European Perspectives

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Spotlight: Bryan Williams, MD, FRCP, FESC, FAHA

"If We Don't Measure Central [Aortic] Pressure and We Don't Know What Drugs Are Doing to Central Pressure, It Is Difficult to Know Whether We're Optimally Treating a Patient"

Bryan Williams, professor of medicine, Department of Cardiovascular Sciences, University of Leicester, Leicester, England, talks to Jennifer Taylor, BSc, MSc, MPhil.

As a clinician scientist unafraid to stir things up, Bryan Williams, MD, FRCP, FESC, FAHA, professor of medicine in the Department of Cardiovascular Sciences at the University of Leicester, Leicester, England, published a landmark study in *Circulation* in 2006 that provided a mechanistic background explaining why β-blockers might be less effective than other drugs at lowering blood pressure.[1] It contributed to the decision to downgrade β-blockers as a routine treatment for blood pressure in the United Kingdom because ultimately they are less effective than other drugs at reducing the risk of stroke. The decision remains controversial. Professor Williams says, "Some cardiologists still struggle to accept it because β-blockers have been a comfort blanket." β-blockers have been used for many years and seemed to be as effective as other drugs at lowering blood pressure when blood pressure was measured in the arm using conventional methods. However, Professor Williams showed that the pressure reduction in the aorta was much less efficient than with other drug systems.

Professor Williams is a past president of the British Hypertension Society (2001–2003), chair of the ongoing UK's National Institute for Health and Clinical Excellence Hypertension Guideline update, and is recognised as one of the world's leading experts on blood pressure. The Blood Pressure Clinic in Leicester was designated a European Society of Hypertension Centre of Excellence in 2007.

"I Don't Want to Be Hidden Away in Some Research Unit or Some Office and Not Have the Opportunity to Apply My Research Acumen to My Clinical Practice"

Born in Liverpool, England, Professor Williams was the first in his family to attend university. He gravitated towards medicine because of an interest in science and in the hospital environment, which he was exposed to following a number of sporting injuries! He applied to St. Mary's Hospital Medical School at the University of London, London, England, because it had a reputation for encouraging an interest in sports, and he was excited by the prospect of studying in the capital.

Professor Williams' interest in blood pressure developed by chance after encounters with several key and powerful people in the field. The first encounter was with Sir Stanley Peart, MD, professor of medicine at St Mary's. Professor Williams says, "I was impressed by his flamboyance and clear knowledge. He was an engaging and stimulating character and I got interested in blood pressure through him."

After house jobs, Professor Williams was advised that Leicester, a relatively new medical school, was a good place for further medical training, and Professor John Swales, MD, the first professor of medicine at Leicester (Professor Williams is the second), became another important influence. Professor Swales, who died in 2000, was a charismatic and respected international figure for his work on hypertension.

Professor Williams describes Professor Swales as "an extraordinary character" and "a towering intellect" whose interests went beyond medicine to cultural areas such as antique books. He was fascinating to interact with, and he had time for people—the door of his office was always open. It was an era in which professors of medicine and surgery were often charismatic people who provided leadership scientifically and clinically and through their ability to inspire people. Part of that was because they retained contact with patients, a model Professor Williams has mirrored and

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Young Investigator Spotlight: Holger Hetterich, MD
Dr Hetterich, a PhD student and resident in internal medicine, University of Munich, Munich, Germany, is investigating the link between low shear stress and atherosclerosis. **Page f89**

fought hard to retain. He says, "I don't want to be hidden away in some research unit or some office and not have the opportunity to apply my research acumen to my clinical practice."

Professor Swales quickly identified people with promise for academia and was good at opening doors. Professor Williams says, "He wouldn't necessarily lift you and push you through them. That was up to you. But he subtly created opportunities." As a result, Professor Williams was given his first opportunity to carry out research and was inspired to consider an academic career by Professor Swales together with Professor John Walls, MD, a nephrologist in Leicester who was interested in blood pressure and the kidney.

Professor Williams decided to dedicate several years to research. His attraction to charismatic figures led him to the University of Colorado, Denver, Colo., where he met Robert Schrier, MD, chair of medicine, and completed a research fellowship between 1989 and 1991. Professor Schrier was a prominent academic working on salt and water balance, blood pressure, the kidney, and the interaction with the cardiovascular system. Professor Williams describes him as "a huge figure in American nephrology" and "a man of enormous intellect and tremendous presence and communication skills," and says Professor Schrier inspired through his enthusiasm and passion for finding answers to research questions, and not just for about the kudos of publishing in a top journal.

Professor Williams thinks the United Kingdom has a lot to learn from the United States about the infrastructure required for developing clinical academia. Even 20 years ago, the United States had embedded a culture of academia into medical training, with most fellows encouraged to dedicate at least 2 years to research. People with an aptitude for research were then encouraged to develop academic careers and the others still benefited from that time as they pursued their clinical careers.

Professor Williams with Dr Peter Lacy, a young investigator mentored by Professor Williams, receiving the American Heart Association's "Clinical Science Publication of the Year" award in 2007 for their 2006 article in Circulation *showing that central pressure is an independent predictor of clinical outcomes, over and above the measurement of brachial blood pressure. Photograph courtesy of Dr Lacy.*

Professor Williams' time in Colorado confirmed his desire to continue with a mix of academic and clinical training. To do that in the United Kingdom, he had to apply for a competitive research fellowship because National Health Service funding is largely for clinical work, and he secured a British Heart Foundation clinician scientist fellowship.

"The Interaction Between the Heart and the Aorta, and the Function of the Aorta as an Organ Itself, Is Crucial to the Way the Circulation System Works, and That Has Really Been Underemphasised"

In the 1990s, Professor Williams' research training and early career focused on molecular biology. His primary interest, however, was physiology and understanding how the human body integrates various systems, but it was almost impossible to obtain funding for that kind of research. He recalls, "I remember in the United States, people were lamenting the fact that some of the truly outstanding physiology labs were simply being closed because the funding had shifted towards molecular cell biology, which was undergoing a sort of explosion and the early part of developing genetics."

Professor Williams enjoyed the training, and now that he is an established investigator, he can pursue his passion for physiology, in particular his fascination for the arterial system. He explains, "It's obvious that the interaction between the heart and the aorta, and the function of the aorta as an organ itself, is crucial to the way the circulation system works and that has really been underemphasised."

In the early 1900s, the shape of the pulse wave and the characteristics of flow in the circulation were of great interest, but this waned when the mechanism of measuring circulatory function was simplified to measuring blood pressure as 2 numbers. The fundamental work from the turn of the 20th century is now being reinvigorated with new technology that allows the arterial pulse to be studied noninvasively. Professor Williams says, "We can now estimate central aortic systolic pressure accurately from simple mathematical computation of the radial artery pressure wave. This is providing novel insights into the effects of ageing on the vascular system and how drugs might be developed to counteract these effects."

For a number of years, several groups have been looking at arterial stiffness and pulse wave characteristics. However, the real importance of the work was obscured because many groups focused on parameters derived from the pulse wave (eg augmentation index), which meant little to people outside the field. Professor Williams says, "It was perceived to be a niche area of interest, but somewhat remote from clinical practice." Professor Williams has now made a major contribution by demonstrating that central pressure is the parameter that should be used. With his colleagues, he was the first to show in *Circulation* in 2006 that central pressure is an independent predictor of clinical outcomes over and above the measurement of brachial blood pressure. He explains, "If we don't measure central pressure and we don't know what drugs are doing to central pressure, then it makes it difficult to know whether you're optimally treating a patient." He adds, "Now that we

can do it, it is difficult to reconcile why we would not want to measure aortic pressure rather than the pressure in the arm when making decisions about treatment, but we do need more data about the prognostic significance of central aortic pressure. I am under no illusions about the magnitude of the change I am suggesting here, but that should not stop us if we can prove it is the right thing to do."

"When You Lower Heart Rate in People With Stiff Aortas, You're Injecting a Larger Stroke Volume Into a Smaller Space. This Tends to Increase the Central Systolic Pressure"

The main thrust of Professor Williams' work now and for the future is focused on central aortic haemodynamics and pressure. An article in *Circulation* in 2009 demonstrated, to many people's surprise, that statins did not have a major impact on central aortic pressure.[2] Thus, the way statins reduce stroke in particular is unlikely to be mediated through haemodynamic mechanisms, but more likely to be related to the lipid-modifying effects. There had been a suggestion at one time that statins might improve endothelial function and therefore improve aortic function and reduce central pressure, but the article disproved that hypothesis.

Also in 2009, Professor Williams and his colleagues published an article in *JACC* demonstrating that β-blockers do not lower central aortic pressure as effectively as other drugs because of their heart-rate lowering effect.[3] Professor Williams says, "When you lower heart rate in people with stiff aortas, you're injecting a larger stroke volume into a smaller space. This tends to widen the pulse pressure and increase the central systolic pressure, making it much more difficult for other drugs to then lower that pressure." It is an important discovery because it suggests that any drug that lowers heart rate in older people will increase central pressure if their aorta is stiff, as it is in most people as they get older.

Professor Williams with Choon Meng Ting, MD, a GP, engineer, and entrepreneur. Professor Williams interest in central aortic pressure has led to an enjoyable collaboration with Dr Ting, who has invented a number of devices to measure physiological parameters noninvasively, including a small tonometer device that can be embedded into the wrist strap of a watch and make repeated recordings throughout the day of the pulse wave. Professor Williams encountered Dr Ting and his invention at a conference and since then they have worked together to develop a novel and simple way of estimating central pressures in the aorta from the pulse wave that is much less complex than many existing systems.[7] They have succeeded in putting it into a very small desk-top blood pressure monitoring device. Professor Williams says, "It has been a fabulous scientific adventure," and he admires the technical sector's ability to move ideas forward much more quickly than could be achieved in a university setting. Photograph courtesy of Professor Williams.

Funding for Professor Williams' research comes principally from the British Heart Foundation and the National Institute for Health Research (NIHR). Professor Williams is 1 of 203 NIHR senior investigators in the United Kingdom, a distinction bestowed on the NIHR's most preeminent researchers, and the NIHR has provided a £5.5 million grant to set up a biomedical research unit in Leicester dedicated to translational research in cardiovascular medicine. As a result, Professor Williams has moved from his previous base at the Royal Infirmary, Leicester, to the Glenfield Hospital, which is a dedicated cardiorespiratory hospital and has the facilities and patients to push forward the unit's research.

"Bureaucracy Is Stifling Research, Delaying Project Starts, and Increasing Costs, so the Pharmaceutical Companies Which Fund the Mega Trials That Provide Outcomes From Drug Interventions, Are Moving Large Parts of Their Research Operations to Brazil, Russia, India, and China"

Professor Williams has participated in numerous recent influential clinical trials, including the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT), the Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evalution (ADVANCE),[4] and the Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial (ONTARGET).[5] He says, "These are examples of academically-led, pharma-funded studies that have influenced guidelines for the treatment of blood pressure across the world. This is a good example of how clinical academics can identify gaps in knowledge and design relevant studies to change clinical practice."

Professor Williams believes that clinical trials themselves are underused as a vehicle for high-quality mechanistic substudies that can better illuminate clinical trial findings. He explains, "The opportunity has never been greater to embed deep phenotyping into mega-trials, via imaging, biomarker, and physiological measurement. This helps to better understand why interventions work and why sometimes, they don't, therein providing the template for even better stratification of those who will benefit most."

One of the "immense frustrations" Professor Williams has faced in moving from lab-based research to clinical research is that it is more difficult to set up a clinical research project. He says, "If you don't have the passion and you don't have the excitement, then it simply wouldn't get done because we are tied up in knots by regulation and bureaucracy." He says that attempts in Europe to create a standardised European Union directive governing research that does not grasp the

complexity and variety of research contributes to this situation. He explains, "For example, the same regulatory framework is used to study a new drug that has never been tried in humans and a drug that has been safely used for 50 years. The bureaucracy is stifling research, delaying project starts, and increasing costs, and as a result, the pharmaceutical companies which fund the mega trials that provide outcomes from drug interventions are moving large parts of their research operations to Brazil, Russia, India, and China."

Professor Williams adds, "Scientists in Europe are missing out on the intellectual interaction with these companies that drives forward ideas. Patients in Europe lose the benefit of having new treatments tested on Europeans." Therefore, he proposes that a high-level policy debate is needed on how to protect European research, and he says, "Industrial science often used to get looked at as second rate compared with the more fundamental lab science, but in reality, this is the science that makes the difference."

The Royal College of Physicians in London awarded Professor Williams the Lord Rayner Research Medal and Lectureship in 2007, the De Wardener Lectureship in 2006 (in association with the Renal Association), and the Linacre Medal and Lectureship in 1996. In 1993, the BUPA Medical Foundation named him doctor of the year for his vascular disease research.

"The Phenotype, Rather Than the Genotype, Is Going to Give Us the Answers"

Much of Professor Williams' work has challenged popular dogma. He admits that it might be a bit "roguish" and "mischievous," but he stands by the view that clinical academics have to challenge popular consensus, particularly in areas where it could influence treatment strategies. He says, "A particular concept may have been founded on good ideas when it was developed, but modern imaging or modern ways of looking at the same problem have begun to identify inconsistencies with the popular concept and to challenge it." One example is an editorial he cowrote for the *Lancet* in 2008, titled "Systolic Pressure Is All That Matters,"[6] which argued that there had been too much focus on diastolic blood pressure as a marker of risk and that elevated systolic blood pressure should be the focus, particularly in people over age 50. It generated controversy, with international commentators saying that diastolic pressure should not be disregarded altogether. Although he does not advocate ignoring diastolic pressure, Professor Williams says it should not receive much attention in people aged >50 years because few of them have high diastolic pressures. He says, "Somewhat paradoxically, as you get older, the lower your diastolic pressure, the higher your risk because it indicates damage to the aorta."

Professor Williams believes that now is one of the most exciting times to be in clinical academic medicine because the research opportunities are more diverse than they were 20 years ago. He also believes the so-called "genetic revolution" has been overhyped, has suffered from poor integration of high-quality physiological phenotyping, and will on its own yield little of translational potential for common cardiovascular disorders. He says, "It is the revolution in imaging and physiology that will provide a better understanding, at the macroscopic level, of how things work and how they go wrong in disease—it is this that we need to reinvigorate. The future is in better disease risk stratification, getting the right intervention to the right patients at the right time. In my view, it is a better understanding of the phenotype, rather than the genotype, that is going to give us the answers."

Professor Williams is chair of the National Institute for Health and Clinical Excellence Hypertension Guideline Development Group in the United Kingdom. This role has enabled him to take his scientific acumen and ability to look at data critically into a public health policy arena, which is what he believes clinical academic science is all about. He says, "It's about using the skills and the talents that you've got both clinically and academically to influence health policy, the way medicine is delivered, and how our patients are treated." He adds, "That's a good use of a clinical academic's time because it helps do something to counter the public perception of science as boffins working away in laboratories." Photograph courtesy of Professor Williams.

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Young Investigator Spotlight: Holger Hetterich, MD

"We're Trying to Find the Link Between Low Shear Stress and Atherosclerosis in Patients Treated in Our Cath Lab"

Holger Hetterich, MD, a PhD student and resident in internal medicine, Department of Medicine, Hospital of the University of Munich, Munich, Germany, talks to Jennifer Taylor, BSc, MSc, MPhil.

Much is known about the systemic risk factors for atherosclerosis, such as hypertension and diabetes mellitus. However, in the past couple of years, a number of articles have shown that local risk factors such as low shear stress are also involved in the development of atherosclerosis. Holger Hetterich, MD, a PhD student and resident in internal medicine in the Department of Medicine, Hospital of the University of Munich, Munich, Germany, is working to translate that knowledge into patient care.

He explains, "We're trying to find the link between low shear stress and atherosclerosis in patients treated in our cath lab." The aim is to develop a tool to help predict where a patient might develop atherosclerosis and, when a patient already has plaques, which plaques will grow further, what kind of plaques will develop, and whether the plaques will be stable in the future or have a high risk of rupturing, with subsequent myocardial infarction. Another aim is to determine which imaging technique to use. Computed tomography has been used so far, but in the future the aim is to also use C-arm computed tomography so that this kind of analysis can be done in the cath lab.

Investigating the Morphological and Functional Characterisation of Coronary Atherosclerosis by Computational Fluid Dynamics

Dr Hetterich wrote his MD thesis, in which he examined bioabsorbable magnesium stents with optical coherence tomography (OCT) and intravascular ultrasound (IVUS), under the supervision of cardiologist Johannes Rieber, MD. Not only did Dr Rieber teach him the principles of computed tomography, OCT, and IVUS, and introduce him to the statistics he would need, he also inspired him with a fascination for science. As a result, Dr Hetterich is now working for a PhD.

*Photograph of Dr Hetterich in Brazil in 2005 when he worked for a time in hospitals and on a social project (*http://www.afink.org/*). He says, "The gap between the poor and the rich is so big. One day we were invited to the Yacht Club by the doctors and had the best party and the next day we worked with a poor family with 9 children who really had nothing." Born in 1981 in Nuremberg, Germany, Dr Hetterich always liked natural sciences and during work experience in a hospital enjoyed working with patients, so from 2002 to 2008 he studied medicine at the Ludwig-Maximilians University in Munich, Germany. During the last 3 years of medical school, he held a scholarship from the German Academic Foundation, which sponsors gifted students. Photograph courtesy of Dr Hetterich.*

Since August 2008, Dr Hetterich has been a resident in internal medicine affiliated with the Department of Cardiology, which pays his salary and is where he conducts research. He will move on to cardiology training in a couple of years. For his PhD, he is working with Dr Rieber on the morphological and functional characterisation of coronary atherosclerosis by computational fluid dynamics (CFD). In 2009, he was awarded a scholarship for this work from the Friedrich-Baur Foundation.

Dr Hetterich has also been involved with a number of other projects. His interest in cardiovascular imaging demands collaboration with other specialists, and in one project using OCT, he worked with radiologists in the hospital. Together they described the general appearance of ex vivo veins and concluded that OCT could be a valuable technique for optimising endovenous therapy in vivo.[1] The working group for the project was founded by Dr Rieber in cardiology and Dr Oliver Meissner, PhD, in radiology, who has been another mentor for Dr Hetterich and helped him with the statistics and write-up of his doctoral thesis.

In another project, Dr Hetterich investigated the use of virtual histology IVUS collaborating with Arash Taki, an engineer working on his PhD thesis in Iran and at the Technical University in Munich. Use of the technique is limited because it requires a special IVUS machine, a special catheter, and a lot of storage space. In addition, it can only be used in new patients, not on archived material. They developed and evaluated a new, simpler technique that allowed them to do the characterisation based only on the grey scale IVUS images.[2]

Because of his interest in cardiovascular imaging, Dr Hetterich embarked on writing a review article about new modalities in cardiovascular imaging. One of the research group's

collaborators, Professor Gozde Unal, PhD, an electrical and computer engineer at Sabanci University in Istanbul, Turkey, asked Dr Hetterich to write an article discussing the potential for the new C-arm computed tomography, which can provide 3-dimensional imaging in the cath lab of the coronary arteries, the cardiac chambers, and the venous system, for the Medical Image Computing and Computer Assisted Intervention (MICCAI) conference.[3] The article also discussed the potential for OCT and IVUS and the use of CFD to calculate the parameters of fluid tissue interactions in relation to the pathogenesis of atherosclerosis.

The collaboration between the groups of Dr Rieber and Professor Unal began after the two met at a conference. They applied for a grant under the Intensified Cooperation programme,[4] which is funded by the German and Turkish ministries of science to foster cooperation between universities in the two countries. The Munich group collects patient data and conducts the CFD analysis, while the Istanbul group focuses on the informatics side, writing programmes and segmentation algorithms.

The CFD project was difficult at first because nothing worked, they were implementing several new methods, they needed technical assistance, they had to find collaborators, and they had to get used to the computer programmes. But the first good results are coming through, and Dr Hetterich is optimistic. He says, "I hope and I think that CFD and analysis of blood flow profiles based on different imaging techniques will help patients in the future."

Dr Hetterich (right) with friends from the University of Munich at Beth Israel Deaconnes Medical Center, Harvard Medical School, Boston, Mass. From left to right: Michael Berger, MD; Lukas Reznicek, MD; Bastian Fatke, MD; and Indradeo Hemraj, MD. Photograph courtesy of Dr Hetterich.

"It [Harvard Medical School] Was Inspiring Because Everybody Is Motivated and Everybody Wants to Move Forward"

Ten students from the faculty of medicine in Munich spend half of their last year of medical school, which is a practical year, at the Beth Israel Deaconess Medical Center, the Brigham and Women's Hospital, or Massachusetts General Hospital, Harvard Medical School, Boston, Mass, for clinical experience in the general medical ward, the Emergency Department, and the Outpatient Department.

In 2007, Dr Hetterich was one of these students, and the experience taught him a great deal about the United States, the American people, Boston, and the big differences in culture and the medical education system between Germany and the United States. He says, "You have more professors than you have students." In some courses, he was the only student, and he was taught by the head of the department and his co-chair. He adds, "It was extremely intense. You had to work all day, study all night, and then go back to work. But I learned a lot. It was inspiring because everybody is motivated and everybody wants to move forward." The group of students worked well together, made close friendships, and remain in contact. Dr Hetterich also met professors in different departments. He hopes the connections will prove fruitful in future research collaborations.

The German students thought so highly of the US mentoring system that they have developed a similar programme at the university in Munich. Students in their first years now have mentors who are students in the final years of training and students in their final years of training have mentors who are doctors or professors.

In 2009, Dr Hetterich published an article about a patient with several drug-eluting stents implanted at the site of coronary artery bypass insertion who had restenosis.[5] On investigation, a stent fracture was discovered. Dr Hetterich says, "One should always consider stent fracture as a main cause of restenosis." After he publishes some of the data on CFD, Dr Hetterich hopes to return to Boston, where a large group is conducting studies on CFD.

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