Assessing ischaemia in stable CAD

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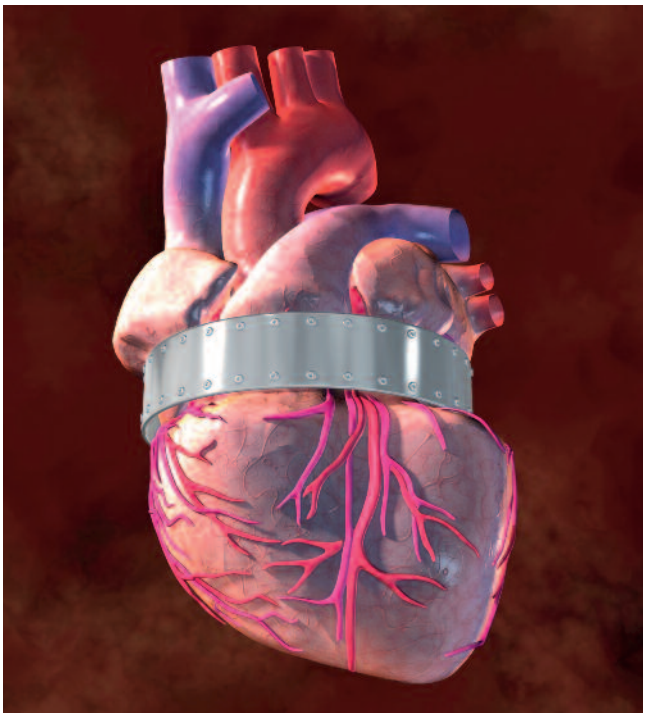
The degree of ischaemia in patients with stable coronary artery disease impacts on the long-term clinical outcome. Noninvasive methods of assessing ischaemia should preferably be used before elective invasive procedures.



Redefining stable angina

Stable angina, a symptom of stable CAD, is often described as a syndrome of chest discomfort occurring predictably and reproducibly at a particular level of exertion and characteristically relieved with rest and/or the use of nitrates. However, approximately 20% of all patients treated for so-called stable angina do not have documented coronary artery disease (CAD) based on coronary angiography (CA) or computed tomography coronary angiography (CTCA). Moreover, approximately 50% of 60-year-olds with non-cardiac chest pain will have abnormalities on a coronary angiogram or CT coronary angiogram. Consequently, a better definition of stable angina is needed, such as intermittent chest pain related to atherosclerotic narrowings that cause reversible ischaemia.

Revascularisation in patients with stable CAD

The goal of therapy in patients with stable CAD is to alleviate symptoms and improve prognosis by treating myocardial ischaemia. The main indications for revascularisation in such patients are:

- the persistence of symptoms despite optimal medical therapy
- intolerance to medical therapy.

Further indications for revascularisation depend on the location, extent and severity of an individual's CAD. There is proven prognostic benefit in revascularisation of left main disease (greater than 50% stenosis), proximal left anterior descending artery disease (greater than 50% stenosis) and multivessel CAD with a reduced left ventricular systolic function.[1]

Key points

- **Intermittent chest pain related to atherosclerotic narrowings that cause reversible ischaemia may be a better definition of stable angina than currently used descriptions.**
- **Society guidelines on myocardial revascularisation recommend the documentation of ischaemia by functional testing, preferably using noninvasive methods, before elective invasive procedures.**
- **Both coronary angiography and computed tomography coronary angiography can demonstrate atherosclerotic CAD; however, neither will provide information on the functional significance of the disease.**
- **Myocardial fractional flow reserve is an index of the functional severity of a coronary stenosis.**
- **Coronary angiography accompanied by fractional flow reserve is the 'all-in-one' method that can confirm the presence of atherosclerosis, evaluate for ischaemia and allow for the appropriate treatment, at one point in time.**

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The COURAGE trial and trend towards medical therapy for stable CAD

In 2007, the authors of the Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) trial concluded that the strategy of percutaneous coronary intervention (PCI) in patients with stable CAD did not reduce the risk of death, myocardial infarction or major adverse cardiovascular events when added to optimal medical therapy (intensive pharmacological therapy and lifestyle intervention).[2] Following this well-publicised trial, there was a paradigm shift in the management of patients with stable CAD towards medical therapy. However, major flaws, listed below, were evident in this trial.[3]

- The generalisability of the study is questionable given that only 2287 of the 35,539 patients screened for study enrollment were actually enrolled.
- Prior studies evaluating the effect of PCI failed to demonstrate a mortality benefit; however, the COURAGE investigators, as part of their statistical assessment, expected to observe a 22% reduction in mortality with PCI.
- Approximately 70% of patients had at least two-vessel disease, but only 36% of those assigned to PCI received more than one stent. It is well documented that incomplete revascularisation, whether by PCI or surgery, is associated with worse clinical outcomes than is complete revascularisation. In particular, there is a greater need for repeat revascularisation. Could this perhaps help explain the observation that 21% of the PCI patients in the COURAGE trial required repeat revascularisation?
- The evolution of drug-eluting stents has significantly reduced the rate of angiographic restenosis by up to 70%. However, in the COURAGE trial only 2.7% of the PCI group received these stents.
- The study results were based on an 'intention-to-treat' analysis. (In an intention-to-treat analysis, data from all subjects regardless of whether they completed the study or adhered to protocol requirements are analysed; in an as-treated analysis, data only from subjects who completed the study and adhered to protocol requirements are analysed.) As such, one-third of the medical arm actually underwent revascularisation – approximately a 33% medical treatment failure rate. It would be interesting to observe the outcome presented in an 'as-treated' analysis.
- Not all patients underwent stress testing for ischaemia, many had no functionally significant disease at all and disease severity was moderate at best, which would portend an excellent outcome.
- In the PCI group, selection of coronary lesions to be stented was on the basis of angiography despite the limitations that this method has in assessing lesion severity and functional significance. Consequently, approximately 30% of lesions would have been unnecessarily stented.
- A glossed over fact was that revascularisation was significantly better than medical treatment alone at relieving angina.[3]

In the never-ending quest for treatments to offer increasingly greater mortality benefits, sometimes we fail to appreciate that treating morbidity is inherently valuable in itself.

Figure 1. Contrast-enhanced multidetector row computed tomography coronary angiography demonstrating the course of the left anterior descending coronary artery in a patient with coronary artery disease. Note significant stenosis (arrow) caused by noncalcified coronary artery lesion proximal to a calcified nodule.

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The importance of the degree of ischaemia in stable CAD

Demonstrable ischaemia has long been recognised to impact on long-term clinical outcomes in patients with stable CAD. Symptomatic patients without significant demonstrable ischaemic myocardium do not gain prognostic benefit from revascularisation, whereas asymptomatic patients with a moderate to significant degree of myocardial ischaemia do.[1] Marie and colleagues investigated 442 patients treated with optimal medical therapy and found that residual ischaemia was associated with significantly lower survival and major event-free survival ($p \leq 0.001$).[4]

Hachamovitch and colleagues examined more than 10,000 patients with positive myocardial perfusion stress tests and no prior history of myocardial infarction or revascularisation.[5] Revascularisation compared with medical therapy had greater survival benefit in patients with moderate to large degrees of reversible ischaemia. On the other hand, PCI in those without demonstrable ischaemia led to a higher cardiac death rate.

In the COURAGE Nuclear Substudy, the PCI-based approach in the COURAGE trial was more effective at reducing the total burden of ischaemia, and the greatest reduction in ischaemia was among patients who initially had moderate to severe ischaemia.[6] Furthermore, the higher the burden of residual ischaemia, the lower the cumulative event-free survival across the five-year follow up.

Thus, in patients with suspected angina we should seek to confirm the diagnosis of CAD and then assess the degree of ischaemia. In those patients with confirmed stable CAD and evidence of moderate to severe ischaemia, we should undertake revascularisation to improve prognosis.

The role of angiography in stable CAD

Both CA and CTCA can demonstrate atherosclerotic CAD (Figure 1)[7]; however, neither will provide information about the functional significance of the disease. A recent study showed that when compared with fractional flow reserve (FFR; see below), CA and CTCA do not reliably predict the functional significance of obstructive lesions.[8] In clinical practice, this means that decision-making based on CA would result in revascularisation in the absence of ischaemia in 16% of patients and inappropriate deferral of PCI in 12% of patients. With respect to CTCA, 22% of patients would undergo revascularisation in the absence of ischaemia and PCI would be inappropriately deferred in 7% of patients.[8]

Noninvasive assessment of ischaemia

The European Society of Cardiology guidelines on myocardial revascularisation recommends the documentation of ischaemia using functional testing, preferably using noninvasive methods, before elective invasive procedures.[1] Noninvasive tests demonstrate either a reduction of perfusion or ischaemic wall motion abnormalities during exercise or pharmacological stress.

Exercise ECG stress testing

Exercise ECG stress testing is cheap and has a diagnostic accuracy of up to 70% in patients with single vessel disease,[9] it is not diagnostic in the presence of resting ECG changes, such as left-bundle branch block, a paced rhythm or evidence of Wolff–Parkinson–White syndrome. Exercise ECG testing is also less accurate in females and in patients with multivessel disease, is unable to provide spatial resolution and can lead to false-positive results in patients with left ventricular hypertrophy or electrolyte abnormalities.[9]

Myocardial perfusion imaging

Myocardial perfusion imaging is considerably more expensive, but offers better diagnostic accuracy (85%) than exercise ECG stress testing. It is able to quantify and localise areas of ischaemia, particularly in single or double vessel disease, but it is less well suited to assessment of multivessel disease due to the concept of balanced ischaemia.[9] Balanced ischaemia refers to a false-negative finding on a single photon emission computed tomography (SPECT) myocardial perfusion imaging study. Rest and stress myocardial perfusion scans show perfusion relative to other regions of the heart. It is possible for all regions of the heart to have reduced perfusion during stress, thus the perfusion images may show that all regions relative to each other have similar perfusion, albeit significantly reduced. More importantly, myocardial perfusion imaging carries the potential risk associated with radiation exposure.

Figure 2. Stress echocardiography (modelled by Dr Palmer and Dr Brendan Flaim).

Stress echocardiography

Compared with myocardial perfusion imaging, stress echocardiography is radiation-free, is less expensive and offers similar diagnostic accuracy (80%) with a slightly greater specificity (Figure 2). Unfortunately, in 5 to 10% of the population adequate echocardiographic windows are unattainable.

Both stress echocardiography and myocardial perfusion imaging can be performed in patients who are unable to exercise, with the use of pharmacological agents such as dobutamine and persantin. They are both the preferred techniques in patients who have had PCI or a coronary artery bypass graft.[9]

Invasive assessment of ischaemia: fractional flow reserve

A US study of 23,887 Medicare patients undergoing elective PCI in 2004 demonstrated that 55% of patients presenting for CA did not undergo prior noninvasive stress testing.[10] Myocardial FFR is an index of the functional severity of a coronary stenosis. It is calculated from pressure measurements made during CA by passing a pressure wire distal to a coronary stenosis.

FFR is based on the principle that at maximum vasodilation, blood flow to the myocardium is proportional to the myocardial perfusion pressure. It is defined as the ratio of maximal blood flow distal to a stenosis relative to the maximal blood flow proximal to that stenosis, measured during adenosine-induced hyperaemia.

Numerous clinical studies have compared FFR with noninvasive

stress testing and established an ischaemic FFR threshold of 0.75 or less.[11-13] Other studies have shown that an FFR value of up to 0.78 may be more predictive of reversible ischaemia on myocardial perfusion imaging. This has lead to a grey zone of FFR values between 0.75 and 0.8. Recent studies have used a cut-off value of 0.8 or less to determine the physiological significance of a lesion.[11,14] An FFR value of greater than 0.8 is associated with negative ischaemia and has a predictive accuracy of 95%.

The evidence for an FFR-guided strategy

Deferral versus Performance of PCI of Non-Ischemia Producing Stenoses trial

The first major randomised trial to use FFR values to determine treatment strategy was the Deferral versus Performance of PCI of Non-Ischemia Producing Stenoses (DEFER) trial.[15] The study looked at 325 patients with stable CAD, who had not had prior stress testing, who were scheduled to undergo PCI of an intermediate coronary lesion. The FFR was measured just before the planned intervention. If FFR was 0.75 or above, patients were randomly assigned to deferral of PCI or performance of PCI.

This landmark study demonstrated that over a five-year follow-up period, deferral of PCI in patients with intermediate coronary stenoses and an FFR of 0.75 or above was associated with excellent clinical outcomes (p=0.52). In other words, there is no benefit in PCI of a functionally nonsignificant stenosis (a stenosis not responsible for reversible ischaemia). The risk of death or myocardial infarction in those patients with deferral of PCI was less than 1% per year.[15]

Fractional Reserve versus Angiography for Multivessel Evaluation study

The second major randomised trial that demonstrated the clinical utility of FFR in the decision-making concerning PCI was the Fractional Reserve versus Angiography for Multivessel Evaluation (FAME) study.[14] In this study the investigators randomised 1005 patients with multivessel disease to angiography or FFR-guided PCI. Patients were required to have stenoses 50% or greater in at least two of the three major coronary arteries. For those randomised to the FFR-treatment arm, lesions with an FFR of 0.8 or less received a drug-eluting stent, while those with an FFR above 0.8 did not undergo PCI.

The trial demonstrated that, compared with angiography, an FFR-guided treatment strategy in patients with multivessel disease resulted in:

- a significant lower rate of cardiovascular adverse events (death, myocardial infarction and repeat revascularisation at one year; 18.3% *v.* 13.2%; p=0.02)
- fewer stents deployed
- reduced contrast load
- all at a significantly lower cost.[14]

Furthermore, the clinical outcome benefits, resource utilisation and cost-effectiveness were all demonstrated at two years' follow up.[16,17]

Conclusion

All patients with CAD should be treated with aggressive risk-factor modification. It is well established that the presence of ischaemia has prognostic implications for patients with CAD. Hence, all patients with suspected stable angina should be assessed for evidence of ischaemia. In most cases, the initial approach should be with noninvasive stress testing. However, in those with high-risk features or equivocal results, CA with FFR should be undertaken. Currently, CA accompanied by FFR is the only method that can confirm the presence of atherosclerosis, evaluate for ischaemia and then allow for the appropriate treatment, all at the one point in time. **CT**

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COMPETING INTERESTS: None