The limitations of coronary angiography in estimating the severity of stenosis are well known. Intracoronary measurement of myocardial fractional flow reserve (FFR) has emerged as a reliable index to quantify the physiological impact of a stenosis; a value of 0.75 reliably identifies stenosis associated with inducible ischemia. Using a pressure guide wire, FFR can be estimated from the ratio of hyperemic distal to proximal coronary pressure. FFR is useful as a diagnostic tool in the catheterization laboratory. Studies conducted by Pijls et al. showed that deferring treatment of intermediate lesions with an FFR greater than the 0.75 cutoff is safe and results in good clinical outcome. Moreover, it has been shown that a high FFR value after balloon angioplasty is associated with a lower clinical event rate. In a recent study, Pijls et al. have further suggested that the FFR value after stenting was the most significant independent predictor of outcomes at 6 months. For patients with FFRs greater than 0.95 after stenting, the event rate was 4.9%; for FFRs between 0.90 and 0.95 after stenting, the event rate was 6.2%; for values between 0.80 and 0.90, the event rate was 20.3%; and for values less than 0.80, event rate was 29.5%.

Other than assisting decision-making in whether or not to revascularize a coronary stenosis and assessing the results of catheter-based treatment, coronary pressure-derived FFR measurements are also helpful in managing complex pathological conditions.

Features of FFR

FFR is defined as the ratio of the maximum myocardial blood flow in the presence of a coronary stenosis to the normal maximum flow in the same vessel during hyperemia, and can be calculated by:

$$\text{FFR} = \frac{P_d - P_v}{P_a - P_v} \leq \frac{P_d}{P_a}$$

Where Pa is the mean aortic pressure from the guiding catheter, Pd is the distal pressure from the pressure guide wire, and Pv is the central venous pressure, all measured at maximum coronary hyperemia. Since central venous pressure is close to zero, Pv can be neglected. Thus, an accurate estimation of FFR can be derived from the ratio of mean distal coronary artery pressure to aortic pressure during maximal hyperemia. The basis of the FFR concept is illustrated in Fig. 1.

FFR is a lesion-specific index of the severity of epicardial stenosis; relating maximum myocardial blood
flow in the presence of an epicardial stenosis to normal maximum flow. In other words, FFR represents the fraction of normal maximum flow that remains despite an epicardial stenosis. The theoretical value of FFR for normal coronary arteries should be 1.0. As a normal reference vessel is not required, FFR can be used in multivessel disease. The measurement of FFR is highly reproducible and is independent of changes in systemic blood pressure, heart rate or myocardial contractility.\textsuperscript{12}

Instrumentation

Measurement of FFR with a pressure guide wire is a safe method, and only prolongs the intervention procedure slightly. At present, 2 FDA-approved 0.014-inch high fidelity pressure guide wire systems are available: Pressure Analyzer (RADI Medical Systems, Uppsala Sweden) and WaveMap (Volcano Therapeutics Inc., Rancho Cordova, California USA). Intracoronary nitroglycerin and heparin are first administered according to standard practice. After calibration, the pressure guide wire is introduced into the guiding catheter and advanced to its tip. At this point, equality of pressures recorded from both pressure guide wire and guiding catheters is verified. The wire is then advanced into the coronary artery and positioned across the stenosis. Once the pressure has stabilized, maximum coronary hyperemia is then achieved by either intracoronary (IC) bolus administration or continuous intravenous (IV) infusion of a vasodilator agent, and FFR is obtained.

Pharmacological Vasodilators

An important prerequisite of the principle of coronary pressure-derived FFR is to achieve maximal arteriolar vasodilation. If maximal vasodilation is not achieved, lesion severity will be underestimated and the cardiologist may be misled regarding the physiological significance of the stenosis. Several vasodilator agents (Table 1) have been used for this purpose, including papaverine,\textsuperscript{13} adenosine,\textsuperscript{14} adenosine 5’-triphosphate (ATP)\textsuperscript{15-17} and dobutamine.\textsuperscript{18} Practically speaking, a vasodilator agent fulfilling the following criteria is desirable: rapid onset time, cheap, short duration of action, steady state, and the lack of significant side effects. Thus, in view of its high safety profile, low cost and ease of use, a bolus of intracoronary ATP is the agent of choice.

Recently, De Bruyne\textit{ et al.}\textsuperscript{19} examined the differences in FFR among ATP, adenosine, papaverine and contrast medium in 39 patients, and the results showed that by providing a sufficient dosage, ATP, adenosine and papaverine were able to induce maximal hyperemia relative to contrast medium. Also, IC ATP or adenosine (20 to 40 μg) induced a degree of hyperemia similar to that of an IC bolus of 20 mg papaverine. However, only IC papaverine and IV ATP or adenosine induced complete, true steady-state hyperemia, thus allowing the creation of pressure pull-back curves, which provide clear information on the exact location and severity of the stenosis in the presence of diffuse disease or multiple lesions.

FFR and Complex Coronary Intervention

Left main coronary artery disease

The optimal treatment method for left main coronary artery (LMCA) disease remains a controversial issue. The technique of percutaneous transluminal coronary angioplasty (PTCA) has been used in attempts to treat
LMCA disease; however, the results were not favorable, with high rate of procedural complications and an unacceptably high mortality rate. Recently, it has been shown that coronary stent implantation overcomes the limitations of PTCA, and may be a promising alternative to bypass surgery in some patients with unprotected LMCA disease. However, anatomical features such as disease in the ostium of the left anterior descending (LAD) or circumflex arteries may preclude coronary stent implantation. Given the shortcomings of PTCA and stent implantation for LMCA disease, surgical treatment remains the therapy of choice. However, surgical mortality for patients with LMCA disease and prior coronary bypass may be up to 20%. 

Most recently, coronary pressure-derived FFR measurement has emerged to assist decision-making in patients with intermediate LMCA disease, especially in deciding whether or not bypass surgery should be performed. If a lesion is not physiologically significant, surgical treatment may not be necessary, and medical treatment, which is safer and may eventually result in a better outcome, can be used instead. Bech and co-workers studied 54 patients with equivocal LMCA stenosis. In 24 patients whose FFRs were greater than 0.75, bypass surgery was deferred and medical treatment was selected. In the remaining 30 patients, FFRs were less than 0.75 and coronary artery bypass grafting was undertaken. The results showed that survivals among patients at 3 years of follow-up in the medical and surgical groups were 100% and 97%, respectively, while event-free survivals were 76% and 83%. All these findings support the concept that coronary pressure-derived FFR is a reliable and lesion-specific index of reversible ischemia caused by LMCA disease, and deferral of coronary bypass surgery is safe if the FFR value is greater than 0.75.

Multivessel disease

Multivessel coronary angioplasty is feasible and provides excellent early results; however, the long-term outcome is tempered by the frequent need for repeat intervention. Thus, on the basis of the results of randomized studies, coronary artery bypass graft (CABG) surgery remains the standard treatment. Until recently, several studies using coronary stenting for multivessel disease showed that in selected patients with normal left ventricular function, coronary stenting can be performed with high success rate and offer an effective alternative to bypass surgery. However, although coronary stenting has many benefits, it also brings with it inherent problems and cost. In multivessel disease, it is important to know which par-

| Table 1. Comparison of four different pharmacological vasodilator agents |
|----------------|----------------|----------------|----------------|----------------|
|                | Papaverine    | Adenosine      | ATP            | Dobutamine     |
| Intracoronary (IC) or Intravenous (IV) |                |                |                |                |
| **Dosage**    | IC: 15 mg for RCA | IC: 15 to 20 µg for RCA | C: 15 to 20 µg for RCA | IV: 40 µg/kg/min |
|               | 20 mg for LCA  | 20 to 40 µg for LCA | 20 to 40 µg for LCA | 140-160 µg/kg/min |
| **Time to onset of hyperemia** | IC: 30 to 60s | IC: 5 to 10s | IC: 5 to 10s | IV: 2 minutes |
|               | IV: 2 minutes | IV: 2 minutes | IV: 2 minutes |                |
| **Duration of hyperemia** | IC: Up to 2 minutes | IC: 10s | IC: 10s | IV: Infusion stop |
| **Pullback curve** | IC: Possible | IC: Impossible | IC: Impossible | IV: Possible |
| **Side effects** | IC: Polymorphic ventricular tachycardia, ventricular fibrillation, and QTc prolongation | IC: Transient AV block (Overdose) | IC: Transient AV block (Overdose) | IV: Increase heart rate |
|               | IV: Decrease blood pressure, Increase heart rate, Unpleasant angina like burning sensation in chest | IV: Decrease blood pressure, Increase heart rate, Unpleasant angina like burning sensation in chest | IV: Increase heart rate |                |
ticular disease is physiologically significant, may cause symptoms, and is responsible for reversible ischemia. As FFR is a lesion-specific index of the severity of epicardial coronary stenosis, it is extremely useful for identifying one or more culprit lesions in cases of multivessel disease. In a number of patients, bypass surgery can be avoided and PTCA of a culprit lesion can be performed. Also, if acceptable physiological assessment criteria are met, no further intervention may be needed and stent placement can be safely deferred. Thus, coronary pressure-derived FFR measurement is very useful in identifying patients with multivessel disease who might benefit from surgical revascularization.

Studies conducted by Chamuleau and colleagues showed that deferring angioplasty for an intermediate stenosis is safe, when based on FFR criteria, and FFR is more useful than single-photon emission computed tomography for clinical decision-making and risk stratification in patients with multivessel disease.

Transplant vasculopathy

Cardiac allograft vasculopathy (CAV) is one of the most crucial problems in heart transplantation, and is the major cause of mortality and morbidity after the first year of transplantation. Although revascularization therapy options such as percutaneous coronary intervention (PCI), repeat cardiac transplantation and CABG are available, the long-term results are poor. Thus, techniques that can be used for on-line decision-making to justify intervention procedures on the one hand, and to avoid unnecessary intervention in stable CAV patients on the other are attractive. Casella and co-workers reported a case of successful PTCA guided by coronary pressure measurement in a CAV patient. Once an acceptable physiological assessment criterion was achieved after balloon angioplasty, no further intervention was performed; and the results seem very promising. Recently, a study by Fearon et al. on 53 cardiac transplant patients further demonstrated that physiological assessment techniques were useful for screening asymptomatic cardiac transplant recipients for angiographically inapparent transplant arteriopathy. However, the feasibility and safety of using coronary pressure-derived FFR measurement on cardiac transplant patients needs to be further explored.

Diffuse and long lesions

Coronary pressure measurements are also useful in dealing with diffuse and long lesions. A study by De Bruyne and colleagues demonstrated that in diffusely atherosclerotic coronary arteries without focal stenosis at angiography, by withdrawing the pressure guide wire from distal to proximal during maximal hyperemia, there was a gradual, subtle decrement in the pressure gradient that was not seen in normal arteries. Furthermore, they demonstrated that sometimes a marked pressure drop occurred between the distal and proximal part of the artery under investigation, and this observation was believed to reflect the hemodynamic effects of a flow-limiting lesion. Thus, it is believed that in order to quantify the lesion severity of a diffusely affected coronary vessel, maneuver to obtain a pressure pull-back curve during maximal hyperemia is needed. This curve represents the pressure gradient over the entire length of the artery and provides a clear demonstration of the exact location and severity of the stenosis in the presence of diffuse disease or multiple lesions. For this measurement, a true steady-state hyperemic condition is necessary.

DISCUSSION

Even though coronary pressure-derived FFR index can accurately determine the physiological significance of epicardial artery stenosis and is a valuable tool to assist decision making in patients with complex coronary diseases and for deciding whether or not bypass surgery should be performed, there are two known major limitations.

Firstly, this pressure-derived index does not take into consideration the contribution of abnormal microvasculature. The value might be overestimated in patients with microvascular disease, as the increase of epicardial blood flow during maximal hyperemia is limited. Thus, the ideal means of assessing patients with microcirculatory abnormalities is a combination of coronary flow reserve (CFR) and FFR measurement. A high FFR with a low CFR indicates significant microcirculatory abnormality, whereas a low FFR with a low CFR indicates significant epicardial disease. Recently, a new pressure guide wire equipped with both pressure
and temperature sensors has been developed. The pressure sensor measures FFR and the temperature sensor measures CFR by the thermodilution method. Secondly, in patients with left ventricular hypertrophy, the response to coronary vasodilators is very poor, so the FFR values measured may be overestimated. Therefore, in taking care of this kind of patient, FFR values greater than 0.75 should not be used to rule out inducible ischaemia.

In general, coronary pressure-derived FFR measurement is very useful in identifying patients who might benefit from surgical revascularization. Also, if acceptable physiological assessment criteria are met after balloon angioplasty, further intervention procedures are not needed, reducing the number of stents used. Thus FFR guided PCI can be a useful strategy with the benefit of decreased cost.

REFERENCES


