Institution:	Imperial College London
Unit of Assessment:	12 Engineering
Title of case study:	Instantaneous Wave-free Ratio (iFR) for the Diagnosis of Coronary Heart Disease
Period when the underpinning research was undertaken:	2000 - 2018

Details of staff conducting the underpinning research from the submitting unit

Name(s):	Role(s) (e.g. job title):	Period(s) employed:
Prof Kim Parker	Emeritus Professor of Physiological Fluid Mechanics & Senior Research Investigator, Department of Bioengineering	1988 to present
Dr Justin E Davies	Senior Research Fellow, National Heart & Lung Institute, Faculty of Medicine	2004 to present
Prof Jamil Mayet	Professor of Cardiology, National Heart & Lung Institute, Faculty of Medicine	2000 to present

Period when the claimed impact occurred: 1 Aug. 2013 – 31 Dec. 2020

Is this case study continued from a case study submitted in 2014? Yes

1. Summary of the impact

Coronary heart disease accounts for nearly 12% of all deaths in the UK and results from abnormal narrowing, or stenosis, of blood vessels feeding the heart. **Instantaneous wave-free ratio** (iFR) is a diagnostic tool, developed at Imperial, to assess the severity of coronary artery stenosis.

iFR received a CE mark and FDA approval in 2014 and is now recommended by all major international guidelines to stratify selection of patients to undergo either coronary stenting or bypass surgery. iFR can assess stenosis severity within a few heartbeats and reduces both procedural time and costs by 10% compared to the leading alternative (Fractional Flow Reserve; FFR), resulting in a savings of USD896 per patient. Importantly, iFR obviated the need for costly and unpleasant hyperaemic drugs that are required for FFR. By performing the measurement without these drugs, iFR reduced adverse procedural symptoms by 90% relative to FFR.

iFR has been licensed to Volcano-Philips in 2014 and has now been integrated into their product. It is now being used in more than 5000 clinical cardiac catherization laboratories in more than 30 countries. iFR has been used more than 100,000 procedures between 2018 and 2020 in Europe alone. The estimated saving in these cases alone is in excess of USD100,000,000.

2. Underpinning research

<u>Background</u>

When the left ventricle contracts, it generates waves of blood pressure and flow that propagate along the arteries. When waves reach discontinuities in vessel shape or wall compliance, as occur at vessel branches, some of the wave energy is reflected. With each heartbeat, 100's to 1000's of reflected waves superimpose to determine the pressure and flow at each point in the arterial tree. Such a myriad of interacting waves creates a complex dynamic environment that complicates clinical measurements of arterial pressure. A notable example is the catheter-based measurement of the pressure drop across a coronary stenosis (a focal narrowing of coronary arteries that feed the heart) that serves as a key indicator for severity of coronary heart disease, which is a leading cause of death worldwide. The traditional method to measure the pressure drop across a coronary stenosis, known as Fractional Flow Reserve (FFR), is performed after administering a powerful vasodilator (adenosine) to minimise downstream vessel resistance and thereby reduce the confounding effect of downstream pressure waves.

Wave analysis is typically based on Fourier decomposition, but this method is inadequate for analysing arterial flow. That is because Fourier decomposition, producing only sinusoidal waves with no beginning or end, is unable to specify the position of individual wavefronts in space and time, which is necessary to discriminate upstream from downstream waves and account for their interactions. To overcome these limitations, Prof. Kim Parker in 1990 introduced **Wave Intensity Analysis (WIA)** to analyse non-linear wave propagation in arteries. WIA conceptualises pressure and flow waves as a superposition of infinitesimal wavefronts (as opposed to sinusoidal wavetrains as in Fourier analysis). Mathematically, WIA is formulated based on Riemann's method of characteristics, but the equations derived for its practical application are surprisingly simple. By 2000, WIA had been successfully applied to systemic and pulmonary arteries, but these applications were relatively straightforward because all waves could be attributed to primary waves generated by ventricular contraction with superimposed reflections and re-reflections of these primary waves.

<u>Research Conducted since 2000</u>

It was not until 2000 that Parker, working with a team of international colleagues, first applied WIA to coronary arteries of dogs [R1]. This is particularly challenging because the downstream arteries that branch from the main coronaries are embedded within heart muscle that cyclically contracts and compresses the vessels during each heartbeat. This generates additional waves and introduces a time-varying downstream resistance that further complicates the interpretation of pressure measurements in the coronary arteries.

Prof. Parker, working closely with colleagues in the Faculty of Medicine, Dr. Justin Davies and Professor Jamil Mayet, then applied WIA to analyse pressure and flow waves in the coronary arteries of human patients [R2]. This team used WIA to identify the dominant waves and attribute wave generation to the downstream compressive effect of the surrounding heart muscle [R3]. Differences in wave propagation between the right and left coronary arteries (which have the same upstream pressure) were shown to originate from differences in the strength of muscular contraction between the right and left ventricles [R4].

Importantly, WIA revealed a brief **"wave-free" period** within the coronary arteries that occurs during the middle of the resting or diastolic phase of the cardiac cycle. During the wave-free period, heart muscle relaxes, minimising downstream resistance and reducing the compressive forces responsible for generating pressure waves in the coronary arteries [R5]. Identification of the wave-free period inspired the development of iFR (**Instantaneous wave-free ratio**), the new diagnostic tool capable of assessing the severity of coronary artery stenoses. When using iFR, one first identifies the wave-free period, then computes the ratio of distal coronary pressure (downstream of the stenosis) to upstream aortic pressure during this period. This works because during the wave-free period, the pressure drop across the coronary stenosis is unaffected by downstream pressure waves and thus the pressure drop can be measured directly using pressure transducers within the angiogenic catheter. Most importantly, this measurement can be done without administering powerful vasodilators.

A proof-of-concept study with patients indicated that the pressure ratio measured by iFR was a good indicator of the functional effect of the stenosis on flow, and clinical trials were started to compare the efficacy of iFR analysis against the current standard FFR [R6]. These studies showed that iFR yields equivalent classification as FFR for coronary stenosis severity, but without requiring the use of powerful hyperaemic drugs that are responsible for adverse procedural symptoms.

3. References to the research

R1. Sun YH, Anderson TJ, **Parker KH**, Tyberg JV. Wave-intensity analysis: A new approach to coronary hemodynamics. *J Appl Physiol*, 2000. 89(4): 1636-1644. DOI: 10.1152/jappl.2000.89.4.1636

R2. Aguado-Sierra J, **Parker KH**, **Davies JE**, Francis D, Hughes AD, **Mayet J**. Arterial pulse wave velocity in coronary arteries. Conf Proc IEEE Eng Med Biol Soc. 2006;1:867-870. DOI: 10.1109/IEMBS.2006.259375

R3. **Davies JE**, Whinnett ZI, …, **Parker KH**, **Mayet J**. Evidence of a dominant backward-propagating “suction” wave responsible for diastolic coronary filling in humans, attenuated in left ventricular hypertropy. *Circulation*. 113:1768-1778, 2006. DOI: 10.1161/CIRCULATIONAHA.105.603050

R4. Hadjiloizou N, **Davies JE**, …, **Parker KH**, …, **Mayet J**. Differences in cardiac microcirculatory wave patterns between the proximal left mainstem and proximal right coronary artery. *Am. J. Physiol. Heart Circ. Physiol*. 295: H1198-H1205, 2008. doi:10.1152/ajpheart.00510.2008.

R5. Sen S, Escaned J, …. **Parker KH**, … **Mayet J**, **Davies JE**. Development and validation of a new adenosine-independent index of stenosis severity from coronary wave–intensity analysis: results of the ADVISE (ADenosine Vasodilator Independent Stenosis Evaluation) study. *J. Amer. Coll. Cardiol*. 59(15):1392-1402, 2012. DOI: 10.1016/j.jacc.2011.11.003

R6. Sen S, Kaleab N, …. **Parker KH**, … **Mayet J**, … **Davies JE**. Diagnostic classification of the instantaneous wave-free ratio is equivalent to fractional flow reserve and is not improved with adenosine administration: results of CLARIFY (Classification Accuracy of Pressure-Only Ratios Against Indices Using Flow Study), *J. Amer. Coll. Cardiol.* 61(13):1409-1420, 2013. DOI: 10.1016/j.jacc.2013.01.034

4. Details of the impact

Background

Coronary heart disease is a leading cause of death, killing 3.8 million men and 3.4 million women per year worldwide. The primary cause is a build-up of fatty plaque-like material in the wall of the coronary artery that narrows the artery lumen (stenosis). Coronary heart disease is life-threatening because the stenosis reduces blood flow to the heart, resulting in angina (chest pain), heart attack and stroke and can lead to heart failure and abnormal heart rhythm.

Coronary heart disease can be treated with drugs or, in more extreme cases, coronary artery bypass surgery or stenting (placing an intravascular metallic frame to force open the artery). Each year, stenting is performed in more than 500,000 patients worldwide. Selecting patients for different treatments is often tricky and based on diagnostic angiography, which generates 2D images of the coronary artery lumen. Cardiologists examine these images to decide the best treatment option, but this is subjective and can be inaccurate due to anatomical differences between patients. A more accurate “functional” assessment of the severity of the stenosis can be obtained by measuring the pressure-drop across the stenosis using iFR or FFR. Pressure is measured by threading a thin wire, or catheter, containing a miniature pressure transducer into the coronary artery, guided from an incision in the femoral or radial artery.

<u>Impact of iFR</u>

Based on pressure measurements in the coronary artery, either iFR or FFR can be used to assess the severity of disease and the need for stenting. However, iFR and FFR differ because FFR requires use of hyperaemic/vasodilatory agents such as adenosine, while iFR does not. Adenosine is a powerful drug that may cause severe chest pain and is counter-indicated in children, asthmatics and people with low blood pressure. Eliminating the need for adenosine means that the procedure can be performed faster, with less discomfort and risk. iFR can also be performed on patients who are contra-indicated for adenosine and so could not otherwise undergo FFR for coronary assessment. During the current REF period, clinicians conducted detailed studies on efficacy of iFR as an alternative to FFR. It has been demonstrated that, **relative to FFR, iFR achieves a 90% reduction in adverse procedural symptoms, 10% reduction in procedure time and a 25% reduction in readmissions [E1, E2].** Emerging data suggest that iFR is superior to FFR [E3]. These are evidence that the scientific advancements from Parker, Davies, and others from Imperial have been successfully translated from research to clinical applications [E4].

iFR estimation being used on a Philips machine mapping physiology information into the anatomy image

iFR was CE marked and was approved by the FDA in 2014 [E5, E6]. These regulatory approvals provided a springboard for iFR to progress from a research phase to large scale clinical use after 2014. The invention, which was patented by Imperial Innovations in 2010, was licensed to Volcano-Philips in 2014. iFR is now part of their product offerings and is used in over 5000 catheter labs around the world, having been studied in over 15,000 patients as part of clinical trial [E7].

iFR is included in the 2018 clinical guidelines published by the European Society of Cardiology (ESC) and European Association of Cardio-Thoracic Surgery (EACTS), where **iFR receives a Class IA recommendation** (meaning that there is general agreement that a treatment is beneficial, useful and effective based on data from multiple randomized clinical trials) [E8; see table on page 98]. In the worldwide 2017 guidelines published by the American College of Cardiology, American Heart Association and Society of Cardiovascular Angiography and Interventions (among other professional clinical societies), iFR is included as a measurement tool that can be appropriately used to assess the physiological significance of coronary artery stenosis without use of hyperaemic agents [E9, see pages 2218 §3 and Table 1.1 on page 2224].

With its inclusion in worldwide guidelines for cardiologist and its integration into Volcano-Philips' interventional cardiology devices, the impact of iFR as a standard diagnostic tool has accelerated since 2018. Outside of clinical trials, it is estimated that such interventional cardiology procedure has been used approximately 400,000 times in Europe alone between 2018 and 2020 [E10]. While it is impossible to determine whether iFR made a difference to clinician's decision in each case, it is not unreasonable to estimate that, iFR helped in at least 50% of cases. Therefore the number of patients benefitted from our underpinning research is estimated to be in hundreds of thousands. Volcano-Philips estimated that iFR provides a cost reduction of approximately USD900 per patient [E11]. Therefore the estimated cost saving attributed to iFR since 2018 in Europe alone is estimated to be at least USD100,000,000.

5. Sources to corroborate the impact

E1 Götberg M, et al., Instantaneous wave-free ratio versus fractional flow reserve to guide PCI. *New Engl. J. Med*. 376(19): 1813-1823, 2017. PDF available here.

E2 Davies, J.E., et al., Use of the instantaneous wave-free ratio or fractional flow reserve in PCI. New Engl. J. Med. 376(19): 1824-1834, 2017. PDF available here.

E3 Götberg M, et al., The evolving future of instantaneous wave-free ratio and fractional flow reserve. J. Am. Coll. Cardiol. 70(11): 1379-1402, 2017. PDF available here.

E4 Video showing iFR being applied in a clinical setting. https://www.youtube.com/watch?v=5HoiKbWeg30 Link archived here.

E5 iFR received FDA approval (2014) https://www.nsmedicaldevices.com/news/volcano-obtains-fda-clearance-of-its-instant-wave-free-ratio-modality-200314-4200181/ Link archived here.

E6 Philips-Volcano's proprietary coronary pressure measurement modality iFR receiving FDA approval (2014). http://www.ptca.org/news/2014/0319_VOLCANO_IFR.html Link archived here.

E7 "Proven outcomes. Superior value." by Philips on their iFR product. https://www.philips.sa/en/healthcare/education-resources/ifr-outcome-data Link archived here.

E8 2018 ESC/EACTS Guidelines on myocardial revascularization: The task force on myocardial revascularization of the European society of cardiology (ESC) and European association for cardio-thoracic surgery (EACTS). Eur Heart J. 2018;00:1-96. https://doi.org/10.1093/eurheartj/ehy394 PDF available here.

E9 Patel M, et al., ACC/AATS/AHA/ASE/ASNC/SCAI/SCCT/STS 2017 Appropriate Use Criteria for Coronary Revascularization in Patients with Stable Ischemic Heart Disease. J Am Coll Cardiol. 2017 May 2;69(17):2212-2241. PDF available here.

E10 Market Insights on Interventional Cardiology Devices, Medtech 360 by Millennium Research Group Inc., with estimate of the use of iFR and FFR devices in Europe since 2018. PDF available here.

E11 "iFR in a class of its own" by Philips with quantitative data on impact of iFR. https://www.philips.com/c-dam/b2bhc/master/education-resources/technologies/igt/images/ifr-class-of-its-own-flyer.pdf?_ga=2.11020532.130870662.1599822809-1614149729.1599822809. Link archived here.