Pharmacological Achievement of Hyperaemia in the Catheter Laboratory for the Assessment of Fractional Flow Reserve

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Introduction

The coronary microcirculation is a key regulator of myocardial blood flow. Through alterations in microvascular resistance, the microcirculation controls the delivery of blood to the myocardium over a wide range of perfusion pressures and myocardial oxygen demand through the process of autoregulation. In humans, coronary blood flow can increase up to five times basal flow to meet increased demand. Such an increase in blood flow is referred to as a hyperaemic response, and in humans is commonly observed in response to ischaemia and exercise. Quantifying the hyperaemic response is a critical step in understanding the coronary circulation and is applied in most physiological assessments of myocardial blood flow. In particular, the attainment of maximal hyperaemia is essential for an accurate assessment of fractional flow reserve (FFR).

In the catheter laboratory the attainment of a hyperaemic response is limited. Coronary occlusion to produce ischaemia (and thus reactive hyperaemia) is a method used in animal models but is not practical or safe to be used in humans who are not undergoing percutaneous intervention due to the inherent risk of vessel injury. Exercise is also not practical for most patients undergoing invasive coronary assessment. Thus, pharmacologically induced hyperaemia is the main method of producing hyperaemia in the catheter laboratory setting.

Anatomy of Hyperaemia

In the absence of hyperaemia, the arteriolar vessels are the primary components determining resistance. In the presence of hyperaemia following adenosine, total resistance decreases by approximately 68%; arteriolar resistance and venous resistance reduced by 86% and 98%, respectively. However, capillary hydrostatic pressure changes very little as a result of a similar fall in arteriolar and venous resistances. Thus, the capillaries are the main determinant of microvascular resistance at hyperaemia, and hyperaemic indices will reflect capillary structure as well as arteriolar function. See Figures 1 and 2.

Keywords
- Coronary hyperaemia
- Fractional flow reserve (FFR)
- Adenosine
- Hyperaemic agent

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Figure 1: Distribution of Coronary Resistances at Rest and During Hyperaemia in the Normal Coronary Artery

Figure 2: Regulation of Coronary Blood Flow

GTN = Glyceryl trinitrate
The Importance of Hyperaemia for FFR

In order to ensure a near linear relationship between coronary pressure and flow, it is crucial to ensure minimal resistance is achieved. For this to occur, both epicardial and microvascular compartments require vasodilation. Epicardial vasodilation is most commonly produced with intracoronary nitrates, and microvascular vasodilation can be achieved using a variety of agents (e.g., adenosine, papaverine). If maximal hyperaemia* is not achieved, then FFR may not reflect the true haemodynamic impact of a coronary stenosis and could be falsely elevated. This also holds true for assessments made at rest without hyperaemia. Therefore, even if the FFR without hyperaemia is in the ischaemic zone, it is recommended that FFR be assessed at rest with hyperaemia in order to maximise the hyperaemic response so that any treatment effect can be quantified. It is also pertinent to consider the clinical history/presentation of the patient when embarking on FFR assessment. Any process that impacts upon the coronary arterioles and capillaries (e.g., myocardial infarction, left ventricular hypertrophy) will potentially limit the hyperaemic response and impact the FFR value.

Currently Available Agents for Hyperaemia in the Catheter Laboratory

Many agents are available to produce hyperaemia for the assessment of FFR (see Table 1). However, the choice of agent depends on availability, cost and efficacy. Practically, the ideal hyperaemic agent should have a rapid onset, short duration of action and low cost with no significant side effects. For these reasons adenosine, administered by either the intracoronary (IC) or intravenous (IV) routes, has become the most widely employed method of achieving hyperaemia in clinical practice.

Adenosine

Adenosine is a naturally occurring endogenous purine nucleoside. Activation of A2A and A2B adenosine receptors produces potent vasodilation of most vascular beds, including the coronary circulation, resulting in an increase in myocardial blood flow. Adenosine exerts its predominant vasodilatory effect on coronary microvessels <150 μm diameter. It is widely available worldwide and relatively inexpensive, producing stable and reproducible effects.

Methods of Administration

In the context of achieving maximal hyperaemia in the catheter laboratory, both IC and IV routes are available. IC administration of adenosine is simple and quick. The peak effect is less than 10 seconds after administration, and it has a duration of approximately 20 seconds. For this reason, the IC route is not used in cases where a longer period of steady-state hyperaemia is required such as when performing an FFR pullback or more complex assessments of microvascular function. Earlier studies had suggested a maximum IC dose of adenosine of 16 μg for the left coronary artery (LCA) and 12 μg for the right coronary artery (RCA), with increasing doses of two orders of magnitude to ensure maximal vasodilation. These protocols were challenged by animal data suggesting higher doses of adenosine may be needed to achieve maximal hyperaemia and clinical studies that suggested standard adenosine dosing failed to achieve maximal hyperaemia when compared with papaverine and IV adenosine. Current recommendations for IC adenosine dosing are 40 μg in the RCA and 60 μg in the LCA increasing the doses incrementally by 30 μg to a maximum of 150 μg. It is suggested to use initial adenosine doses of 60–100 μg, increasing in 40 μg increments depending on dose response.

Whether the IC route is as efficacious at producing maximal hyperaemia compared with the IV route is a controversial area that has been addressed in several clinical studies. In general, IC adenosine is considered inferior to IV adenosine. The lower efficacy

<table>
<thead>
<tr>
<th>Drug</th>
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<th>Dose</th>
<th>Side Effect</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Adenosine</td>
<td>IC</td>
<td>60–100 μg initial dose, increasing in 40 μg increments depending on dose response</td>
<td>AV Block.</td>
<td>Not suitable for pullback.</td>
</tr>
<tr>
<td></td>
<td>IV</td>
<td>140 μg/kg/min</td>
<td>Dyspnoea, chest pain, flushing, headache, bronchospasm.</td>
<td>Side effects more common with the IV route.</td>
</tr>
<tr>
<td>Adenosine 5’triphosphate</td>
<td>IC</td>
<td>60–100 μg initial dose, increasing in 40 μg increments depending on dose response</td>
<td>As for IC adenosine</td>
<td>Not suitable for pullback.</td>
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<tr>
<td></td>
<td>IV</td>
<td>140 μg/kg/min</td>
<td>As for IV adenosine</td>
<td>As for IV adenosine. Limited availability.</td>
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<td>Papaverine</td>
<td>IC</td>
<td>12–16 μg RCA</td>
<td>QT interval prolongation, increase in coronary venous lactate.</td>
<td>Can produce steady-state hyperaemia for FFR pullback assessment. Correcting potassium and ensuring no other QT interval prolonging drugs are being taken can minimise risk of arrhythmia.</td>
</tr>
<tr>
<td></td>
<td>16–20 μg LCA</td>
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<td>Sodium nitroprusside</td>
<td>IC</td>
<td>0.6 μg/kg</td>
<td>Decrease in systemic blood pressure, nausea, headache.</td>
<td>Longer duration of action than IC adenosine. Suboptimal hyperaemic response compared with IV adenosine. May be useful in patients with contraindication to adenosine (e.g., asthma).</td>
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IC = intracoronary; IV = intravenous; RCA = right coronary artery; LCA = left coronary artery. Adapted from Layland et al.†† Author’s recommendations.

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*Jet Medical PressureWire® guiderwire and FFR measurement systems are instructed to be used with a hyperaemic agent. They are not indicated for use with any specific brand or brands or types of hyperaemic agents. This article is not intended to promote any specific agent to use with Jet Medical PressureWire and FFR measurement systems.

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Table 1: Available Agents Used to Produce Hyperaemia for FFR Assessment

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of IC adenosine compared with IV adenosine has been highlighted in a study by Casella et al. They compared the effects of IC vs IV adenosine in 50 stable patients; 60 μg of adenosine was used with increasing doses up to 150 μg. At the lower, “standard” dose of 60 μg, 10% of vessels with an initial FFR value > 0.75 had a subsequent value less than this cut-off point with higher IC doses or IV administration.

Leone et al. also examined the dose-response of IC adenosine compared with IV adenosine. They demonstrated that only the higher doses of IC adenosine (600 μg) produced similar hyperaemic efficacy to IV adenosine and that standard dosing (60 to 300 μg) with IC adenosine was not sufficient. Importantly, lower doses of adenosine were associated with inferior diagnostic accuracy compared with IV adenosine. However, at higher doses of IC adenosine, nearly 25% of patients developed transient atrioventricular block.

De Luca et al. demonstrated similar results in 46 patients with intermediate coronary stenoses undergoing diagnostic FFR evaluation. They showed that FFR values progressively decreased with increasing doses of IC adenosine up to 720 μg. With this, the number of patients identified with FFR values <0.75 increased. Of interest, and in contradiction to Leone et al., increasing the adenosine dose did not increase the incidence of side effects, which was very low.

Thus, it appears from studies to date that the IV route of administration has a greater efficacy for achieving maximal hyperaemia compared with conventional IC dosing with the added advantage that FFR pullback and more complex physiological assessments can be made. However, in most situations, the use of IC adenosine will be sufficient to assess the significance of a stenosis. In a minority of borderline cases, the IV route may need to be utilised.

Central vs Peripheral Route of Administration

Central venous infusion of adenosine through the femoral vein is regarded as the gold standard method of hyperaemia induction for the assessment of FFR. However, it requires femoral vein access and is inconvenient during transradial catheterisation, which is an increasingly preferred method of arterial access. In a study by Seo et al. involving 71 patients, no difference was found in the hyperaemic efficiency of IV administration of adenosine via the forearm compared with the femoral vein. The number of functionally significant stenoses (FFR < 0.75) was also not different between the two routes, and there was no difference between the hyperaemic mean transit time and index of microcirculatory resistance (IMR), suggesting that the maximal hyperaemic response was achieved with both routes of administration. Consistent with these findings, De Bruyne et al. showed that the hyperaemic efficacy of adenosine was similar between central and peripheral venous infusions, and increasing the dose to greater than 140 μg/kg/min did not improve the vasodilatory action of adenosine. In both of these studies, the time to maximal hyperaemia was longer with forearm vein infusion of adenosine than with the femoral vein infusion, with a mean difference of approximately 15 seconds, suggesting that when a peripheral venous route is selected, adenosine should be infused for a greater length of time.

In contrast to these findings, Lindstaedt et al. compared the hyperaemic efficacy of adenosine infusion between the femoral vein and the antecubital vein in 50 patients and reported that a 140 μg/kg/min infusion of adenosine via the antecubital vein was slightly less effective than the femoral vein infusion with a higher frequency of lesion severity underestimation. However, the mean FFR difference between the two routes was only 0.0126. Of interest, the group administered adenosine at higher doses (170 μg/kg/min) peripherally and found no difference in hyperaemic efficacy compared with the femoral route. For this reason, they recommended administering a higher dose of adenosine via the antecubital vein to achieve similar hyperaemic efficacy as the femoral route.

The concept of increasing the dose of adenosine to improve hyperaemic efficacy appears intuitive. However, unlike the findings of Lindstaedt et al. described above, other groups have not found such a relationship. In one study, the addition of an IC bolus of adenosine did not result in any change in FFR compared with standard adenosine infusion though it did increase the incidence of transient AV block. These findings were in agreement with other investigators who also showed no evidence of any change in FFR with doses of up to 240 μg/kg min. It is recommended to use IV adenosine at a dose of 140 μg/kg/min and either the peripheral (via a large caliber vein) or central route depending on operator preference. If using the peripheral route, it is suggested to use higher doses of adenosine in situations where the FFR result is borderline, but this level is not advocated for all patients.

During the initial phase of adenosine infusion, there can be differential changes to proximal and distal coronary pressures such that the FFR value may fluctuate during this period. This is a critical point because if FFR values are taken without the attainment of steady-state hyperaemia, the value may be inaccurate and lead to incorrect assumptions regarding the haemodynamic significance of a lesion.

Papaverine

Papaverine is an opium alkaloid that at IC doses of 20 mg has been shown to be as efficacious as adenosine at producing coronary hyperaemia. Its longer half-life (1–2 hours) produces a sustained hyperaemic response so that, unlike IC adenosine, FFR pullbacks can be performed. However, papaverine can cause prolongation of the QT interval and thus, predisposes to ventricular arrhythmias. It can also increase coronary venous lactate. For these reasons, its use as a first-line agent for producing hyperaemia for FFR assessment is not recommended.

Sodium Nitroprusside (SNP)

SNP is a potent vasodilator administered at an IC dose of 0.6 μg/kg. It has a longer duration of action than adenosine (approximately 60 seconds) and so may be useful when performing FFR pullback in diffuse/serial lesions. Initial data had shown equi-vocical efficacy for IC adenosine compared with SNP, but this was in small numbers of patients using lower than normal adenosine doses. However, the recent NASCI (Nitroprussiato versus Adenosina nelle Stenosi Coronariche Intermedie) study compared IC and IV adenosine with IC SNP in a larger cohort of 45 patients assessing 50 intermediate lesions. In general, SNP had suboptimal efficacy for achieving hyperaemia when compared with adenosine with FFR being higher for a given lesion when SNP was used.

Furthermore, and in accordance with earlier studies, compared with adenosine, SNP resulted in a significant hypotensive effect. Thus, this author advocates using SNP as a second-line agent and only in situations of adenosine allergy or in patients with severe chronic obstructive pulmonary disease (COPD).
Newer Agents
Regadenoson

Regadenoson is a selective adenosine A2A receptor agonist and in theory should produce similar hyperaemic effects to adenosine without the additional side effects often seen with A1, A2B and A3 receptor activation. It is given as an IV bolus and due to its longer half-life when compared to adenosine (2–3 mins), has a longer duration of action. Importantly, there is similar efficacy in terms of time taken to achieve hyperaemia compared with adenosine. Regadenoson produces similar blood pressure lowering effects to adenosine but causes a significantly higher heart rate response. The adoption of regadenoson for perfusion imaging followed two large randomised studies showing that it produced similar diagnostic information compared with a standard adenosine infusion. Furthermore, although side effects were common, they appeared to be less than those reported in patients receiving adenosine. Due to its A2A receptor selectivity, regadenoson appears to be safe in patients with mild asthma. However, as yet there are a lack of data to support its use in more severe forms of airways obstruction.

Arumugham et al. compared regadenoson with adenosine for the assessment of FFR in 20 patients with intermediate coronary stenoses and showed an excellent correlation between the two drugs (R2 = 0.933, p < 0.001). Furthermore, the minimum value of FFR appeared to be achieved earlier with regadenoson compared with adenosine. More recently, Prasad et al. demonstrated that, in 57 patients undergoing clinically indicated FFR assessment in the catheter laboratory, regadenoson was as efficacious as adenosine at inducing hyperaemia, with FFR in both groups being 0.79. There were fewer (but not statistically significantly fewer) side effects with regadenoson, and the nadir to hyperaemia was shorter in the regadenoson group.

Noricandil

Noricandil was also compared with adenosine among 210 patients with an intermediate coronary stenosis. Hyperaemic efficacy was compared with IC and IV adenosine vs IC nicorandil. The investigators found that the hyperaemic efficacy of IC nicorandil (2 mg) was noninferior to that of IV adenosine. There was also no significant difference between IMR with IV adenosine compared with IC nicorandil, suggesting that similar levels of steady-state minimal resistance were obtained with both drugs. Moreover, there were no side effects/adverse reactions with nicorandil whereas with adenosine, AV block occurred in 12 patients with IC administration and four patients with the IV route.

Conclusion

Hyperaemia is vital in the assessment of coronary stenoses with FFR. Of the agents currently available, adenosine remains the most widely used and well studied and should be the first-choice agent in most situations. However, newer agents such as regadenoson and nicorandil hold great promise for the future, but as yet there are a lack of data to warrant their generalised use.

References