Intracoronary infusions and the assessment of coronary blood flow in clinical studies

Intracoronary drug administration may be desirable for a number of reasons and is used in therapeutic, diagnostic, interventional, and clinical research settings. One of the main indications for intracoronary drug administration is in the assessment of coronary blood flow either as a guide to intervention or as a clinical research tool. There are many methods of assessing coronary blood flow including the use of the angiogram derived corrected TIMI (thrombolysis in myocardial infarction) frame count and the rate of decorrelation of the radiofrequency signal from intravascular ultrasound (IVUS) imaging catheters. However, the most direct and widely used method of assessing coronary blood flow is the Doppler flow wire—a piezoelectric cell mounted on the tip of a 0.014 inch guide wire.

The Doppler flow wire measures coronary blood flow velocity and, in order to measure coronary blood flow, knowledge of the cross sectional area of the vessel is required. The latter is usually estimated using quantitative coronary angiography (QCA), which assumes circular or elliptical luminal geometry, although greater accuracy can be obtained by using IVUS imaging catheters. Indices such as coronary flow reserve—the ratio of maximal to basal hyperaemic flow velocity—can be used to assess the functional severity of coronary stenoses and the dynamic integrity of the microcirculation without determining luminal cross sectional area. However, fractional flow reserve, which is measured using a pressure wire (guide wire with ability to measure distal coronary artery pressure), is increasingly being used to determine the functional severity of coronary stenoses since it is more reproducible, lesion specific, and less dependent on systemic haemodynamic parameters.

Clinical research studies assessing coronary vasomotor responses to drug infusion have used endothelium dependent and independent vasodilators as well as agonists and antagonists of physiological mediators (table 1). The magnitude and variability of coronary responsiveness is highly dependent on the agent used and crucially on the method of measurement and the mode of administration.

Assessment of coronary vasomotor responses: QCA or IVUS

Although well established, QCA has many limitations in the measurement of vasomotor and blood flow responses. It tends to underestimate the luminal area and functional severity of coronary stenoses. Contrast agent injection not only necessitates the interruption of the drug infusion and aspiration of the catheter, but may itself be vasoactive and directly alter coronary blood flow and confound measurements. Finally, many agents, especially endothelium dependent vasodilators (for example, acetylcholine, see fig 1), have a near instantaneous onset and offset of action, and performing QCA a minute after injection is likely to result in misleading measurements.

The use of IVUS can circumvent many of these limitations and provide continuous ECG gated cross sectional area and compliance measurements of the coronary artery. In addition, IVUS provides more detailed morphometric information of the coronary artery including plaque volume, composition, severity, and distribution. Moreover, the combined use of IVUS and Doppler wire does facilitate the functional assessment of both conduit and resistance vessel function. Although cross talk can occur between the IVUS and Doppler systems owing to frequency overlap, meaningful image or signal loss is unusual and rarely affects cross sectional area or velocity measurements. However, the IVUS imaging catheter (cross...

Table 1 Intracoronary administration of agents commonly used in the functional assessment of the coronary circulation

<table>
<thead>
<tr>
<th>Agent</th>
<th>Dose</th>
<th>Receptor/mediator</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adenosine</td>
<td>Bolus: 12–36 µg</td>
<td>Purine receptors</td>
<td>Causes transient heart block.</td>
</tr>
<tr>
<td></td>
<td>Infusion: 1–2 mg/min</td>
<td></td>
<td>Causes maximal coronary vasodilatation and is also used for the assessment of fractional flow reserve</td>
</tr>
<tr>
<td>Glycerol trinitrate</td>
<td>Bolus: 50–200 µg</td>
<td>Nitric oxide donor</td>
<td>Predominant action on epicardial vessels</td>
</tr>
<tr>
<td>Papaverine</td>
<td>Bolus: 4–12 mg</td>
<td>Opiate derivative causing vascular smooth muscle relaxation</td>
<td>Causes maximal coronary vasodilatation. Potentially arrhythmogenic</td>
</tr>
<tr>
<td>Sodium nitroprusside</td>
<td>Infusion: 5–40 µg/min</td>
<td>Nitric oxide donor</td>
<td>Predominant action on coronary resistance vessels</td>
</tr>
<tr>
<td>Acetylcholine</td>
<td>Bolus: 1–100 nmol</td>
<td>Muscarinic receptors</td>
<td>Causes transient heart block. Target effective intracoronary concentration of $10^{-10}$ to $10^{-8}$ M. May cause paradoxical vasocoonstriction in presence of atheroma</td>
</tr>
<tr>
<td></td>
<td>Infusion: 1–1000 nmol/min</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bradykinin</td>
<td>Bolus: 60–600 pmol</td>
<td>Bradykinin type 2 receptor</td>
<td>Tachyphylaxis and chest discomfort may occur</td>
</tr>
<tr>
<td></td>
<td>Infusion: 30–2500 pmol/min</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Substance P</td>
<td>Infusion: 5–40 µmol/min</td>
<td>Neurokinin type 1 receptor</td>
<td></td>
</tr>
<tr>
<td>L-NMMA</td>
<td>Infusion: 32–64 µmol/min</td>
<td>Nitric oxide synthase inhibitor</td>
<td>Slow onset and offset of action (10–20 minutes)</td>
</tr>
</tbody>
</table>

Boluses should be given in 2 ml followed by 3 ml saline flush. The bolus dose should be reduced by 30–50% for right coronary artery injection.

To avoid directly influencing coronary flow, infusion rates are usually low at 1–2 ml/min.

Adenosine and papaverine may additionally cause endothelium dependent flow associated epicardial vessel vasodilatation.

Except L-NMMA, all agents have a rapid onset and offset of action with flow velocity usually returning to baseline within ~2 minutes.
of coronary responses.\textsuperscript{20} Effects which will confound the subsequent interpretation of coronary drug administration. The method of administration of vasoactive agents under investigation has been variable and inconsistent. For example, acetylcholine has been administered as a continuous infusion,\textsuperscript{10,14} slow hand injection\textsuperscript{15} or rapid bolus.\textsuperscript{12} Moreover, instillation of drug into the coronary circulation has been achieved either via the instrumenting catheter\textsuperscript{11,16} or a dedicated 2–3 French selective intracoronary infusion catheter.\textsuperscript{17,18} Indeed, some workers have used selective monorail infusion catheters which have remained within the guide catheter.\textsuperscript{15} Finally, systemic intravenous infusions of agents, such as adenosine (140 \(\mu\)g/kg/min), have been administered but this approach can cause pronounced systemic haemodynamic and arrhythmogenic effects which will confound the subsequent interpretation of coronary responses.\textsuperscript{20}

**BOLUS INJECTIONS**

Consideration should be given to the catheter dead space which can be significant, particularly when drugs are given via the guide catheter. The administration of even a small volume bolus will necessitate a 3 ml saline flush to eject the drug from the catheter into the proximal coronary artery. This will cause an instantaneous increase in blood flow velocity which is attributable to the mechanical ejection of fluid down the artery. Thereafter, a second rise or a subse-

quent fall in blood flow velocity will occur which is attributable to drug action (fig 1). Prolonged injection or large volume boluses have the potential to obscure the second phase response because of superimposition of mechanical and pharmacological flow effects as well as inducing shear stress and flow associated dilatation. Bolus injections should, therefore, be kept to a minimal volume and must be compared with control saline injections. Finally, bolus injections of acetylcholine and adenosine into the right coronary or dominant circumflex artery can result in atrioventricular block and transient ventricular standstill (fig 1). If prolonged, this will confound the assessment of vasodilatation and flow responses, and continuous infusions of acetylcholine or adenosine into these arteries should be avoided.

**CONTINUOUS OR GRADED INFUSIONS**

The administration of drugs via the diagnostic or guide catheter may be satisfactory for the application of drug boluses by hand injection when maximal vasodilatory responses are being assessed, such as with high dose (30 \(\mu\)g bolus) adenosine. However, there is a concern that continuous or graded infusions via the coronary guide catheter do not reliably permit precise and selective intracoronary drug administration. The turbulence induced by blood ejection from the heart and the potential incomplete engagement of the catheter with the coronary ostium will result in a variable degree of drug reflux into the aorta. Furthermore, in the left coronary system, a variable amount of the delivered drug will be administered to the adjacent epicardial vessel. Consequently, there is the theoretical concern that guide catheter infusion will result in a wide variability in the effective intracoronary drug concentration attained. When assessing the coronary vasomotor response by QCA, these concerns are further compounded by the necessity to aspirate the drug from the diagnostic or guide catheter before contrast injection.\textsuperscript{10,14} Finally, impaction of the guide catheter in the coronary ostium due to superselection, or the use of large guide catheters, should clearly be avoided as this will impair anterograde coronary flow. Administration of drugs through guide catheters with side holes is equally inappropriate, and it is likely that smaller guide catheters will increasingly be used with the wider use of 6 French compatible IVUS catheters.

We have recently been conducting a study to look at the relation between endothelial function and atheromatous plaque volume in the coronary circulation of patients with normal or mildly diseased coronary arteries. The plaque volume of the proximal left anterior descending coronary artery was determined using three dimensional reconstruction of an initial IVUS examination, and coronary blood flow responses to incremental five minute infusions (1 ml/min) of substance P were assessed by combined Doppler wire and IVUS measurements. In 10 patients, substance P was selectively infused via the flush port of the IVUS catheter which caused significant and consistent increases in coronary blood flow (fig 2). However, in a further 10 patients, where substance P was administered via the guide catheter, the magnitude and consistency of the coronary blood flow response was low and did not result in significant increases in coronary blood flow despite a comparable degree of proximal coronary atheroma (6.2 (1.0) \(v\) 4.8 (1.4) \(\mu\)m/mm of vessel, respectively). Therefore, we believe that, to achieve reproducible vasomotor responses, continuous or graded intracoronary drug administration should be given using a selective intracoronary infusion catheter which, to date, has not been universally employed.

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Conclusions

The measurement of coronary blood flow responses to vasactive agents and investigational agents is an important and essential area of clinical research. However, it would appear that the method of assessment and the route of intracoronary drug administration will have a significant influence on subsequent coronary vasomotor responses. Consequently, the method and technique used will depend on the specific question under investigation and should be guided by the limitations of each approach.

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Dr David Newby is currently conducting research in this area supported by grants from the British Heart Foundation (PG-98150; FS/99026) and the Scottish Office. I am grateful to Drs NA Boon, NG Uren, and AL McLeod for their assistance and guidance in the preparation of this manuscript.