Next Generation Fractional Flow Reserve and Intravascular Ultrasound Technology: Catheter-based and High Definition Intravascular Ultrasound

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Abstract
A satellite symposium, sponsored by ACIST® Medical Systems, was held at EuroPCR 2016 to introduce new technologies in fractional flow reserve (FFR) and intravascular ultrasound (IVUS). FFR is the mainstay of functional haemodynamic assessment of coronary artery lesions, guiding decisions in percutaneous interventions (PCIs). The new RXi™ Rapid Exchange FFR system, featuring an ultra-thin monorail pressure microcatheter (Navvus®) has the potential to simplify PCI procedures as well as to allow the use of a workhorse coronary wire to facilitate both complex and routine FFR assessments. The system has been shown to be feasible and safe in everyday clinical practice and clinical studies. This session also introduced the first 60 MHz high definition (HDi™) IVUS system, which provides improved image quality over traditional IVUS systems, and is able to visualise bioresorbable vascular scaffold (BVS) without the need for contrast clearing.

Keywords
Fractional flow reserve, microcatheter, intravascular ultrasound, coronary artery disease

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Fractional flow reserve (FFR) assesses the reduction in flow resulting from a coronary artery stenosis. Intravascular ultrasound (IVUS) imaging provides a picture from within a coronary artery showing the vessel wall, plaque and lumen in precise detail. Both are essential tools in the evaluation of the physiological significance and proper treatment of coronary stenosis in the catheterisation laboratory. However, as increasingly complex lesions are being treated, there is a need for improved technologies.

A satellite symposium, sponsored by ACIST® Medical Systems, was held on 17 May 2016 at EuroPCR 2016, Paris, France. The symposium had the following aims:

• To understand the value of FFR-guided percutaneous intervention (PCI).
• To discuss the clinical relevance and benefits of microcatheter-based FFR technology.
• To learn how a new microcatheter-based FFR device and high definition (HDi) IVUS, which improves image quality compared with traditional IVUS systems, can optimise the quality of pre- and post-stent assessments.

The use of FFR is increasing worldwide, and with this growing demand comes the need for new technologies to improve speed, accuracy and ease of use. The ACIST RXi™ Rapid Exchange FFR system, which features the Navvus® microcatheter, allows FFR assessment after crossing the lesion with any 0.014” guidewire of choice. The symposium also introduced the high definition 60 MHz IVUS catheter, which is notable for its superior pullback speed and spatial resolution, affecting image quality and procedural time.
Dr Daemen began by describing the new ACIST RXi Rapid Exchange FFR system, which utilises an ultra-thin monorail pressure microcatheter (Navvus, ACIST Medical Systems) and is illustrated in Figure 1. This unique microcatheter allows the use of a guidewire of choice, and may facilitate negotiating complex anatomies, as well as allowing multiple pullback measurements while maintaining guidewire position. The Navvus FFR to Reduce Contrast, Cost and Radiation (CONTRACT) study was an investigator-initiated, single-centre prospective, observational cohort study that aimed to assess whether the use of the RXi Rapid Exchange FFR device reduces cost, contrast and radiation compared with conventional wire-based FFR systems. The study enrolled all consecutive patients referred to the centre for coronary angiography or PCI and an indication to perform FFR at the discretion of the operator, between 1 September 2014 and 28 February 2015. Patients undergoing a procedure on odd dates (i.e. 1st, 3rd, 5th, etc.) were assigned to a conventional FFR system, while those on even dates (2nd, 4th, 6th, etc.) were assigned to the RXi Rapid Exchange FFR system (Navvus group). Of the 238 patients enrolled, 97 patients underwent FFR using the Navvus microcatheter. Of these, 15 patients required the use of two or more devices: in three cases the microcatheter did not cross the lesion, a device defect occurred in eight cases (a manufacturing issue that has since been resolved), the result was questioned in one and unclear in two. The remainder of the patients (n=141) were assigned to conventional FFR (cFFR): St Jude Medical Aeris™/Certus™ (n=120), Radi Medical (n=11) and Volcano Prime/ComboWire® (n=10). Of these, five patients required the use of two or more devices: one was due to a connection problem, two were due to a device defect, one because of unsterile equipment and one because the results were unclear. Final analyses were performed on the cohort in which only one device as used (82 in the Navvus group and 136 in the cFFR group).

There were no significant differences in baseline risk profile and procedural characteristics with the exception of a higher number of small vessels in the Navvus group. Multivessel disease was present in 52.4 % in the Navvus group versus 40.4 % in the cFFR group (p=0.09), leading to multivessel FFR in 22.0 versus 24.2 % (p=0.70) in both groups, respectively. Not including the cFFR wire, the mean number of additional guidewires used was higher in the Navvus group as compared with the cFFR group (2.5 ± 1.2 versus 2.0 ± 1.8, respectively; p=0.03). However, when disregarding the first wire needed to use the Navvus system, the average number of additional wires needed was lower when the Navvus system was used, namely 1.5 versus 2.0; p=0.02.

The mean number of FFR measurements was comparable between both cohorts (1.57 ± 0.84 versus 1.52 ± 0.77; p=0.69) in the Navvus and cFFR group, respectively. Mean FFR values were slightly, though non-significantly, lower in the Navvus compared to the cFFR group (0.82 ± 0.08 versus 0.83 ± 0.10, respectively; p=0.42), leading to a somewhat higher number of positive FFR measurements in the Navvus group (51.9 %) as compared to the cFFR group (43.8 %; p=0.25).

The procedural costs were €1,994 in the Navvus group, compared with €1,930 in the cFFR group (p=non-significant). Subgroup analysis revealed that the use of the Navvus system was associated with numerically (though not significantly) lower costs in patients with positive FFR measurement and those with multivessel disease. The use of contrast agent was similar across the patient population, but a non-significant lower usage of contrast agent was reported in the Navvus group in patients undergoing multivessel FFR and with multivessel disease. Use of radiation was slightly higher in the Navvus group, but again the difference was non-significant. Finally, the procedural time was slightly lower in the Navvus group but once more differences were non-significant (see Figure 2). In a multivariate analysis, significant predictors of cost included bifurcation (p=0.001), number of stents, number of balloons and use of optical coherence tomography (OCT) (all p<0.001), but when correcting for these, use of the Navvus system did not result in a reduction of cost. The same was found with contrast and radiation use.

The investigators concluded that the RXi Navvus FFR system, as compared to conventional pressure wire-based FFR in daily clinical practice, was associated with comparable procedural costs, amounts of radiation and contrast used. A trend was seen to potential advantages in patients with multivessel disease or positive FFR, in which the use of the Navvus system was associated with lower costs, contrast and a shorter procedure time. The study had several limitations: it was a single-centre, non-randomised study with a limited number of patients. In addition, the final analyses were only performed in procedures in which only one device was used. The cost analyses based on local list prices and the potential specific technical advantages of the system were not evaluated.
This presentation discussed the comparison of imaging tools from ACIST and Boston Scientific, together with optical coherence tomography (OCT). Dr. Chieffo has found IVUS particularly useful in the assessment of multivessel disease and complex lesions. The importance of IVUS guidance in PCI is well established. A meta-analysis of 24,849 patients from three randomized controlled trials (RCTs) and 12 observational studies between 2005 and 2013 that compared IVUS- and angiography-guided PCI showed that IVUS was associated with a lower rate of major adverse cardiac events (odds ratio [OR] 0.79, 95% confidence interval [CI] [0.69–0.91]; p=0.001). IVUS-guided PCI was also associated with significantly lower rates of all-cause mortality (OR 0.64; 95% CI [0.51–0.81]; p<0.001), MI (OR 0.57; 95% CI [0.42–0.78]; p<0.001), TVR (OR 0.81; 95% CI [0.68–0.95]; p<0.01) and stent thrombosis (OR 0.59; 95% CI [0.42–0.82]; p=0.002). The authors concluded that IVUS guidance is associated with a significant reduction in adverse events following PCI when compared with angiography guidance alone.4

The imaging tools available in the Milan laboratory are ACIST high-definition IVUS system with a 40 and 60 MHz operation mode, Boston Scientific 40 MHz iLab™ and OCT. Table 1 shows the key features of these systems. Dr. Chieffo presented three clinical cases to illustrate the differences between the systems. In the first case, high-definition IVUS was compared to OCT in a typical patient with diffuse left anterior descending artery disease. The procedure involved the use of bioresorbable vascular scaffolds (BVS) and drug-coated balloon catheters. With these new technologies, accurate imaging tools are essential to guide procedures and to decide which stent is the most appropriate for the patient, if they are suitable for BVS and to assess the final result. Figure 3 shows the difference in images obtained by IVUS and OCT. With the 40 MHz system, the strut was not easy to detect. The OCT imaging was superior in terms of determining overlapping, gaps in the BVS, branch coverage, malapposition, dissection behind the struts and asymmetric expansion with calcification. However, the use of OCT requires additional contrast and is considerably more expensive than IVUS, therefore cost-effectiveness is a factor when selecting imaging modalities.

The next case was a comparison of the high-definition IVUS 60 MHz versus the Boston Scientific 40 MHz IVUS during BVS implantation. Images at different points of the affected vessel were compared. The images obtained by the 60 MHz system are not equal to the quality of OCT but are superior to the 40 MHz system and can help in decision-making. Importantly, the 60 MHz system allows imaging of the BVS without the need for contrast clearing. Another case was presented of a complex bifurcation lesion in which a drug-eluting stent was implanted. The images from the 60 MHz system are clearly superior in quality compared with the 40 MHz system (see Figure 4). In conclusion, in routine imaging, more data are needed to guide complex interventions. The 60 MHz high-definition IVUS system may become a cost-effective means of providing superior images.
Assessment of Catheter-based Interrogation and Standard Techniques for Fractional Flow Reserve: The ACIST-FFR Trial

Dr Price began by presenting clinical data on imaging utilisation from the Scripps Clinic from 2013 to 2015. The usage of FFR has increased by approximately 50% during these years, while the use of IVUS has fallen. In general, FFR is used in diagnostic procedures and IVUS is used to guide treatment.

A number of practical considerations need to be taken into account regarding the broad clinical application of FFR. First is the occurrence of technical errors. Pressure sensor drift can lead to falsely high or low FFR values. Falsely high FFR can result from equalisation with the guide not sufficiently being disengaged, inadequate hyperaemia or deep seating of the coronary guide catheter. On occasions, it is impossible to perform FFR due to an inability to deliver the wire distal to the target lesion. In addition, operator frustration can occur since pressure wires do not have the performance characteristics of workhorse coronary wires. Challenges associated with the use of pressure wires include wire kinking or lack of support when advancing or removing balloons and stents; the need for multiple pull-backs and rewiring for tandem lesions. These challenges contribute to long procedural times, particularly for cases involving more than one vessel. Using FFR in patients with multivessel disease requires multiple advances and withdrawals and therefore durable wires are needed. A coronary workhorse wire is often needed in addition to pressure wires in these cases.

Evidence in support of the use of FFR comes from the Fractional Flow Reserve Versus Angiography for Multivessel Evaluation (FAME) study, a multicentre trial in which patients (n=1,005) with multivessel coronary artery disease (CAD) were randomised to undergo angiography-guided PCI or FFR-guided PCI. Recent 5-year data confirms the long-term safety and interventions are performed on the remaining lesions as needed according to FFR. Repeat pullbacks and advancements, as well as multiple wires, are needed when performing interventions across.

Two types of FFR technologies are commonly employed in clinical practice. Pressure wire technology involves a specially constructed 0.014” wire. A pressure sensor is incorporated into the distal end at the junction of the radiopaque and radiolucent sections. Piezoelectric technology is most commonly used, which has inherent problems, including pressure drift. In addition, the performance of pressure wire technology is not as robust as a dedicated workhorse coronary wire. Microcatheter technology employs a low-profile catheter with a pressure sensor that employs fibre-optic technology incorporated into the distal end. It can be delivered over a standard 0.014” coronary wire.

The RXi Rapid Exchange FFR technology features a marker band located 2.5 mm from tip, a fibre-optic sensor 2.5 mm proximal from the marker band (5 mm from the tip), tip diameter 0.016” and a profile comparable to 0.022” diameter at the lesion site. This system has the potential to overcome some of the limitations associated with conventional pressure wire systems. Equalisation of the catheter is a straightforward procedure: the guide is disengaged from the ostium, the catheter sensor positioned distal to the guide tip and proximal to left main ostium and the guide flushed with saline. The distal workhorse wire facilitates guide catheter disengagement during maximal hyperaemia and re-engagement once complete. There is also no risk of losing the guide position, unlike with a pressure wire, where even gentle orientation can cause the position to be lost.

Tandem lesion assessment is very common and can be quite laborious with a pressure wire. The microcatheter FFR can help evaluate which target lesion is functionally significant. For example, using a pressure wire, the wire is advanced into the distal vessel. Next, wire pullback is performed across lesions during hyperaemia. The lesion that is associated with the greatest absolute drop in FFR is rewired and the necessary intervention performed. Pullback is repeated, then rewiring and interventions are performed on the remaining lesions as needed according to FFR. Repeat pullbacks and advancements, as well as multiple wires, are needed when performing interventions across.
Dr Morice ended by summarising the key learning points of the session. Microcatheter-based FFR technology has the potential to simplify PCI procedures as well as allow the use of a workhorse coronary wire to facilitate both complex and routine FFR assessments. It can locate lesion position with microcatheter pullback, leaving the workhorse wire in place. It can also perform post-stent FFR measurements. This session also introduced the first 60 MHz IVUS system, which significantly improves IVUS imaging.

In summary, with increased use of FFR, particularly in multivessel disease and tandem lesions, convenience and accurate technique are important. Catheter-based FFR is easy to use and helps avoid technical errors. Contrast FFR together with catheter-based FFR is a quick and painless procedure. The prospective, multicentre ACIST-FFR study will address unanswered questions about this technology.

### Summary and Concluding Remarks

A growing body of clinical evidence is available to support the use of FFR- and IVUS-guided PCI. Ongoing microcatheter-based FFR studies will increase the evidence for the use of resting metrics and contrast media to reduce the need for adenosine. In addition, the utility of post-stent FFR is being investigated. Finally, ongoing studies will reinforce the clinical and procedural benefits of microcatheter-based FFR.


