFR that low (40 to 80 μg) doses of adenosine achieved the same FFR results as higher boli (200 to 400 μg).

On the contrary, Lopez-Palop et al. [21] showed that IC doses of 600 μg revealed a significantly greater percentage of lesions with an FFR < 0.80 compared to lower dose boli or intravenous infusion. Similarly, we previously documented in 50 intermediate lesions [9] assessed with FFR that an escalation to high doses of intracoronary adenosine (up to 720 μg) increased the sensitivity of FFR in the detection of hemodynamically relevant coronary stenosis.

However, few data have been reported so far on the duration of the hyperemic effect with IC adenosine: Wilson et al. [6] reported in 39 patients with normal coronary arteries that the duration of the effect progressively increased from 2 to 16 μg of adenosine. An analogous dose-duration relationship has been recently observed by Adjedj et al. [13] in 30 patients with normal coronary arteries, although not exceeding boli of 500 μg of adenosine. Despite the dose-response curve of coronary flow did not significantly increase beyond doses of 60 to 160 μg, they observed a progressive increase in the duration of the hyperemic peak and in the period required to return at baseline, continuing up to the largest doses of adenosine and not experiencing the same plateau of the effect documented for the coronary flow. Thus, the authors hypothesized that the repeated induction of hyperemia with the boli of adenosine determined a recruitment of adenosine receptors and an up-regulation of other mediators involved in the microcirculatory vasodilatation, thus favoring a more sustained hyperemic effect.

However, no study has so far assessed the impact of adenosine dose on the hyperemic period in patients undergoing FFR for intermediate coronary stenoses, and especially with high-doses of adenosine, that was the aim of present study.

Similarly to the previous reports in normal coronary arteries, we observed a progressive increase in the duration of peak hyperemia and time to recovery to baseline FFR values after the administration of larger boli of adenosine. Moreover, the period of hyperemic peak was not conditioned by the quantitative parameters of the lesion and neither by the functional significance of the stenosis, but was only conditioned by the dose of adenosine.

Oppositely, the total time required for the restoration of baseline FFR values was larger in case of longer stenosis, a higher descent of FFR to lower values and in smaller vessels, where the reduced blood flow could have conditioned a higher persistence of adenosine.

Our data also underline the existence of a fraction of adenosine receptors further subject to recruitment by an escalation in the dosing, therefore remarking the importance of the use of very high-doses of adenosine in order to achieve the maximal hyperemia. In fact, differently from previous studies in normal arteries, in the presence of intermediate lesions, repeated ischemic episodes may contribute to preconditioning and upregulation of adenosine receptors [22], with a larger response to higher doses.

However, the exact mechanisms mediating this increase in the duration of peak hyperemia with adenosine, as much as the potential involvement of other mediators sustaining the vasodilatation, is still poorly defined. Indeed, the existence of a phenomenon of recruitment of adenosine receptors in microcirculatory vessels would offer interesting therapeutic opportunities in patients undergoing coronary revascularization, where such kind of pharmacological stimulation might protect from the ischemia-reperfusion injury induced by the repeated balloon inflation [23]. Nevertheless, whether the same phenomenon could have been induced with an opposite protocol of decreasing-doses of adenosine has never been explored and would potentially deserve further investigation.

We found no impact of clinical variables on the peak and duration of hyperemia, with the only exception of female gender that was associated with reduced hyperemic effect, in terms of peak intensity and duration. The significant impact of female gender on FFR assessment has already been described [24,25]. While the difference in microvascular reactivity and in myocardial mass may help to explain the reduced intensity in hyperemia observed with females, a different distribution of ADA deaminase polymorphisms may potentially contribute to explain the remarkable longer hyperemia observed in man as compared to women [26,27].

Our findings have a high clinical relevance, as the use of higher doses of adenosine could favor the identification of significant coronary lesions and enhance the duration of peak hyperemia, potentially allowing pullback of the wire for the assessment of the FFR in tandem stenoses, as previously reported for intravenous administration. Nevertheless, larger studies are certainly deserved for the validation of such a strategy and for the definition of its safety and potential outcome benefits. In fact, despite some discomfort can have occurred in patients experiencing bradyarrythmias, the very short duration of the symptoms rendered them neglectable in the majority of the cases, with no major safety concern in our cohort of patients. On the contrary, the improvement in the classification of ischemia-related lesions, allowed by a high-dose adenosine strategy, could carry a more relevant clinical impact, potentially conditioning the risk of recurrent cardiovascular events and long-term prognosis.

Limitation

A first limitation can be represented by the inclusion of a heterogeneous, high-risk population, comprising elderly, patients with arterial hypertension, diabetes mellitus, and myocardial infarction, which are known to be associated with a higher rate of microvascular dysfunction, potentially conditioning the vasodilating potential of adenosine. Nevertheless, in present study, the use of FFR instead of coronary flow, which is known to be less dependent on microcirculation, should have allowed to achieve a more accurate assessment of coronary lesions. Moreover, we did not perform a multivariate analysis for evaluating the impact of risk factors or baseline hemodynamic parameters on the measurement of FFR. However, due to the reduced number of FFR ≤ 0.80, we preferred to consider the results as a continuous variable, not applying any potential discriminating cut-off. In addition, we did not compare our measurements with a different hyperemic stimulus, as intravenous adenosine or papaverine, that still represent a gold standard, as a control. However, previous studies have reported a good correlation between IC adenosine boli and other vasodilating agents [8]. Indeed, we did not consider the habitual use of caffeine, which could interfere with the effects of adenosine. However, patients were fasting for >12 h at the time of angiography, including caffeine abstention, which is approximately double the time of caffeine half-life (about 6 h).

In addition, the majority of the lesions assessed did not achieve pathological values of FFR, therefore we cannot tell whether a different impact on hyperemic duration would have been obtained when evaluating more severe coronary stenosis.

A lower occurrence of bradycardia and blocks with high-doses of adenosine was observed in our experience as compared to a previous report [13]. Technical issues, preventing the systemic spread of the effects of adenosine, could have contributed to this observation [13].

Finally, we did not provide any pathophysiological explanation on the mechanisms and molecular funding of our results, therefore certainly requiring further studies to clear out the basis of our findings.

7. Conclusions

The present study shows a progressive raise in the duration of hyperemia, after the administration of increasing doses of intracoronary adenosine for the assessment of FFR. Therefore, considering the potential advantages of a high-dose adenosine protocol, allowing a more prolonged hyperemia and a more precise and reliable measurement of FFR, further larger studies with such FFR strategy should certainly be advocated to confirm its safety and benefits, before its routinely use recommendation.

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Conflict of Interest

The authors report no relationships that could be construed as a conflict of interest.

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