COMMENTARY

ROLE OF INTRA CORONARY IMAGING AND PHYSIOLOGY IN DIAGNOSIS AND MANAGEMENT OF CORONARY ARTERY DISEASE

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Coronary artery disease (CAD) is the leading cause of death in the Indo-Pakistan subcontinent as well as globally. Coronary angiography is considered the gold standard test for the diagnosis of CAD. Therefore, an accurate interpretation of coronary angiography is of paramount importance in decision-making to treat patients with CAD. Coronary angiography has the inherent limitation of being a two-dimensional X-Ray lumenogram of a complex three-dimensional vascular structure. Visual assessment of angiogram can lead to both inter- and intra-observer variability in the assessment of the severity and extent of the disease which can lead to differences in management strategies. This issue becomes even more relevant when assessing left main stem (LMS), bifurcations, diffuse coronary artery disease or situations involving complex coronary morphology. Interventional cardiology has been revolutionised by recent advances in techniques, and innovative technologies in the catheterisation laboratory. Today, a modern catheterisation laboratory is equipped with adjunctive technologies, such as Quantitative Coronary Angiography (QCA), Fractional Flow Reserve (FFR), Intra-Vascular Ultra-Sonography (IVUS), and Optical Coherence Tomography (OCT), to help clinicians make a well-informed decision based on detailed anatomical and physiological assessment of a coronary artery rather than judgement based solely on visual assessment. In this article, we have briefly described the utility and evidence behind these adjunctive modalities and have provided examples of clinical cases to highlight their use in aiding physicians to make a well-informed treatment decision.

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INTRODUCTION

Invasive coronary angiography is considered the gold standard test for assessing the severity and extent of coronary artery disease (CAD).[1] Coronary angiography has been in use for over 70 years. We have seen significant developments and innovations in the technology in recent years and currently it is routinely used in clinical practice all over the world.[2] Millions of coronary angiograms are performed annually worldwide to obtain critical information about the coronary anatomy which along with clinical presentation helps physicians to make treatment plans for patients suffering with CAD. Despite the fact that X-ray angiography is believed to be gold standard to diagnose epicardial coronary disease, one needs to bear in mind that it only provides a two-dimensional lumenogram of a complex three-dimensional arterial structure. Modern X-ray equipment in the cardiac catheterisation laboratory with flat panel detectors and advanced image enhancement algorithms, provide excellent angiographic images with good spatial and temporal resolution. Nevertheless, decisions based solely on X-ray angiography are prone to error, both in deciding whether a particular lesion is significant or not, and making a strategy for the treatment of a particular lesion that is causing ischemia. Cardiologists, often need more information about a particular disease process like, vessel anatomy, extent and severity of the lesion, plaque characteristics such as calcification, fibrosis, plaque rupture, and precise vessel sizing to plan the interventional strategy in a particular case.

There is ample evidence in the literature to suggest that when a particular lesion is viewed by different operators, they can assign various degrees of the stenosis to that specific lesion if based solely on visual estimation.[3] Therefore, from very early on, it was felt that there is a need to reduce or eliminate this inter-observer variability in assessing the degree of stenosis and in the last few decades emergence of newer techniques and technology used both inside and outside the catheterisation laboratory have revolutionized the field of invasive cardiology. Several adjunctive techniques have emerged to improve the diagnostic accuracy and help guide the decision-making process to improve the clinical outcomes.[4] In the era of modern interventional cardiology, cardiologists are performing increasingly complex and challenging cases.[5] A modern catheterisation laboratory is now equipped with adjunctive modalities such as quantitative coronary angiography (QCA), fractional flow reserve (FFR), intravascular ultrasound (IVUS), and optical coherence tomography (OCT). Use of these adjunctive technologies is of great help when

assessing borderline lesions (i.e diameter stenosis of 40–70%), complex left main stem[6, 7] and bifurcation disease[8].

In this article, we provide a brief overview of how the decision-making process has evolved from simple 'eye-balling' of coronary angiogram to one that employs intra-coronary imaging techniques and coronary physiology assessment. These modalities which were predominantly research tools in the past, are now used on daily basis to help make decisions in critical clinical scenarios. In addition to the modalities mentioned in this paper, several other are in development or in clinical use e.g. Near-Infrared Spectroscopy (NIRS), Index of micro-circulatory resistance, (IMR) and are beyond the scope of this paper.

Visual assessment based on Coronary Angiography (CA):

X-ray angiography is widely available and relatively cheap and easy to perform. It has good spatial and temporal resolution and remains the gold standard for diagnosing CAD. Traditionally, the CAD severity is assessed by visual estimates that are based upon multiple views of a coronary artery obtained during an angiogram. Several studies have shown that there is a significant difference in visual estimation of a particular lesion when reported by a physician at different time intervals, or in comparison with other colleagues.[3,8] Despite the potential harmful implications of visual estimation techniques, it still remains the most commonly used form of lesion evaluations and is still widely practised.[9] Although in the majority of cases, it provides diagnostic information, it is not very good at assessing physiological significance of intermediate lesions. Further, X-ray angiography provides limited information about microvascular status. There are many factors that independently contribute to decreased blood flow across a stenosed area (eg, diastolic pressure time, microvascular resistance and effective luminal area.[10] Visual assessment of the CA does not provide this information that is critical to making the decision for patients' care. The interventional community has been well aware of these limitations of CA and many adjunctive modalities, as mentioned earlier, have been developed to overcome these shortcomings of angiography.

Quantitative Coronary Angiography (QCA):

The clinical importance of a coronary narrowing is dependent upon the degree of narrowing, shape, length, eccentricity, number of side branches involved and the presence of subsequent stenosis in a given artery[11,12], Therefore, when coronary luminal effective area is reduced and an attempt is made to estimate the coronary area by simple visual estimation, there is inherent tendency to make mistakes and these limitations were realized in the very early days of coronary angiography and as such attempts at improving this assessment were made. QCA technique is probably the earliest technique to angiographically quantify the degree of stenosis. QCA was done for the first time by Brown and his companions and they were able to manually trace the arterial tree.[13] Then computer programming was used to digitally construct a 3-D representation of the arterial segment and calculate not only the degree of stenosis but also obtain physiological data. The QCA measurements have shown good correlation with visual estimates from cine–film and with haemodynamic significance as depicted by various test for assessment of ischemia.[14]

Although this technique is a well-validated tool for accurately and reproducibly defining coronary lesion severity, it requires additional time and effort. Furthermore, since QCA indirectly defines the anatomy of the vascular wall through inference about the lumen, it may not accurately report the variable and diffuse nature of the atherosclerotic lesion, a finding confirmed by post-mortem studies as well as by IVUS imaging techniques.[15–17] Furthermore, QCA has methodological limitations in assessing bifurcation lesions.[18] Finally, several studies have shown that endovascular techniques such as IVUS, OCT and angioscopy are better at delineating vascular features that accompany unstable ischemic syndromes alongside plaque morphology.[19]

In our opinion estimation of coronary stenosis based on QCA is a simple and low-cost tool with easy learning and should be used routinely, particularly in health care settings where other imaging and physiology based assessments are difficult to access and implement.

Intra-vascular Ultra-Sonography (IVUS):

Intra vascular ultrasound (IVUS) was first introduced by a Japanese group to study intra-cardiac structures in the 1960s.[20] It is now widely used as an intravascular imaging modality to visualise coronary anatomy from the inside of a coronary artery and has excellent penetration power to better delineate and highlight a diseased segment. It has the ability to provide 360° detailed information about an artery with real-time images. This technique yields unique point-of-view pictures, generated in real time, providing information that is far superior to simple angiography or QCA.[21] IVUS can help in the detailed assessment of lumen, vessel size, extent and distribution of plaque. The information obtained by IVUS can help the cardiologist to understand the detailed anatomy of the lesion. Advanced techniques

employing spectral analysis of ultrasound has enabled the development of Virtual histology intravascular ultrasound (VH-IVUS), which can provide further tissue characterization of plaques.

The utility of IVUS is more evident in the treatment of complex coronary lesions, particularly interventions performed on the LMS.[6,7] IVUS can be useful in the diagnosis of dissections spontaneous or iatrogenic.[22] The efficacy and usefulness of IVUS has been validated in several studies.[23,24] The potential utility of IVUS has been recognized by various cardiac societies and recommended in decision-making process in the cardiac catheterization laboratory. The use of IVUS has been particularly encouraged in the assessment of intermediate lesions, guiding stent implantation, and for understanding the mechanisms of stent failure. (Table-1)

IVUS as a modality has been useful particularly in the assessment of cardiac transplant patients.[25,26] Some institutions have used this modality to develop a 'Zero contrast PCI program' to treat patients at high risk of developing contrast-induced nephropathy.[27] IVUS is also a useful tool in the setting of acute emergencies and can help diagnose acute aortic and coronary dissections.[28] IVUS is an excellent modality to optimize the results for various stent based techniques and has shown to improve outcomes compared with angiography-based treatment.[23,24]

The concerns related to cost of this modality have been addressed and it has been demonstrated that although it is associated with higher initial cost, the IVUS guided procedures are more cost effective incomparision to angiography based decisions.[29] We would highly recommend IVUS particularly for assessment of LMS, and large calibre coronary arteries due to excellent penetration power. IVUS is a preferable intracoronary imaging modality in patients with renal disease as it requires no additional contrast. IVUS should be used for optimizing the stents to get the best possible results for patients to minimize the chances of stent failure. This will be cost saving for a system with minimal health care resources.

Table-1: Current guidelines recommendations for use of FFR/IVUS /OCT

Modality	ACC/AHA/SCAI guidelines (2011)	ESC guidelines (2014)
FFR	Recommended to use in intermediate lesions (Level of Evidence A)	1. Recommended to use in intermediate lesions (Level of evidence 1A) and 2. to help decide PCI in multi-vessel disease (Level of evidence 2A)
IVUS	1. Assessment of left main stem disease (Level of Evidence B) 2. Assessment of moderate coronary artery lesions (Level of Evidence B) 3. To guide coronary stent implantation especially (Level of Evidence B) 4. Understanding the mechanism of stent failure (Level of Evidence C) 5. For assessment of cardiac transplant patients. (Level of Evidence B)	1. Assessment and treatment of LMS (Level of evidence 2A) and 2. To optimise stent implantation (Level of evidence 2A)
OCT	The routine use of optical coherence tomography is not established yet. [NB Guidelines are from 2011/2014 and there has been good literature supporting these modalities in recent years and we expect an update in coming years.]	Can be used to understand the mechanism of stent failure and also to optimise the stent results [Level of evidence 2B).

Optical Coherence Tomography (OCT):

Optical coherence tomography (OCT) is another technique to image the coronary artery. OCT evolved from the pioneering work done by Tanno and Fujimoto during the 1990s.[30] It uses light[31], and has the advantage of the higher axial resolution of 10–15 μm, compared to 150–200 μm for IVUS.[32] OCT clearly delineates the three layers of an arterial wall. The excellent resolution of OCT gives detailed information about tissue characteristics and plaque morphology. Information after the implantation of stents like stent apposition, intraluminal thrombi (red and white), dissection, tissue prolapse, can be studied by OCT.[33] OCT has the ability to identify vulnerable plaques and can potentially help treat them even before an event occurs.[34] Moreover, OCT can precisely measure the length and vessel diameter during the PCI that is useful in optimising the size of balloons and stents. OCT, with its superior resolution compared to IVUS, can also help identify the angle and location of the dissection flap more accurately,tissue prolapse, stent edge dissection, and stent malapposition.[35] OCT is particularly useful in understanding the potential mechanism of stent failure. Current OCT techniques require the replacement of the blood in the vessel with a contrast agent and this causes limitation of technology, when assessing vessels of

large diameter or lesions at ostia of coronary arteries.

The safety of OCT technology has been well documented in large-scale clinical trials[36]; However, routine clinical use of OCT still requires further clinical trials to validate the technology, establish standard protocols and to test its safety and efficacy in improving clinical outcomes.[33] Cost remains an important factor in the world-wide uptake of this technology.

We would suggest using OCT in cases where the mechanism of acute coronary syndrome presentation is not clear and this technology can help in the quantification of plaque morphology, and tissue characterization. OCT is an extremely useful tool when an operator is not sure about post procedure dissection, thrombus, stent expansion and apposition. Whenever there is a case of stent failure OCT should be used to understand the mechanism of restenosis and stent thrombosis.

Fractional Flow Reserve (FFR):

Intra-coronary imaging modalities like IVUS and OCT provide a detailed anatomical assessment of coronary lesions, but give limited information about the functional severity of these lesions. Fractional flow reserve (FFR) measurement goes one step further in determining the lesion severity as it calculates the ratio between the maximum achievable blood flow in the stenosed segment of the artery and the theoretical maximum flow in a normal segment of the same artery.[37] FFR can be measured by using a coronary guidewire or a microcatheter (MC) equipped with a pressure sensor that first measures the pressure distal to the stenotic segment of the artery and then measures the aortic pressure under conditions of maximum myocardial hyperaemia. In general, if this FFR ratio is lower than 0.80, and then it is generally considered to be associated with myocardial ischemia. The concept of measuring the blood flow across a stenotic lesion is as old as coronary angioplasty itself. FFR technique has further been validated and evaluated to reduce mortality and morbidity associated with the treatment of intermediate coronary lesions.[38–40] The FAME and FAME II studies have examined the role of FFR in the assessment of multi-vessel CAD, and there is strong evidence now that a revascularization strategy using FFR yields much better clinical outcomes in patients with stable angina and multi-vessel CAD compared to optimal medical treatment alone.[40–42] Current, AHA/ESC guidelines have encouraged the use of this technology to further assess angiographic intermediate coronary lesions (50%-70% diameter stenosis) and its use can be beneficial when making revascularization decisions in patients with stable ischemic heart disease.

Despite the clinical utility and cost-effectiveness of FFR as a modality, it is surprising to note that uptake of FFR is still low with only 6–10% of patients in the United States receiving physiologic FFR assessment prior to percutaneous coronary intervention (PCI).[33,43]

Contrary to the perception that physiology based intervention increases the cost of the procedure, there is evidence that physiology based interventions actually can reduce the cost to half over a period of one-year due to minimising the cost of medications and inappropriate stenting.[44] This can be of particular benefit in a country like Pakistan, where patients and public are struggling to meet the health care costs associated with stent-related procedures.

We would recommend as per guidelines that whenever there is a moderate lesion with stenosis of (40–70%), FFR should be used to make the decision about PCI.

Summary:

Modern X-ray equipment in the catheterisation laboratory provides diagnostic coronary angiograms of excellent quality and resolution. However, a decision based on a simple visual assessment of angiogram can lead to erroneous and sometimes devastating consequences. Thus, an operator must utilise the adjunctive techniques and tools available at his/her disposal to make an informed and well-planned treatment choice. The use of these adjunct techniques like QCA, IVUS, OCT and FFR require the operator to be well trained in their use. Other limiting factors that must be overcome, especially in developing countries, include initial cost, procedure duration, education and training. However, the first step in this journey is for the interventional community to recognise the limitations of angiography.

CASE-1

A coronary angiography of right coronary artery (RCA) demonstrating a lesion in distal RCA. The severity of lesion is assessed differently in different views. The lesion appears significant in (LAO 17.70-Caudal 25.30) (Figure-1A) and non-significant in (LAO 7-Cranial 23.30) (Figure-1B). To assess the functional severity of this lesion an FFR was performed and it demonstrated a functionally non-significant (FFR=0.90) lesion, (Figure-1C, Figure-1 D). Based on this information patient was treated with medical therapy and avoided unnecessary stenting of the coronary artery. The case highlights the limitations of visual estimation of CAD in a single angiographic view and use of FFR to help guide the treatment strategy.

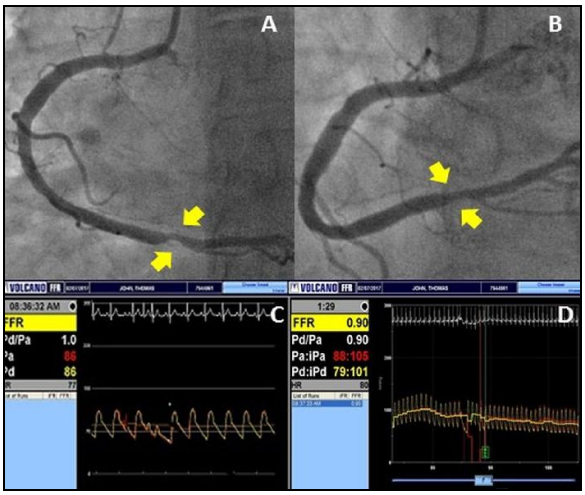

Figure-1: Discrepancy in angiography and physiology measurements.

CASE-2

Angiographic and IVUS measurement discrepancy is highlighted in the following case. Angiogram panel (A) shows a lesion in LMCA but IVUS (A1) demonstrated that lesion is non-significant with an MLA of 8.6 mm^2. Another angiogram (B) shows possible lesion in LMCA and IVUS (B1) showed it to be significant with MLA of 4.6 mm^2.

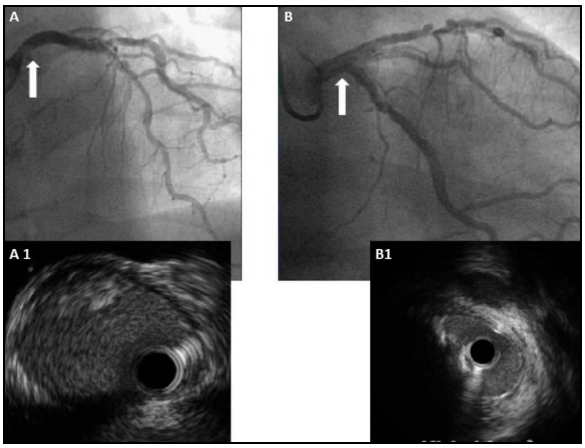

Figure-3: Discrepancy in measurements by IVUS and Angiography

CASE-3

A patient presented with Non- ST elevation myocardial infarction (NSTEMI), and coronary angiography of right coronary artery (RCA) demonstrated three mild to moderate lesions in mid region, (White and red arrows). Based on angiography it was not clear which one is culprit lesion and a decision was made to image the lesions with IVUS and OCT. The Proximal and distal lesions (white arrows) were non-significant (non–culprit) and middle lesion (red arrows) demonstrated plaque rupture with superimposed thrombus.

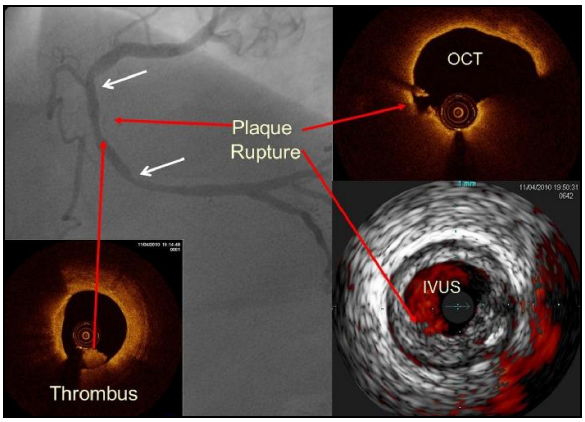

Figure-3: Role of OCT in helping to decide the mechanism of acute coronary syndrome.

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