Institution: University of Leicester

Unit of Assessment: UoA01

Title of case study: Improved assessment of hypertension: development of non-invasive measurement of central aortic pressure as a better predictor of clinical outcomes

1. Summary of the impact

Around 25% of UK adults have high blood pressure (hypertension), accounting for more than half of all strokes and heart disease. The pressure that the heart and brain senses that leads to these diseases is central aortic pressure. The Unit's research developed and evaluated methods for the non-invasive assessment of central aortic pressure, demonstrating its important relationship to clinical outcomes. The work has contributed to improvements in the way high blood pressure is treated for millions of people, nationally and worldwide, by **(i)** providing a rationale for one of the biggest-ever changes in treatment guidance in 2006; **(ii)** stimulating major growth in medical devices for the non-invasive measurement of aortic pressure with a simple, easy-to-use wristwatch invention; **(iii)** and developing central aortic pressure as a better biomarker for pharmaceutical companies to develop new drugs to treat hypertension.

2. Underpinning research

For more than a century, blood pressure (BP) has traditionally been measured over the brachial artery in the arm and has long been assumed to accurately represent the true pressure in the large arteries (central aortic pressure) and to accurately reflect the cardiovascular risk related to high blood pressure. Effects on brachial artery pressure are widely used to evaluate the beneficial effects of blood-pressure lowering medication. In 2000, Professor Bryan Williams and other researchers at the University of Leicester, one of the leading high blood pressure centres in Europe, challenged this dogma and designed and led the first large-scale comparison of aortic versus brachial pressure and the differential effect of commonly used drugs to treat hypertension on these two measures.

CAFE study

The Unit used non-invasive radial artery tonometry, calibrated to brachial blood pressure, to derive central aortic pressure measurements and demonstrated that beta-blockers, among the most widely used blood pressure lowering treatments in the world, were much less effective at reducing aortic pressure than other treatments, even though they lower blood pressure to the same extent when measured in the arm.[1] Importantly, this detailed mechanistic study (the Conduit Artery Function Evaluation – CAFE study) was embedded within a larger clinical outcomes trial (the Anglo-Scandinavian Cardiac Outcomes Trial – ASCOT) in which Williams and the Unit were investigators. ASCOT subsequently demonstrated that beta-blocker treatment was also less effective than the other blood pressure lowering drugs at protecting against cardiovascular outcomes, especially stroke, thus highlighting the importance of central aortic pressure as the principal determinant of cardiovascular risk related to blood pressure.

The Unit subsequently showed that the lesser reduction in aortic relative to brachial pressure with beta-blockers was directly related to their heart rate lowering effect and made the important observation that this effect was likely to be common to all heart rate lowering drugs.[2] Further work characterised, for the first time, the effects of statin therapy on aortic pressures.[3]

A simpler approach to measuring aortic pressure

At this stage, the expensive equipment used by the team to measure aortic pressure was impractical for more routine clinical use. Williams therefore collaborated with a small biotech company in Singapore (HealthSTATS International) that had developed a wristwatch device with a tonometer embedded within the strap that could repeatedly capture the radial artery wave form non-invasively. The Unit recognised that the radial wave form captured by this device contained all the information needed to estimate aortic pressure and worked with the Singapore team to develop

and validate a novel but simple mathematical model to calculate central aortic pressure.[4] Recognising its importance, this methodology gained fast-tracked approval by the FDA for clinical use in the USA and its potential for improved assessment of the effectiveness of new drugs was soon recognised by the pharmaceutical industry. Specifically, the wrist-watch device conveniently allows not only single but repeated measure of aortic pressure to be made throughout the day with the individual carrying out their normal activities. Indeed, working in collaboration with Novartis, Williams and colleagues reported the first-ever description of the non-invasive measurement of ambulatory aortic pressure in humans and the impact of blood pressure lowering therapy on ambulatory aortic pressure.[5]

Key Staff
Leicester: Professor Bryan Williams, Professor of Medicine (1991 – 2012); Dr Peter Lacy (2000 - 2012); Professor H Thurston, Professor of Medicine (1975 - 2007)
Other: Dr Choon-Meng Ting, Dr Chua-Ngak Hwee and Dr Liang (all HealthSTATS, Singapore)

3. References to the research

1. **Williams B, Lacy PS**, Thom SM, Cruickshank K, Stanton A, Collier D, Hughes AD, **Thurston H**, O'Rourke MF, for the CAFE investigators. Differential Impact of Blood Pressure Lowering drugs on Central Aortic Pressure and Clinical Outcomes - Principal Results of the Conduit Artery Function Evaluation study: The CAFE Study. Circulation 2006; 113: 1213-1225

2. **Williams B, Lacy PS.** Impact of heart rate on central aortic pressures and hemodynamics. Analysis from the CAFE study: CAFE-heart rate. J Am Coll Cardiol. 2009; 54: 705-513.

3. **Williams B, Lacy PS**, Cruickshank JK, Collier D, Hughes AD, Stanton A, Thom S, **Thurston H**, for the CAFE investigators. Impact of Statin Therapy on Central Aortic Pressures and Hemodynamics - Principal Results of the Conduit Artery Function Evaluation study Lipid Lowering Arm: The CAFE-LLA Study. Circulation 2009; 119: 53-61.

4. **Williams B, Lacy PS**, Yan P, Hwee C, Liang C, Ting C. Development and Validation of a Novel Method to Derive Central Aortic Systolic Pressure From the Radial Pressure Waveform Using an N-Point Moving Average Method. J Am Coll Cardiol. 2011;57(8):951-961. doi:10.1016/j.jacc.2010.09.054.

5. **Williams B, Lacy PS,** Baschiera F, Brunel P, Düsing R. Novel Description of the 24-Hour Circadian Rhythms of Brachial Versus Central Aortic Blood Pressure and the Impact of Blood Pressure Treatment in a Randomized Controlled Clinical Trial: The Ambulatory Central Aortic Pressure (AmCAP) Study. Hypertension, 2013; 61, 1168-1176. doi:10.1161/HYPERTENSIONAHA.111.00763

Related grants:

NHS R&D Project Grant Award (B. Williams CI). Comparison of central arterial blood pressure in diabetic and non-diabetic subjects (February 1998 – January 2000). £45,374

Anglo Scandinavian Cardiac Outcomes Trial (ASCOT Study) grant awarded via Imperial College London (B. Williams Local CI) (Aug 1998 – July 2003). £1,240,000

CAFE study (Pfizer – Investigator-led grant award – PI: B. Williams) Conduit artery functional end-point study (September 2000 – August 2006). £550,000

NIHR/MRC Efficacy Mechanisms Evaluation (EME) Programme - B. Williams CI: Evaluation of blood pressure treatment stratified according to Central Aortic Systolic Pressure (CASP) in Young Hypertensive Patients - The TREAT CASP study (2013-2016). £756,000

4. Details of the impact

High blood pressure (hypertension) is one of the most preventable causes of premature morbidity and mortality. It is a major risk factor for strokes, myocardial infarction, heart failure, chronic kidney disease, cognitive decline and premature death. At least one quarter of all adults in the UK, and more than half of those older than 60, have high blood pressure. The clinical management of hypertension is one of the most common interventions in primary care, accounting for approximately £1 billion in drug costs alone each year.

The measurement of blood pressure is one of the most frequent clinical evaluations and the method has changed little in over 100 years. It has long been assumed that the pressure measured in the arm by conventional methods is representative of the true pressure in central circulation, so-called central aortic pressure. The Unit's work has had a major impact in this field in three ways: (i) changing blood pressure treatment guidance; (ii) stimulating growth in medical devices for the non-invasive measurement of aortic pressure; and (iii) developing central aortic pressure as a biomarker to improve drug development.

(i) Changes to Blood Pressure Treatment Guidelines

The CAFE study in *Circulation* remains the most cited paper (see 3.1) in the field of non-invasive aortic pressure measurement, with over 200 citations per year since publication in 2006. The findings, that the beta-blocker atenolol was less effective than expected at reducing aortic pressure when compared to alternatives, and that aortic pressure may be a better predictor of clinical outcomes than conventional brachial pressure, underpinned major changes to blood pressure management guidelines and widespread change in clinical practice, affecting millions of people in the UK and beyond. They influenced revisions to NICE guidelines for the treatment of hypertension, published in 2006 and revised in 2011, relegating beta-blockers from their prior position as a mainstay of routine treatment for high blood pressure to a lesser role. Williams was Clinical Advisor to the NICE hypertension guideline in 2006[1] and Chair of the NICE Guideline Development that updated the guidance in 2011.[2]

(ii) Stimulating major growth in medical devices for non-invasive measurement of aortic pressure

Interest in the non-invasive measurement of aortic pressure has exploded since the publication of the CAFE study in 2006. The term central aortic pressure has become part of routine discussion at specialist meetings and many new commercially available devices have emerged, expanding from a single device seven years ago to more than 50 today.

Williams' more practical and less expensive solution to the measurement of central aortic pressure was a sensor worn on the wrist to record the pulse wave. Using computerised mathematical modelling (n-Point Moving Average) of the pulse wave, doctors are able to accurately estimate blood pressure close to the heart. Patients who tested the device found it easier and more comfortable, as it can be worn like a watch. The new measurement devices, BPro®, CASPro® and CASPal®, are designed for clinical and home use. In the US, the FDA has recognised the Leicester-developed n-Point Moving Average as a clinically valid method for the measurement of aortic pressure and all three medical devices have attained the FDA 510(k) listing and CE (MDD) Mark.[3] [Text removed for publication] This indicates that assessment of aortic pressure is being increasingly incorporated within clinical practice.

The impact of the work has been widely recognised beyond scientists and clinicians.[5, 6] In 2011, Health Secretary Andrew Lansley said: "This is a great example of how research breakthroughs and innovation can make a real difference to patients' lives." [7] The device also won the 2011 Times Higher Education Award for Innovation and Technology. Ann Mroz, editor of the THES, was quoted as saying that the University of Leicester project was "among the research achievements that captured the imagination of our judges." [8]

(iii) Developing aortic pressure as a biomarker to differentiate the actions of drugs to treat hypertension

A major impact of the research relates to its benefits in terms of improving drugs to treat blood pressure. As indicated, major pharmaceutical companies such as Novartis have recognised the importance of aortic pressure as a biomarker of drug efficacy and have incorporated the technology and concepts developed by the Unit into the evaluation of new drug therapies in international multicentre trials such as ALTITUDE (ClinicalTrials.gov NCT00549757) and ATMOSPHERE (NCT00853658). Indeed, the research opens up the opportunity to identify drugs that specifically target central aortic pressure.

5. Sources to corroborate the impact

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