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Intracoronary Adenosine

Dose–Response Relationship With Hyperemia

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ABSTRACT

OBJECTIVES The present study sought to establish the dosage of intracoronary (IC) adenosine associated with minimal side effects and above which no further increase in flow can be expected.

BACKGROUND Despite the widespread adoption of IC adenosine in clinical practice, no wide-ranging, dose-response study has been conducted. A recurring debate still exists regarding its optimal dose.

METHODS In 30 patients, Doppler-derived flow velocity measurements were obtained in 10 right coronary arteries (RCAs) and 20 left coronary arteries (LCAs) free of stenoses >20% in diameter. Flow velocity was measured at baseline and after 8 ml bolus administrations of arterial blood, saline, contrast medium, and 9 escalating doses of adenosine (4 to 500 μg). The hyperemic value was expressed in percent of the maximum flow velocity reached in a given artery (Q/Q_{max}, %).

RESULTS Q/Q_{max} did not increase significantly beyond dosages of 60 μg for the RCA and 160 μg for LCA. Heart rate did not change, whereas mean arterial blood pressure decreased by a maximum of 7% ($p < 0.05$) after bolus injections of IC adenosine. The incidence of transient A-V blocks was 40% after injection of 100 μg in the RCA and was 15% after injection of 200 μg in the LCA. The duration of the plateau reached 12 ± 13 s after injection of 100 μg in the RCA and 21 ± 6 s after the injection of 200 μg in the LCA. A progressive prolongation of the time needed to return to baseline was observed. Hyperemic response after injection of 8 ml of contrast medium reached 65 ± 36% of that achieved after injection of 200 μg of adenosine.

CONCLUSIONS This wide-ranging, dose-response study indicates that an IC adenosine bolus injection of 100 μg in the RCA and 200 μg in the LCA induces maximum hyperemia while being associated with minimal side effects.
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State-of-the-art management of stable coronary artery disease requires both anatomical and functional evaluation (1,2). Although anatomy indicates the presence and location of a stenosis, physiology best assesses its ischemic potential and the anticipated benefit from revascularization. Based on over 2 decades of clinical data (3–6), guidelines have endorsed pressure-derived fractional flow reserve (FFR) as the invasive standard of reference for functional evaluation (1,2).

FFR relates the current maximum blood flow in a stenotic artery to the potential maximum blood flow in the absence of the lesion (7,8). Only under conditions of maximal hyperemia does the pressure ratio between the distal coronary artery and aorta equal the maximum flow ratio between stenotic and normal conditions. Although the first FFR paper employed intracoronary (IC) papaverine, the development of intravenous (IV) adenosine (9) offered a superior safety profile given the occasional torsades de pointes

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with papaverine. Due to its safe and sustained hyperemia, IV adenosine was used exclusively in the landmark FAME (FFR versus Angiography for Multivessel Evaluation) trial (5).

However, for a variety of reasons, IC adenosine has been used more commonly in daily practice and in the clinical published data (10). Despite this widespread adoption of IC adenosine, a recurring debate still exists regarding its optimal dose. Therefore, our study sought to define the dose-response relationship between IC adenosine and its resulting hyperemia.

METHODS

STUDY POPULATION. Patients with stable coronary artery disease undergoing routine diagnostic coronary angiography for a variety of indications were approached for participation between April 2014 and November 2014. All patients had documented coronary atherosclerosis, but the measurements were performed in vessels free of any stenosis with >20% diameter reduction. Each subject provided written informed consent as approved by the institutional ethics committee.

SEE PAGE 1431

INTRACORONARY DOPPLER VELOCITY MEASUREMENT. Following standard diagnostic coronary angiography, 200 μg of intracoronary nitroglycerin was administered to minimize epicardial vasomotor tone. Then a 0.014-inch Doppler wire (FloWire, Volcano Corporation, San Diego, California) was introduced via a 6-F guiding catheter into the target coronary artery and was positioned under fluoroscopy to obtain an optimal and stable flow velocity signal. In all patients, the guidewire was manipulated to place the Doppler sensor facing the oncoming coronary flow.

First, resting Doppler velocity was measured and recorded for at least 1 min to ensure a steady-state baseline. Next, Doppler velocity was measured and recorded for at least 1 min after an 8-ml IC bolus administration of arterial blood, saline at room temperature, contrast medium (iodixanol 270 mg/ml), 9 escalating doses of adenosine (4, 12, 20, 60, 100, 160, 200, 300, and 500 μg), and finally, a mixture of 200 μg of adenosine plus contrast medium. For the sake of this protocol, the adenosine solution prepared by the pharmacy contained 100 μg/ml and the dilutions were adjusted to reach 8 ml for all injections. To obtain optimal flow velocity tracings, we elected not to flush the "dead space." This allowed the duration of interruption of the aortic pressure signal to be minimized (approximately 1.5 to 2 s). At the end of the measurements performed after administration of contrast material, the remaining contrast was removed from the catheter prior to the next injection.

After each IC administration, no further injection was performed for 2 min to allow the Doppler velocity to return to its baseline value. Heart rhythm and hemodynamic parameters of heart rate and mean aortic pressure were recorded for each Doppler velocity measurement.

Figure 1 depicts a typical Doppler velocity tracing and indicates the indexes measured for each IC bolus. We defined the plateau hyperemic period as the time during which flow velocity reached at least 95% of its maximum. The time needed to come back to baseline was defined by the return to <10% above the starting value.

MODEL FOR FFR DEPENDENCE ON ADENOSINE DOSE. To translate the IC adenosine dose into its effect on FFR, a model based on standard coronary physiology linked the degree of hyperemia to the relative distal coronary pressure (P_d/P_a). It started with the classic pressure loss versus flow relationship for a vascular stenosis (11):

$$\Delta P = P_a - P_d = C_v \times Q + C_e \times Q^2$$

then transformed it into a more portable, unitless form:

$$P_d/P_a = 1 - (C_v \times Q_r/P_a) \times (Q/Q_r) - (C_e \times Q_r^2/P_a) \times (Q/Q_r)^2$$

where C_v and C_e are the viscous and expansion coefficients that depend on vessel and stenosis geometry, P_d is the distal coronary pressure, P_a is the proximal coronary pressure, Q_r is the resting flow, and Q is the current flow. At rest, $Q/Q_r = 1$ and P_d/P_a is termed rest P_d/P_a; at maximum hyperemia, Q/Q_r is termed the coronary flow reserve (CFR) and P_d/P_a = FFR.

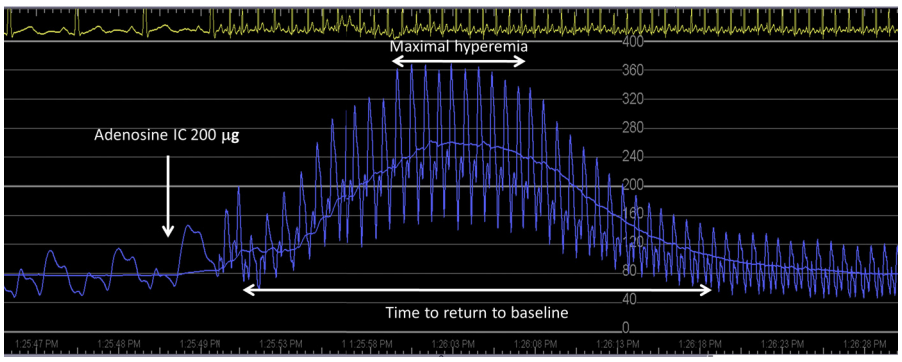
The specific values chosen for rest Pd/Pa = 0.93 and FFR = 0.79 were based on the median values from 1,593 lesions assessed by pressure wire (12), and CFR = 2.0 was based on the weighted average from 1,118 lesions assessed by Doppler wire (13). Using these values in the model yielded a relationship between P_d/P_a and percentage of maximum hyperemia starting at 0% (rest, $Q/Q_r = 1$) and ending at 100% (hyperemia, Q/Q_r = CFR).

STATISTICAL ANALYSIS. Analyses were performed using Prism GraphPad version 5.0 (GraphPad Software, San Diego, California) and R version 3.1.2 (R Foundation for Statistical Computing, Vienna,

ABBREVIATIONS AND ACRONYMS

AV = atrioventricular
FFR = fractional flow reserve
IC = intracoronary
IV = intravenous
LCA = left coronary artery
RCA = right coronary artery

FIGURE 1 Example of a Typical Doppler Velocity Tracing and Illustration of the Various Measurements Performed in the Present Study



See text of the Methods section for the definition of these measurements. IC = intracoronary.

Austria) with standard summary statistics. Applicable tests were 2-tailed, and $p < 0.05$ was considered statistically significant.

An analysis of variance (ANOVA) model with mixed effects (to account for repeated measurements from the same subject) tested for a significant interaction between contrast and adenosine in their 2-by-2 factorial design (baseline, contrast, 200 μg adenosine, and both together). Similarly, an ANOVA mixed-effects model compared Doppler velocity among the 3 viscosity conditions (saline, contrast, and blood). If an overall ANOVA p value was significant, then a Tukey all-pair comparison was applied to determine which conditions provided a different response.

Dose-response analysis was performed in 2 ways (14). First, an ANOVA mixed-effects model with potential Tukey all-pair comparison analyzed the flow response over 10 conditions (baseline plus 4, 12, 20, 60, 100, 160, 200, 300, and 500 μg IC adenosine). Flow response was assessed by the normalized flow, a unitless ratio Q/Q_{max}, where Q equals the Doppler velocity and Q_{max} represents the largest observed Doppler velocity in response to IC adenosine. Hemodynamic response assessed both heart rate and mean arterial pressure.

Second, a model-based approach used an explicit formula for the relationship between IC adenosine dose and normalized flow (Q/Q_{max}). Because adenosine follows an enzymatic reaction to produce hyperemia, it makes physiological sense to employ the Michaelis-Menten model for enzyme kinetics (14). Two minor modifications were necessary to customize the general model for the specifics of IC adenosine hyperemia. Because Q/Q_{max} approaches a maximum value of 1 at high/infinite adenosine concentration and equals >0 at baseline due to endogenous adenosine in the coronary circulation, our customized model was

$$Q/Q_{max} = (\text{dose} + \text{offset})/(k + [\text{dose} + \text{offset}])$$

where the constant "k" describes when $Q/Q_{max} = 50\%$ and the constant "offset" adjusts for baseline, physiological adenosine. The variable "dose" equals the IC adenosine amount in μg. The R package lme4 was used for nonlinear fitting of the model to the data. Because a mixed effects model (to account for repeated measurements from the same subject) produced similar results to a fixed effects model (not accounting for repeated measurements from the same subject), results and figures employ the fixed effects model given more robust and accepted techniques for its confidence intervals.

RESULTS

The characteristics of the 30 subjects are summarized in Table 1. One subject received only 3 doses of IC adenosine (4, 12, and 20 μg), and was excluded from the ANOVA dose-response analysis but included in all other analyses. Although all vessels were free of any visible stenosis, the CFR varied from 1.42 to 4.88. The baseline flow velocity was higher in patients with a low CFR than in patients with a high CFR. (29 ± 11 cm/s vs. 16 ± 7 cm/s; $p < 0.001$). Hyperemic flow velocity was similar in both groups (61 ± 26 cm/s vs. 55 ± 17 cm/s; p = NS).

DOSE-RESPONSE ANALYSIS. Figure 2 summarizes the dose-response relationships and also displays the incidence of high-grade atrioventricular (AV) block for each dose of IC adenosine. One subject received only 20 μg because the quality of the flow

TABLE 1 Patient Characteristics and Medications (n = 30)

Patient demographics	
Age, yrs	65 ± 11
Male	26 (87)
Body weight, kg	77 ± 15
Height, cm	171 ± 9
Hypertension	17 (59)
Hypercholesterolemia	18 (62)
Diabetes mellitus	4 (14)
Smoking	7 (24)
Prior PCI	10 (34)
Prior myocardial infarction	1 (3)
Medications	
Aspirin	24 (80)
Clopidogrel	9 (30)
Ticagrelor	6 (20)
Statin	23 (77)
Beta-blockers	10 (33)
Calcium-channel inhibitors	8 (27)
Angiotensin-converting enzyme inhibitors	10 (33)
Angiotensin II receptor blocker	6 (20)
Nitroglycerin	1 (3)
Oral antidiabetic drugs	1 (3)
Insulin	3 (10%)

Values are mean ± SD or n (%).
PCI = percutaneous coronary intervention.

velocity signal deteriorated and could not be restored. All episodes of AV block were transient, and none required specific treatment. However, episodes of transient AV block occurred at doses higher than 100 μg, precluding the administration of higher amounts than 300 μg of IC adenosine in 5 (17%) patients.

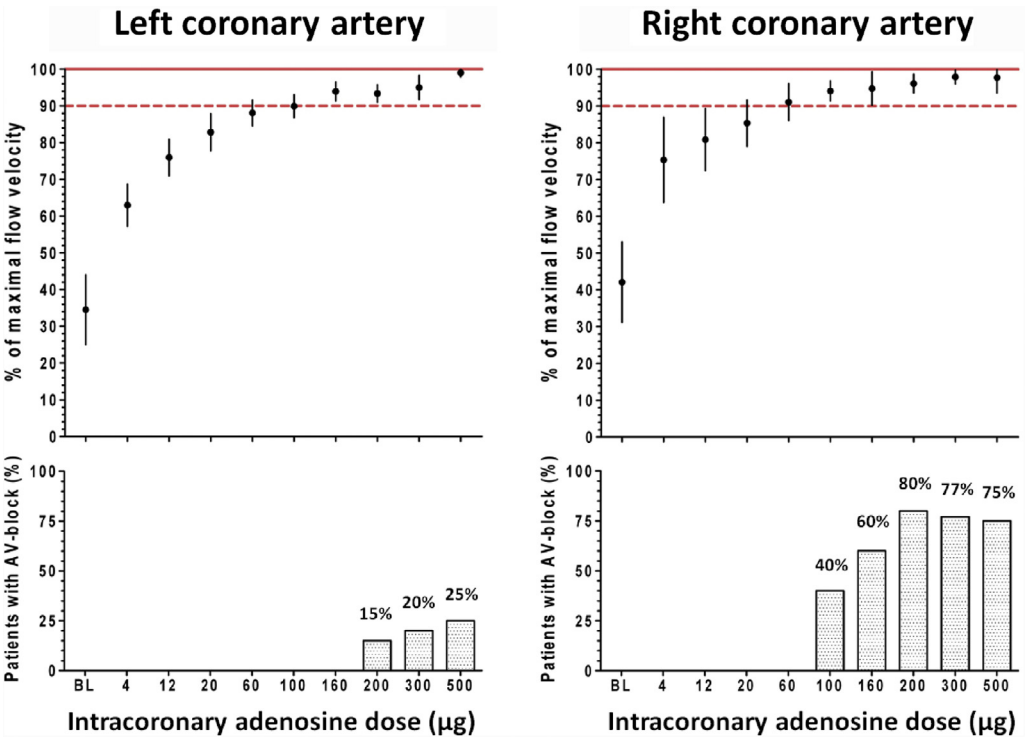
Significant differences in normalized flow velocity (Q/Q_{max}) existed via mixed effects ANOVA analysis for all vessels together and for the right coronary artery (RCA) and left coronary artery (LCA) separately ($p < 0.001$ for all). Table 2 displays the p values from the subsequent Tukey paired comparisons on a per-vessel basis. For the RCA, Q/Q_{max} did not increase significantly at any higher dose than 60 μg. For the LCA and all vessels together, Q/Q_{max} did not increase significantly at any higher dose than 160 μg.

Figure 3 shows the mean duration of plateau hyperemia, the time needed to return to baseline, as well as the effect on heart rate and blood pressure. For a bolus of 100 μg in the RCA, plateau hyperemia lasted 12 ± 13 s. For a bolus of 200 μg in the LCA, plateau hyperemia lasted 21 ± 6 s. The time needed for the flow velocity to return to baseline increased progressively with the IC adenosine dose. In 10% of patients, the flow velocity did not return to baseline within 2 min after at least 1 IC adenosine administration. Although there was no significant change in heart rate among doses of IC adenosine (ANOVA $p = 0.48$), mean arterial pressure was altered (ANOVA $p = 0.001$). Tukey all-pair comparison of mean arterial pressure showed significant decreases with all doses of IC adenosine compared with baseline conditions (all $p < 0.05$) except for 4 μg ($p = 0.24$), but not between adenosine doses (all $p > 0.60$). Mean arterial pressure decreased with IC adenosine by about 6% to 7% from baseline on the basis of the mixed effects model.

EFFECT OF BLOOD, SALINE, AND CONTRAST MEDIUM. Doppler flow velocity varied among 8-ml IC boluses of arterial blood, saline, and contrast ($p < 0.001$ by ANOVA), and all pairwise comparisons were significant ($p < 0.001$ for blood and contrast; $p = 0.041$ for saline and blood; and $p = 0.013$ for saline and contrast). As shown in Figure 4, contrast increased Doppler flow velocity the most (+38 ± 52% over blood, $p < 0.001$ by paired *t* test; +17 ± 28% over saline, $p = 0.019$) and saline was superior to blood (+21 ± 43%, $p = 0.008$). Flow velocity after contrast medium reached 65 ± 36% of the value reached after 200 μg of adenosine. Heart rate and mean arterial pressure did not change significantly after administration of arterial blood, saline, or contrast ($p = 0.19$ for pressure and $p = 0.37$ for heart rate by ANOVA). An 8-ml bolus injection of 200 μg adenosine mixed with contrast medium showed no hyperemic synergy, nor did it prolong hyperemia ($p = 0.14$ for interaction term in ANOVA model).

DOSE-RESPONSE MODEL AND EFFECT ON FFR. Figure 5 (left panel) shows both the raw Q/Q_{max} data and the best-fit models for each artery. Greater flow increases were observed in the RCA than the LCA for the same IC adenosine dose. No important differences existed between model parameters from a fixed effects model (RCA k = 2.84 μg, 95% confidence interval [CI]: 2.05 to 3.93, and offset = 2.21 μg, 95% CI: 1.40 to 3.56; LCA k = 3.95 μg, 95% CI: 3.33 to 4.68, and offset = 2.46 μg, 95% CI: 1.89 to 3.22) and a mixed effects model (RCA k = 3.05 μg, 95% CI: 1.81 to 4.29, and offset = 1.94 μg, 95% CI: 1.43 to 2.46; LCA k = 4.07 μg, 95% CI: 4.02 to 4.11, and offset = 2.26 μg, 95% CI: 2.22 to 2.29). Based on these dose-response models, IC adenosine reaches 80% of maximum hyperemia at 9 or 13 μg (RCA vs. LCA), 90% of maximum hyperemia at 23 or 33 μg, 95% of maximum hyperemia at 52 or 73 μg, and 99% of maximum hyperemia at 279 or 388 μg. Figure 5 (right panel) combines this dose-response relationship with a physiological model linking flow increase to the observed FFR. At 0% hyperemia (baseline conditions), $P_d/P_a = 0.93$,

FIGURE 2 Intracoronary Adenosine Dose-Flow Relationship



(Top) Dose-response data for the right coronary artery (RCA) **(left panel)** and the left coronary artery (LCA) **(right panel)**. The data are expressed as the percent of maximum for each patient (Q/Q_{max}) at each dose of intracoronary (IC) adenosine. The **error bars** represent the 95% confidence intervals for each value. The p values from the subsequent Tukey paired comparisons are given in Table 2. **(Bottom)** The **bars** represent the percent of patients in whom high-grade atrioventricular (AV) block occurred with that dose of adenosine. BL = baseline.

whereas at 100% hyperemia (maximum), FFR = 0.79. IC adenosine doses between 60 and 200 μg provide an FFR within 0.01 of the value at 100% hyperemia.

DISCUSSION

The present dose-response study of IC adenosine on intracoronary Doppler flow velocity suggests that the optimal bolus to induce maximal hyperemia consistently and safely is 60 to 100 μg for the RCA and 160 to 200 μg for the LCA. Although sequential doses above 60 μg for the RCA and 160 μg for the LCA showed no statistically significant further increase in flow (Table 2), the entire dose-response continuum (Figures 2 and 5) demonstrates a reduction in inter-individual variability around 100 to 200 μg, respectively. Additionally, an undefined proportion of adenosine can potentially spill into the aorta during IC administration, further implying the need for a safety margin. Notably, we observed an increased incidence of AV block at high doses (Figure 2). The occurrence of a transient AV block creates an artifact on the tracings. Albeit always transient, such episodes of AV block are disruptive during a catheterization procedure and might cloud the accuracy of the measurements, thus arguing for modest yet sufficient doses. Therefore, our suggested dose of 100 μg for the RCA and 200 μg for the LCA balances hyperemia versus side effects.

The present data confirm that the administration of the IC adenosine does not induce any discomfort in patients or any clinically significant changes in heart rate, blood pressure, or ST-T segment (15). Even at low doses (4 and 12 μg), a marked increase in flow velocity was observed in all patients, eliminating the possibility of any "resistance to adenosine." The plateau phase of maximal hyperemia at suggested optimal doses averaged for the RCA and the LCA is 12 ± 13 s and 21 ± 6 s, respectively, which is long enough to make accurate measurements, but too short to perform pull back recordings. The time to return to baseline was 38 ± 20 s for the RCA and 77 ± 10 s for the LCA, after administration of 100 and 200 μg, respectively. These

TABLE 2 Dose-Response Analysis for Q/Q_{max} Showing Pairwise p Values Comparing Various IC Adenosine Doses (From Baseline to 500 μg) for the RCA and LCA

	4 μg	12 μg	20 μg	60 μg	100 μg	160 μg	200 μg	300 μg	500 μg
RCA									
Baseline	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
4 μg		0.74	0.041	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
12 μg			0.94	0.055	0.002	0.004	<0.001	<0.001	0.008
20 μg				0.71	0.13	0.19	0.019	0.001	0.15
60 μg					0.99	1.00	0.83	0.35	0.93
100 μg						1.00	1.00	0.93	1.00
160 μg							1.00	0.91	1.00
200 μg								1.00	1.00
300 μg									1.00
LCA									
Baseline	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
4 μg		<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
12 μg			0.007	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
20 μg				0.23	0.010	<0.001	<0.001	<0.001	<0.001
60 μg					0.98	0.11	0.28	0.004	<0.001
100 μg						0.77	0.95	0.15	0.011
160 μg							1.00	0.99	0.68
200 μg								0.91	0.38
300 μg									1.00

Pairwise p values via analysis of variance then Tukey all-pair comparison.
IC = intracoronary; LCA = left coronary artery; Q/Q_{max} = percentage of maximum flow velocity; RCA = right coronary artery.

durations of action permit reliable yet quickly repeated measurements. Akin for FFR measurements, we did not flush the dead space to avoid the "flush artifact" on the aortic pressure tracings. This implies that the actual dosage of adenosine reaching the coronary ostium is approximately 15% lower than the amount leaving the syringe.

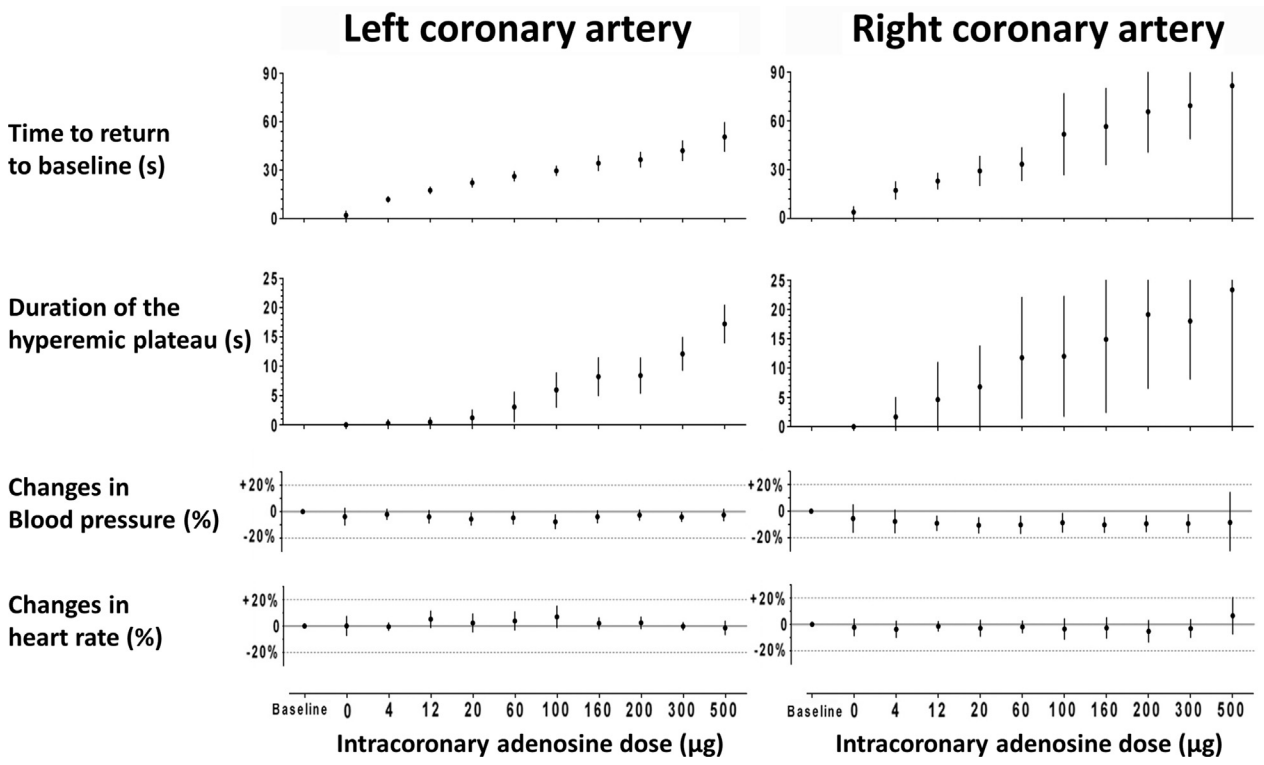
Because of the relatively short-lasting action of IC adenosine, we recommend, in case of FFR measurements, to record at least 10 beats at rest, followed by a short lasting bolus injection, immediate reconnection of the aortic pressure signal, and a total duration of the recording of 60 s. This recording should then be repeated in the exact same manner and stored. This standardization of the recordings is important to allow for their interpretation and review. With increasing dosages, we also observed a prolongation of the time needed to return to baseline. At higher dosages, coronary blood flow velocity did not return to baseline despite waiting for several minutes. It may be speculated that repetitive episodes of hyperemia (and of ischemia) lead to an up-regulation of the adenosine receptors or of other mediators involved in the molecular pathways leading to microvascular dilation. The maintenance of a higher flow after several episodes of hyperemia questions the value of physiological lesion assessment *at rest* soon after coronary intervention without induction of maximal hyperemia.

EFFECTS OF ADENOSINE ON FLOW VELOCITY VERSUS ON FFR. Because of curvilinear relationships between IC adenosine dose and Doppler flow velocity (Figure 2) and between the degree of maximum hyperemia and Pd/Pa as known from fundamental stenosis physiology, the net effect produces clinically similar FFR values for even modest doses of IC adenosine, as will be detailed in this section.

Recent work has determined that the test/retest repeatability of FFR has an SD of approximately 0.02 (16). Thus, FFR differences <0.02, as seen in Figure 5, for adenosine doses above about 40 μg are smaller than the variability of the measurement itself. Interpreting the dose-response curve from this perspective, changes in flow response for IC adenosine doses >40 μg are smaller than the intrinsic variability of the FFR measurement. As such, although large studies might show a statistically significant difference in FFR for higher doses of IC adenosine, test/retest repeatability indicates that these differences are not clinically significant.

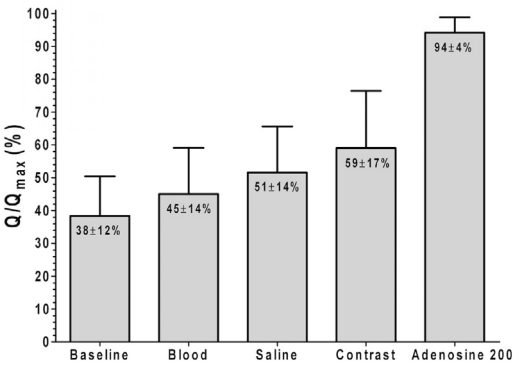
On a related point, earlier work measured FFR using doses of IC adenosine in the 30 to 60 μg (left) and 20 to 30 μg (right) range (17). For example, the pivotal DEFER (FFR-based DEFERal versus performance of coronary angioplasty) trial employed IC adenosine in 42% of cases, delivering 20 μg (left) and 15 μg (right) (4). Our current dose-response relationship in Figure 5 (left panel) clarifies that 15 μg achieves at least 80%

FIGURE 3 Effect Duration and Hemodynamic Effects of Increasing Dosages of Intracoronary Adenosine



Dose-response summary data for duration of hyperemic plateau (seconds), time needed to return to baseline flow velocity value (seconds), systemic blood pressure (mm Hg), and heart rate (beats/min). Data are given as average ± SD for each dose of intracoronary (IC) adenosine.

FIGURE 4 Hyperemic Effects of Intracoronary Injection of Arterial Blood, Saline and Contrast Medium as Compared to Adenosine

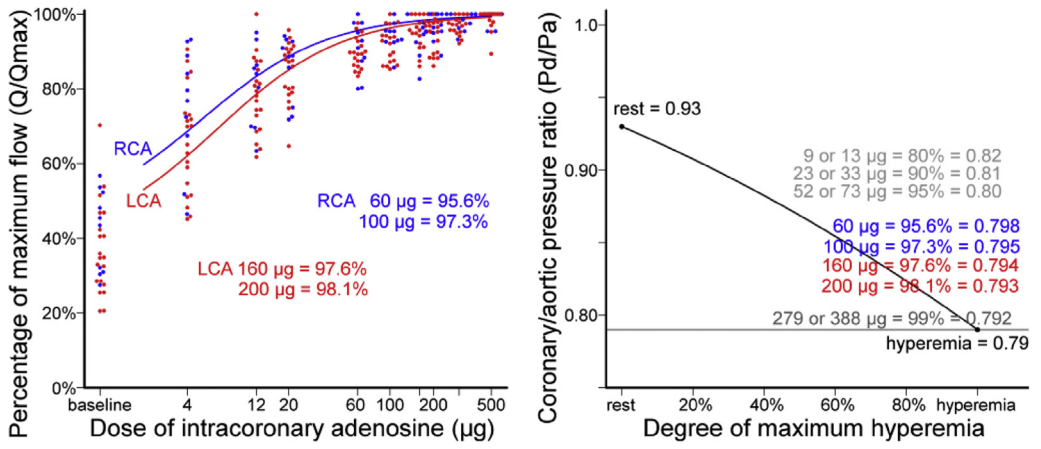


Effect on coronary Doppler flow velocity from the administration of an 8-ml bolus of arterial blood at body temperature, saline at room temperature, and contrast medium at room temperature. Data are given as average ± SD of the percentage of maximum flow velocity for each patient (Q/Q_{max}).

and 35 μg at least 90% of maximum hyperemia. As translated by Figure 5 (right panel), these levels of hyperemia would result in typical FFR measurements within 0.02 to 0.03 of higher doses. Correspondingly, DEFER found average FFR values using IC adenosine that were larger than but still within 0.02 of IV adenosine, albeit in distinct patients (IC vs. IV adenosine: reference group 0.58 vs. 0.56; performance group 0.88 vs. 0.86; and deferral group 0.86 vs. 0.87, all not statistically significant) (4). In agreement with our current findings, these small differences in FFR were neither clinically nor statistically significant in the DEFER trial.

COMPARISON WITH EXISTING PUBLISHED DATA. Although studies of IC adenosine doses and Doppler flow velocity exist in the published data, no prior study has created such a detailed and extensive dose-response curve in patients. The original work applying adenosine to the human coronary circulation recorded Doppler velocity response in 33 arteries for a lower range of IC adenosine from 2 to 16 μg only, using IC papaverine as the comparator (15). They

FIGURE 5 Dose-Response Model and its Effect on FFR



The **left panel** plots the Q/Q_{max} for each patient as **solid dots** with their best-fit line (**red** for the LCA and **blue** for the RCA) as a function of the IC dose on a logarithmic x-axis (baseline placed at 1 µg). Note that overlap occurs among points at high doses. The **right panel** translates the dose-response curve into the observed fractional flow reserve (FFR) as a function of adenosine dose (RCA or LCA) for a typical lesion. This theoretical model shows that at 60 to 100 µg in the RCA and at 160 to 200 µg (colors match **left panel**), the observed FFR is within 0.01 of its minimum value. In addition, at dosages above 23 µg, the observed FFR is within 0.02 of its minimal value. Abbreviations as in Figure 2.

observed that 16 µg produced hyperemia within 10% of papaverine in 90% of patients, consistent with our findings of a large increase in flow at even low doses of IC adenosine but submaximal in some cases. Notably, we systematically explored a much wider range of IC adenosine from 4 to 500 µg.

A smaller study of 21 patients compared Doppler velocity between 30 and 50 µg and found no difference in hyperemic effect (18). By distinction, we systematically injected IC adenosine up to 500 µg and employed a specific dose-response model in our analysis. A larger study of 457 patients found a significant increase in Doppler flow velocity, albeit between 2 modest doses of IC adenosine (average 24 µg vs. 35 to 36 µg) (19).

EFFECT OF SALINE AND CONTRAST MEDIUM. Finally, we found that IC injections of contrast medium and saline increased Doppler flow velocity, with contrast's being more potent. Extensive prior work has demonstrated the hyperemic effect of contrast medium, but mainly used older agents different from modern, low osmolality formulations. Whether current contrast agents produce meaningful hyperemia for FFR measurement remains the subject of ongoing study (CONTRAST trial, NCT02184117). We note only that our results imply that both saline and contrast produce some degree of hyperemia, presumably partially via transient hypoxia from replacement of oxygenated blood and partially by stimulating endothelial paracrine pathways.

STUDY LIMITATIONS. We did not measure FFR simultaneously due to less robust technology for continuous and combined pressure/flow measurements, but we instead used standard physiology to relate changes in flow to changes in pressure loss. A number of additional limitations have to be taken into account. Although our sample size was modest, it was of comparable magnitude to prior dose-response work using IC adenosine and Doppler sensors (15,18). Although each patient served as his or her own control to generate a dose-response curve for IC adenosine, we did not measure the Doppler flow velocity response to IV adenosine or IC papaverine. Yet, several other studies have shown that IV and IC adenosine provided similar degrees of hyperemia (15,20,21). Additionally, we did not explore IC adenosine doses above 500 µg, although our results suggest diminishing returns from such ultra-high levels. Also, the scientific rigor of the study would have been increased by a randomization of the various dosages of adenosine. Finally, only "normal" arteries were studied. Yet, the complete dose-response effect on flow can be investigated only in vessels with minimal or no epicardial resistance. In "critical" stenoses, when the microvascular resistance reserve is already exhausted at rest to compensate for the high epicardial resistance, the flow cannot increase further.

Therefore, an FFR model is suboptimal to investigate the full range of effects of adenosine.

CONCLUSIONS

On the basis of the present dose-response study of IC adenosine and Doppler flow velocity, we recommend dosages of 100 μg in the right coronary artery and 200 μg in the left coronary artery. These dosages do not induce any significant side effects, achieve >95% of maximum hyperemia, and are clinically indistinguishable from higher dosages when applied for FFR measurements.

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PERSPECTIVES

WHAT IS KNOWN? Intracoronary adenosine is often used to induce hyperemia, but there is a persistent debate about its optimal dosage.

WHAT IS NEW? This dose-response study with flow measurements indicates that IC bolus injections of adenosine of 100 μg in the RCA and 200 μg in the LCA induce maximum hyperemia without affecting systemic hemodynamics and with minimal side effects.

WHAT IS NEXT? These findings should help to standardize the measurements and recordings of coronary physiologic indexes both in clinical practice and in the setting of clinical trials.

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