

EDITORIAL COMMENT

Intracoronary Adenosine for Maximal Hyperemia

Less Is More...More or Less?*

Jamie Layland, MBChB, PhD,[†] Colin Berry, MBChB, PhD[‡]



After its introduction to the clinical arena more than 20 years ago (1,2), fractional flow reserve (FFR) has become an increasingly utilized tool for optimizing revascularization decisions in patients with coronary artery disease (3-6). However, despite the evidence base from large randomized trials, registries, and clinical guideline recommendations (7), FFR is not universally adopted. Some of the reasons for this discord relate to cost, difficulty interpreting FFR in certain clinical situations, as well as issues relating to the drugs required for the procedure. Such issues have prompted other researchers to look to 'drug free' indexes to assess stenosis severity (8).

The use of FFR is predicated on the induction of maximal hyperemia such that measures of pressure become proportional to coronary blood flow (9). Adenosine is one of the most commonly used drugs to achieve hyperemia in the catheter laboratory. Both intracoronary (IC) and intravenous (IV) methods of delivering adenosine are capable of producing hyperemia, although the IV method is regarded as the current gold standard (10). However, although the IV route poses several practical advantages, such as the potential to perform a pressure wire pullback in situations of tandem lesions or diffusely diseased coronary arteries, IV adenosine administration can be

more time-consuming and costly due to the larger amount of adenosine required for FFR assessment. Thus, the IC route is potentially a more attractive option in the assessment of FFR.

Earlier studies had suggested a maximal IC dose of adenosine of 16 μg for the left coronary artery and 12 μg for the right coronary artery (11) with increasing doses of 2 orders of magnitude to ensure maximal vasodilation (12). These protocols were challenged by animal data suggesting that higher doses of adenosine may be needed to achieve maximal hyperemia (13) and clinical studies that suggested that standard adenosine dosing failed to achieve maximal hyperemia compared with papaverine and IV adenosine (10,14). Current recommendations for IC adenosine dosing are 40 μg in the right coronary artery and 60 μg in the left coronary artery, increasing the doses incrementally by 30 μg to a maximum of 150 μg (15).

A key and contentious question remaining is whether the IC route is as efficacious at producing maximal hyperemia compared with the IV route. In general, IC adenosine has been associated with lower efficacy compared with IV adenosine (14,16). However, most studies performed to date have used differing methodologies and adenosine doses. Most recently, Leone et al. (17) examined the response of IC adenosine compared with IV adenosine using increasing adenosine doses. Although there was a reduction in FFR at higher IC doses, the absolute difference (and clinical significance) was negligible (60- μg mean FFR, 0.88 vs. 300- μg mean FFR, 0.87). Importantly, as the IC dose increased, the incidence of atrioventricular (AV) block increased (nearly 25% of patients). Thus, it appears from studies to date that although the IV route of administration has a greater efficacy for achieving maximal hyperemia compared with the conventional IC dosing, how important this

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From the [†]St. Vincent's Hospital, Fitzroy, Victoria, Australia; and the [‡]Golden Jubilee National Hospital, University of Glasgow, Glasgow, United Kingdom. Dr. Berry is a consultant and speaker for and has received a research grant from St. Jude Medical; and is a speaker for Pfizer, Bristol-Myers Squibb, AstraZeneca, and Shire. Dr. Layland has reported that he has no relationships relevant to the contents of this paper to disclose.

is in the clinical setting is debatable. Moreover, the use of IV adenosine is associated with more systemic side effects than the intracoronary route such as flushing, chest pain and dyspnea and these unwanted effects are some of the reasons why clinicians do not want to use adenosine (18). However, due to conflicting evidence, clinicians are often reluctant to use IC adenosine due to a perceived lack of confidence in its ability to produce maximal hyperemia.

SEE PAGE 1422

In this issue of *JACC: Cardiovascular Interventions*, Adedj et al. (19) assess the use of intracoronary adenosine in a small-dose response study (19). The authors should be congratulated for a well-performed study adding valuable and reassuring data to the use of IC adenosine for the attainment of hyperemia. Using increasing doses of IC adenosine (up to 500 µg), the group measured pressure and flow velocity in patients with near-normal coronary arteries. Using a dose-response and physiological model-based approach, an optimal cutoff dose for IC adenosine was attained, balancing the incremental effect on hyperemia with the risk of AV block. The group

surmised that the optimal dose for the right coronary artery was 100 µg and 200 µg for the left coronary artery to provide an FFR within 0.01 of the value at 100% hyperemia. Of interest, only doses >100 µg were associated with AV block.

Although these results are informative, the study is limited by the small sample size and the use of a normalized flow velocity in relation to the highest dose of adenosine (500 µg) as the reference standard. An alternative method would have been to also use IV adenosine and use this as a reference standard. Despite these minor shortcomings, the study adds to the weight of evidence that IC adenosine is adequate for achieving a sufficient hyperemic response in most patients. Furthermore, due to its ease of use and lack of side effects for patients, it may be the preferred route of delivery when more complex assessments relating to diffuse disease, tandem stenosis, and microvascular function are not required.

REPRINT REQUESTS AND CORRESPONDENCE: Dr. Jamie Layland, Peninsula Health, Hastings Road, Frankston, Victoria 3199, Australia. E-mail: jlayland@phcn.vic.gov.au.

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