Institution: Imperial College London

Unit of Assessment: 15 (General Engineering)

Title of case study: Wave Intensity Analysis removes the need for drugs in the diagnosis of coronary heart disease

1. Summary of the impact (indicative maximum 100 words)

Professor Kim Parker in the Department of Bioengineering has developed Wave Intensity Analysis (WIA) for characterising pressure and flow waves in arteries. It is being used to assess whether patients need interventions to reduce narrowing of their coronary arteries. Conventional diagnoses require the use of a drug that is costly, time consuming to administer and has unpleasant side effects; it cannot be used in some patient groups. WIA obviates the need for the drug and can be used as the sole diagnostic method in more than half of patients. After being assessed in trials involving >2500 patients, the method became commercially available, and is in routine clinical use in 3 continents. It removes the cost of the drug (which can be US$500 per case in some countries), increases throughput by halving the time taken for the procedure, reduces side effects and makes rigorous diagnosis available to patient groups that cannot tolerate the drug and therefore depended on unreliable, imaging-based methods until now.

2. Underpinning research (indicative maximum 500 words)

When the left ventricle contracts, it generates waves of blood pressure and flow that propagate along the systemic arteries and smaller blood vessels. When the waves reach discontinuities in vessel shape or mechanical properties, such as occur at branches, some of the wave energy is reflected. Maximum (systolic) and minimum (diastolic) blood pressures in large arteries are widely used to indicate cardiovascular health and risk of cardiovascular disease, but the pressure and flow waves and their reflections also depend on cardiac performance and blood vessel properties, so it should be possible to use them as additional – and potentially more informative – diagnostic indicators.

Traditional methods for analysing the waves are based on Fourier analysis. This approach has a conceptual flaw: despite the quasi-regular appearance of the heartbeat, the circulatory system is not in steady-state oscillation. The approach also has a practical flaw: the results are in the frequency domain, which makes it hard to relate them to any physiological property of the vessels. It was therefore a major paradigm shift when Professor Kim Parker, working in the Department of Bioengineering and its forebears at Imperial, introduced Wave Intensity Analysis (WIA) to replace the traditional approach. WIA conceptualises the pressure and flow waves as arising from the superposition of infinitesimal wavefronts. The wavefronts can travel forward or backwards, and can increase or decrease pressure and flow. The mathematical derivation of WIA is complex, being based on Riemann's method of characteristics, but the equations derived for its practical application are surprisingly simple.

Parker published early versions of the WIA concept in 1988 and 1990, but it was developed and systematically applied to physiological data from 1997 onwards, initially to explain successive events in the filling of the left ventricle [1] and to characterise the timing of waves in the aorta [2]. These successes were facilitated by the fact that WIA operates in the time domain, but they were hindered by the inability to determine the local wave speed; separation of forward- and backward-travelling waves can be achieved if the wave speed is known. Subsequent papers presented novel methods for determining local aortic [3] and coronary artery [4] wave speeds using only the pressure and flow measurements that are required for the WIA itself. A further theoretical advance of great practical significance was the separation of pressure due to waves from pressure caused

by the stretching of elastic blood vessels [5]; pressures during the later part of each cardiac cycle are dominated by the latter "reservoir" properties and had been incorrectly attributed to waves in previous work based on Fourier methods.

The development of WIA into a method with practical utility has resulted in it being used to characterise waves in the heart, arteries, and veins by bioengineers, physiologists and clinicians in over 10 countries. It was the subject of an international conference in 2004 and the focus of a dedicated issue of Medical & Biological Engineering & Computing in 2009 [6]. Its application to clinically-important problems has resulted in 7 papers in the two top-ranked cardiovascular journals.

3. References to the research (indicative maximum of six references)
* References that best indicate quality of underpinning research.

1. MacRae JM, Sun YH, Isaac DL, Dobson GM, Cheng CP, Little WC, Parker KH, Tyberg JV. Wave intensity analysis: a new approach to left ventricular filling dynamics. Heart Vessels. 1997;12:53-59. DOI: 10.1007/BF02820867

*2. Koh TW, Pepper JR, DeSouza AC, Parker KH. Analysis of wave reflections in the arterial system using wave intensity: a novel method for predicting the timing and amplitude of reflected waves. Heart Vessels. 1998;13:103-113. DOI: 10.1007/BF01747827 Cited 34 times by 12.10.2013

*3. Khir AW, O'Brien A, Gibbs JS, Parker KH. Determination of wave speed and wave separation in the arteries. J Biomech. 2001;34:1145-1155. DOI: 10.1016/S0021-9290(01)00076-8

4. 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. 10.1109/IEMBS.2006.259375

*5. Wang JJ, O'Brien AB, Shrive NG, Parker KH, Tyberg JV. Time-domain representation of ventricular-arterial coupling as a windkessel and wave system. Am J Physiol Heart Circ Physiol. 2003;284: H1358-H1368. http://ajpheart.physiology.org/content/284/4/H1358

6. Special Issue on Arterial Hemodynamics: Wave Analysis in Frequency and Time Domain Medical & Biological Engineering & Computing, 2009;47: whole of issue number 2 http://www.bg.ic.ac.uk/research/k.parker/wave_intensity_web/special_issue.html

4. Details of the impact (indicative maximum 750 words)

WIA is now being used clinically to diagnose narrowing ("stenosis") of coronary arteries. This narrowing is the underlying pathology of Coronary Heart Disease (CHD), and is the cause of most heart attacks. In the UK, a heart attack occurs every 2 minutes and around half of them are fatal, accounting for approximately one third of all deaths. CHD is also a common cause of severe morbidity.

Non-pharmaceutical, non-surgical treatment consists of making a small incision in an artery in the groin, guiding a catheter up the arterial system into the stenosed area of the coronary artery, and then temporarily inflating a balloon and/or permanently inserting a stent (a cylindrical tube made of wire mesh) to open up the lumen of the vessel. About 90,000 procedures of this type are carried out in the UK each year. However, they are expensive and carry risk for the patient, including precipitation of a heart attack, re-narrowing of the vessel, or occlusion of the stent; the risk of a serious adverse event at the time of the procedure is 1%, and around 3% of cases suffer in-stent restenosis in the longer term. It is therefore important not to use them unnecessarily. On the other hand, the procedures substantially reduce symptoms when the disease is severe so it is also

important to use them in patients who do need them.

Patient stratification was traditionally carried out by X-ray imaging of the stenosis. However, many stenoses that appear significant by such anatomical criteria are not functionally significant, and stenting them worsens patient outcomes. Fractional Flow Reserve (FFR) is a functional method for assessing stenosis, introduced in 1995 [A]. In this method, the ratio of the mean pressure downstream and upstream of the stenosis is measured as an indicator of the severity of the stenosis. FFR is replacing image-based methods; for example, the “appropriate use” criteria in the USA now require a measure of ischaemia (impaired blood supply) in all patients before stenting. However, during FFR measurements, it is necessary to stabilise and minimise the resistance of the smaller blood vessels supplied through the coronary artery by administering a potent dilating drug. That carries serious practical difficulties and adverse consequences. The drugs are unavailable or precipitously expensive (up to US$500 per case) in some countries. Even if the cost is acceptable for a single vessel, multi-vessel assessment in the same patient is usually not feasible. Administration of the drug takes time (about 12 minutes of a 20-30 minute procedure) and requires catheterisation of the femoral vein. Furthermore, the drug is very unpleasant, causing a sensation of “impending doom.” For these reasons, the procedure is inadvisable for some patient groups (children, asthmatics, hypotensives and people with heart block) who therefore have to rely on the less invasive but unreliable imaging-based methods, and patient throughput is reduced with consequent increase in cost.

WIA has permitted the development of an alternative method – instantaneous wave-free ratio (iFR) – that does not require dilating drugs. WIA is used to identify a wave-free period during the cardiac cycle where resistance of the small vessels is naturally low and stable. At that point, the pressure ratio across the stenosis can be used to assess the resistance caused by the stenosis, as in FFR after drug administration.

iFR requires hardware that is already in place in many catheterization clinics – a fine-wire catheter system simultaneously measuring pressure at two locations and flow. Only new software is required; this is based on algorithms developed by Professor Parker and Dr Justin Davies of the National Heart and Lung Institute at Imperial. First-in-man cases using the on-line system were conducted at Hammersmith Hospital London in January 2013. Since then the system, manufactured by Volcano, has been placed in 20 centres, in 3 continents around the world [B]. The updated software was initially distributed for research purposes, and used in the multi-centre international clinical trial ADVISE (ADenosine Vasodilator Independent Stenosis Evaluation), which concluded that iFR gave a drug-free index of stenosis severity comparable to FFR [C]. (The most recent study [D] found in 1500 patients that iFR can achieve a 95% overall match with FFR.) The system is now available commercially and is in regular clinical use; by July 2013, real-time measurements had been made in around 650 cases [D].

Ongoing clinical trials include ADVISE II, an FDA-sanctioned trial to further compare iFR with FFR in 900 patients. Provisional results of ADVISE II were presented at EuroPCR [E]; they showed that the use of iFR alone was sufficient for diagnosis in more than half of patients. Although such clinical trials continue, the technique is already changing routine clinical practice. For example, Dr Sharp, Interventional Cardiologist at Royal Devon & Exeter Hospital, has stated [F]: “After using iFR in real world clinical practice, its simplicity is clearly its strength. In a busy cath lab, saving time is important and the results in my early experience have been consistent and clinically useful."

5. Sources to corroborate the impact (indicative maximum of 10 references.)

A. Pijls NH, Van Gelder B, Van der Voort P, Peels K, Bracke FA, Bonnier HJ, el Gamal MI Fractional flow reserve. A useful index to evaluate the influence of an epicardial coronary stenosis on myocardial blood flow. Circulation. 1995;92: 3183-3193. *A paper that describes the method employing drugs which is superseded by using wave intensity analysis*

B. Executive Vice President and General Manager, Functional Management Business Unit, Volcano Corporation. *Mr Burnett can verify sales of the Volcano system that incorporates the new software.*

C. Sen S, Escaned J, Malik IS, Mikhail GW, Foale RA, Mila R, Tarkin J, Petraco R, Broyd C, Jabbour R, Sethi A, Baker CS, Bellamy M, Al-Bustami M, Hackett D, Khan M, Lefroy D, Parker KH, Hughes AD, Francis DP, Di Mario C, 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 Am Coll Cardiol. 2012;59: 1392-1402. DOI: 10.1016/j.jacc.2011.11.003 *A paper that describes a clinical trial comparing the previous and new methods of coronary diagnosis*

D. Senior Research Fellow and Honorary Consultant Cardiologist at the National Heart and Lung Institute, Imperial College London. *Dr Davies can confirm the number of patients examined using real-time iFR and unpublished data from ongoing clinical trials*

E. Adenosine vasodilator independent stenosis evaluation II (ADVISE II) *J. Escaned.* EuroPCR, Paris, May 23rd 2013. http://solaci.org/en/javier_escaned_europcr.php *Web-published abstract of a EuroPCR talk describing interim data from the ADVISE II trial. Archived on 24/10/2013 at https://www.imperial.ac.uk/ref/webarchive/r1f*

F. http://ir.volcanocorp.com/releasedetail.cfm?ReleaseID=766802 *Source of a quotation from Dr Sharp describing the benefits of adopting iFR in clinical practice at the Royal Devon and Exeter Hospital. Archived on 24/10/2013 at https://www.imperial.ac.uk/ref/webarchive/q1f*