

SCIENTIFIC LETTER

Adequate intracoronary adenosine doses to achieve maximum hyperaemia in coronary functional studies by pressure derived fractional flow reserve: a dose response study

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Coronary pressure derived fractional flow reserve (FFR) is an increasingly used invasive index of the functional significance of coronary lesions. FFR expresses maximum achievable blood flow to the myocardium, supplied by a stenotic artery, as a fraction of normal maximum flow.^{1,2} Achievement of maximal hyperaemia is essential for calculation of FFR. Intracoronary adenosine is widely used to obtain maximal hyperaemia. Although standard doses of intracoronary adenosine to achieve maximal hyperaemia have been well established in previous studies³ (15–40 µg left coronary artery, 10–30 µg right coronary artery), doubts about maximal hyperaemia achieved with these doses have led to the empirical use of higher than standard doses in clinical practice.^{4,5} The aim of this study was to analyse the effects of incremental doses of intracoronary adenosine on FFR measurements.

METHODS

Patients with angiographically intermediate lesions (visual percentage diameter stenosis 50–75%) in a principal coronary artery and indication for study with pressure wire to determine functional significance of lesions were included. The study started on November 2001 and 50 lesions were prospectively and consecutively included. Informed consent was obtained from all patients.

Coronary pressure measurements were performed using a 0.014 inch pressure guidewire (PressureWire, Radi Medical Systems, Uppsala, Sweden), according to a previously described technique.¹ Special attention was paid to avoiding arterial pressure wave damping, unselective catheterisation of coronary ostia, and variation in the position of the pressure guide wire.

Dose administration protocol was started after an initial intracoronary injection of 200 µg of glyceryl trinitrate. Incremental doses of intracoronary adenosine of 0, 15, 30, 60, 90, 120, 150, 180, and 210 µg were tested. Each adenosine bolus was administered diluted in 5 ml of normal saline and was immediately followed by a 10 ml flush of normal saline as transport medium. Immediately after each dose administration, the Pd/Pa ratio was determined from beat-to-beat mean signal. Pd represents the mean coronary pressure distal to the stenotic segment studied measured by pressure wire, and Pa represents the mean aortic pressure simultaneously measured by the guiding catheter. Each dose was given twice and the Pd/Pa ratio value was taken as the average of both measurements. The minimum FFR achieved for each lesion was taken as the nearest approximation to correct FFR (when maximal hyperaemia is obtained) and called true FFR. Comparisons between Pd/Pa ratio value observed with standard doses and true FFR obtained in each lesion were obtained.

Differences between groups were tested using Student's *t* statistic. A probability value of $p < 0.05$ was considered significant. SPSS for Windows, version 11.0, was used for the statistical test.

RESULTS

Sixty lesions in 56 patients were studied. Seventy one per cent of procedures were performed in patients with an acute coronary syndrome. Forty nine (82%) "de novo" and 18 (11%) in-stent restenosis lesions were studied (mean (SD) diameter stenosis 56.11 (8.6)%). The vessels studied were anterior descending (67%), circumflex (15%), and right (18%) coronary arteries. Forty three lesions were medically treated (72%) and 17 (28%) were revascularised according to FFR results.

Seventeen lesions (23%) reached a mean value of FFR < 0.75 with some pairs of doses of adenosine. The mean (SD) of difference between Pd/Pa ratio with the 15 µg dose and true FFR was 0.04 (0.03).

The true FFR value was observed only in 17% of lesions with 15 µg of adenosine and 23% with 30 µg. In 17% of patients 210 µg was necessary to reach the true FFR value. Nine lesions (14%) that achieved an initial Pd/Pa value > 0.75 with 15 µg of intracoronary adenosine had a decrease in Pd/Pa value to < 0.75 with subsequent incremental doses of adenosine. None of 31 lesions with a Pd/Pa value ≥ 0.90 with 15 µg dose achieved a Pd/Pa value < 0.75 with incremental doses. Nine (31%) of 29 lesions with a Pd/Pa value between 0.76 and 0.85 with a 15 µg dose showed a significant Pd/Pa ratio value < 0.75 with higher doses (8 of 9 lesions (89%) if the Pd/Pa ratio value with 15 µg was between > 0.75 and 0.79) (fig 1).

There were no adverse events related to adenosine administration except for transient asymptomatic atrioventricular blocks immediately after the adenosine bolus was administered.

DISCUSSION

This study shows that standard doses of intracoronary adenosine do not achieve maximal hyperaemia in the majority of lesions. Although the mean absolute value of difference between low and high doses was small (0.04), this difference was significantly higher (0.07) in lesions with a borderline (≤ 0.80) Pd/Pa ratio value.

Abbreviations: FFR, fractional flow reserve; Pa, mean aortic pressure simultaneously measured by the guiding catheter; Pd, mean coronary pressure distal to the stenotic segment studied measured by pressure wire

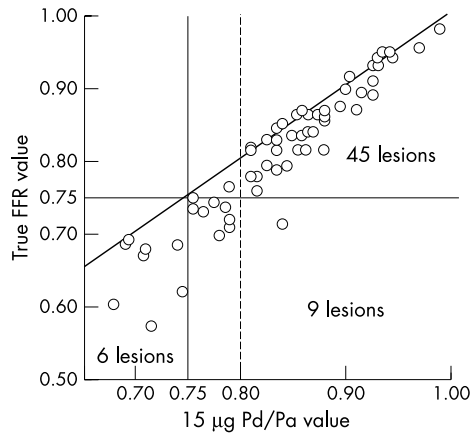


Figure 1 Pd/Pa values obtained with 15 µg dose of intracoronary adenosine versus true fractional flow reserve (FFR) value. Nine lesions with 15 µg intracoronary adenosine dose Pd/Pa value > 0.75 reached a significant value (< 0.75) with higher doses (one of them with 15 µg intracoronary adenosine dose Pd/Pa value > 0.80).

The impaired hyperaemic response caused by microvascular dysfunction in several clinical situations may explain the observed incomplete vasodilatation with the lowest doses of intracoronary adenosine. A damaged microcirculation could respond to high doses but not to low doses of intracoronary adenosine. This “quantitative” response, although theoretically possible, has not been previously demonstrated. On the other hand, first doses would theoretically facilitate the effect of subsequent doses of adenosine, increasing the flow and “effective” local dose of adenosine in the arteriolar region. Finally, in contrast to intravenous administration, the delivery technique of an intracoronary bolus injection is of critical importance. Although experienced interventionists usually take extra care to ensure a correct intracoronary injection, sometimes a backflow into the aorta cannot be avoided and reliable drug administration into the coronary system cannot be warranted.

The results of our study have several clinical implications. Although the average difference observed between FFR obtained with standard and higher doses was small, this difference was higher in lesions with borderline FFR (0.85–0.75), changing the initial functional consideration of these lesions and therefore decisions about their treatment. This study supports the empirical recommendations⁴ and clinical practice⁵ of use of higher doses of intracoronary adenosine, but mainly in lesions with a standard dose FFR value < 0.85. The use of higher than standard doses in all lesions may not be useful, but the use of > 100 µg of intracoronary adenosine or an incremental dose approach if an FFR value < 0.85 is obtained with standard doses may be clearly recommended.

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