Functional assessment of coronary stenosis: it does make sense, but why don’t I do it more often?

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Physiological assessment of coronary stenosis of intermediate severity, as assessed by angiography, during cardiac catheterization, has gained renewed interest in the last few years. The reasons are several and obvious. Angiography, in spite of being the gold standard to assess coronary anatomy and lesion severity, only represents an image of the arterial lumen, and gives no information about the extent of the atherosclerotic process in the remaining artery and its dynamics. The patient could avoid further non-invasive stress tests, and it would save money, time and discomfort for the patient if coronary angioplasty could be performed at the time of the diagnostic procedure.

For this purpose several methods to complement coronary angiography have been tested and the two most commonly used are coronary flow velocity reserve and pressure-derived myocardial fractional flow reserve. Both are relatively easy to perform with the commercially available Doppler-tipped and pressure guide wires and should take place in any updated interventional cardiology laboratory. Resting and hyperaemic flow velocity and pressure measurements after intracoronary adenosine are used to derive the coronary reserve of a particular segment of the coronary tree distal to the stenosis. Several studies have been performed confirming the value of coronary flow velocity reserve and fractional flow reserve in the prediction of stress test results.

In the current issue Piek et al.[1] performed a post hoc analysis of the data of the DEBATE (Doppler Endpoints Balloon Angioplasty Trial in Europe) study. This was a multicentre study of a selected group of patients with single-vessel disease and normal left ventricular function undergoing coronary angioplasty. They concluded that the distal coronary flow velocity reserve, of all Doppler-derived parameters studied, offers the best correlation with percent diameter stenosis and minimum lumen diameter. All three parameters were independent and equally predictive of the results of a symptom-limited exercise test to depict ischaemia and have a complementary role in clinical decision making. The best cut-off value of coronary flow velocity reserve for the result of the stress test was 2·1. The study is also important because it combines measurements before angioplasty and at 6 months follow-up. As in other studies, there was only moderate correlation between coronary flow velocity reserve and diameter stenosis in lesions of moderate severity and the cut-off of coronary flow velocity reserve was 1·9 for patients with intermediate lesions.

There are some known limitations with the use of Doppler coronary flow velocity reserve determinations[2], To obtain a good signal of the instantaneous blood flow velocity it is necessary to achieve optimal placement of the Doppler wire in the vessel axis. Blood flow velocity can be influenced by the severity of the stenosis and by changes in vessel diameter. Coronary flow velocity reserve, although quite reproducible, is very sensitive to haemodynamic changes and microvascular function, and therefore able to give variable threshold values, particularly in moderate stenosis. However, a coronary flow velocity reserve <2·0 usually corresponds to reversible myocardial ischaemia. The main DEBATE study[3] has defined, as optimal cut-off criteria for predictors of clinical events (symptoms, need for target vessel revascularization and angiographic restenosis) after balloon angioplasty, a diameter stenosis of 35% and coronary flow velocity reserve of 2·5.

Because of these limitations, fractional flow reserve with the advantage of only measurements of mean distal coronary pressure and mean aortic pressure performed during maximal hyperaemia, seems to be a more attractive method. It is independent of driving pressure and other loading conditions, applicable in three-vessel disease, incorporates the contribution of the collateral blood supply to maximal myocardial perfusion, is highly reproducible and independent of the position of the wire tip[2]. By definition, its normal value is equal to 1 (or 100%) for any vessel and several studies have established that a functionally significant stenosis has a fractional flow reserve ≤0·75.

The problem of which is the better method to assess the functional significance of a moderate stenosis is, however, not yet solved. Both seemed to be complementary, as fractional flow reserve is specific for epicardial stenosis and coronary flow velocity reserve incorporates both the artery and the microvascular circulation, and neither takes into account stress-induced vasoconstriction that may occur in coronary atherosclerosis. Also, as many studies including the present work of Piek et al.[1] have
shown, both functional and anatomical parameters should be combined in order to play a significant clinical role. Moreover, as Kern et al.\(^5\) had stated ‘coronary guide wire-based physiologic measurements provide only a single “snap-shot” in time and are unable to evaluate the dynamic nature of coronary artery disease’.

In spite of all these limitations, functional assessment of coronary stenosis in the catheter laboratory can be very useful and some recent studies have suggested its importance in the context of coronary interventions and for long-term prognosis.

In the DEBATE II study\(^4\), using the same criteria as in DEBATE, the need for provisional additional stenting after optimal balloon angioplasty was evaluated. It was concluded that stenting further improves the 6 month clinical outcome and should probably be used in all cases.

In a similar study, the FROST (French Optimal Stenting Trial) study\(^3\), also in single vessel disease, the cut-off coronary flow velocity reserve was 2-2 and only 48% of patients required a stent in the guided angioplasty group. The 6 month outcomes were similar with the two strategies.

The DESTINI-CFR (Doppler Endpoints Stent International Investigation) study\(^6\), which included a population of ‘all-comers’ with single and multivessel disease and any type of lesions, compared elective stent placement with Doppler and angiographic guided angioplasty, using diameter stenosis ≤35% and coronary flow velocity reserve >2.0 as endpoints. The clinical outcomes were equivalent. However, only 43% of patients achieve those predetermined end-points and the remaining have received a stent. This study also showed that a low coronary flow velocity reserve was associated with higher incidence of clinical events after stenting in the same predictive way as lesion and stent lengths and final diameter stenosis and minimum lumen diameter\(^7\).

Following single centre experience, the multicentre DEFER study\(^5\) was set up to test the strategy of deferring angioplasty in those patients with fractional flow reserve ≥0.75. The patients with single- vessel disease and without previously documented ischaemia at non-invasive testing, were randomized to angioplasty or deferral. At 1-year follow-up no significant differences were found in event-free survival or functional class between patients in the two strategies.

How can the current knowledge about invasive functional assessment of coronary stenosis influence clinical practice?

The majority of the studies have been performed in patients with single vessel disease who had coronary angiography for typical or atypical angina but no previous history of acute coronary syndromes. Many had not even undergone an exercise test before angiography, and in the paper by Piek et al.\(^1\), for instance, in 26% of patients who underwent angioplasty the exercise test had not been performed and in another 26% the test was negative or non-diagnostic. It can be assumed that many of these patients were not adequately treated for coronary artery disease with therapies such as beta-blocking drugs, antiplatelets or statins. If treated, the medications that can influence reactive hyperaemia were not uniformly kept constant at the time of angioplasty and at follow-up. This is definitively a very selected population, which may not represent more than 20–30% of patients undergoing angiography in the majority of European countries.

However, there is a much larger population in whom angiography is performed for diagnostic purposes or risk stratification for previously known clinical coronary artery disease. In such patients already on medication, previous stress tests positive for ischaemia have indicated vessel lesions of moderate angiographic significance. In many instances, angioplasty is performed only in the culprit lesion or in the most angiographically significant lesions, ignoring those of only moderate severity. In multi-vessel coronary artery disease, the interpretation of non-invasive stress tests for ischaemia, is frequently difficult and misleading due to current medication, inadequate heart rate response, etc. The process of disease progression is inadequately understood and we are all aware that the majority of lesions which progress to infarction, were previously considered of only moderate severity.

The current ease and procedural safety with which angioplasty can be performed, stents implanted and antiplatelet drugs such as glycoprotein IIb/IIIa antagonists administered, is an additional factor of concern both to single and multivessel coronary artery disease patients undergoing angiography with the ‘new’ interventional cardiologists. Many will certainly use the aphorism that ‘when in doubt, dilate’ and the majority might even place a stent, forgetting the possibility of in-stent restenosis.

Because of the concerns expressed above, the possibility of accurately determining the functional significance of an angiographically moderate stenosis at the time of a diagnostic procedure, applicable to all situations, should be most welcome. Much is already known about coronary physiology and the complementary role of coronary flow velocity reserve, fractional flow reserve and quantitative coronary angiography in clinical decision making. While we wait for further studies, any revascularization
procedure should be based on coronary anatomy and on the functional severity of a lesion, without forgetting continuous medical therapy. But why don’t I, as well as the surgeons, use these principles more often?

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References


Neural-natriuretic hormone interactions

See page 498 for the article to which this Editorial refers

Atrial natriuretic peptide (ANP) and brain natriuretic peptide (BNP), are both produced by the heart and secreted into the blood stream. They are of considerable interest to cardiologists. The levels of ANP are raised in cardiac failure[1–3] as are those of BNP[6–8] which is of possible diagnostic use, but their importance in the pathophysiology of cardiac failure remains to be completely clarified. ANP is also raised in patients with cardiac transplantation[9–13] in which situation the heart is denervated, raising a number of questions about the relationships between natriuretic peptide secretion and function and that of the cardiac nerves.

Atrial natriuresis

Our interest in this subject goes back to the 1950s, when it was realized that then unknown circulating substances existed which influenced urine production. Blood volume expansion, caused natriuresis[14], and left atrial distension caused increased sodium excretion and free water diuresis[15]. Although it was already known that these effects were abolished by section of the vagus nerves[16], there was continued interest in a humoral effluent mechanism. The effects are accompanied by falls in plasma arginine vasopressin[17] and plasma renin activity[18].

The discovery that atrial myocardial extract produced a natriuresis when injected intravenous was[19] led to an explosion of interest and publications concerning the mediator, ANP. At this time, the enthusiasm was such that everyone seemed to assume that ANP was the mediator of atrial natriuresis, making it necessary to re-test the hypothesis that the mediator was a neuronal reflex[16]. For this it was necessary to avoid vagal section which denervates many organs and to denervate the heart only. This experiment proved that atrial natriuresis in response to left atrial distension is mediated by the cardiac nerves[20] even though the release of ANP was not impaired[21]. It was subsequently also shown (again with normal ANP responses) that dogs with denervated hearts had an impaired natriuretic response to intravenous saline infusion[22,23]. The residual response in this case appears to be related to higher arginine vasopressin and plasma renin activity levels in the denervated...