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Spotlight: Walter J. Paulus, MD, PhD



“Diastolic Heart Failure Is Clearly a Consequence of Affluence and ‘Overindulgence’ in Western Countries, and There Is a Suspicion That It Is Correctable and Reversible”

Walter J. Paulus, MD, PhD, associate director of the Cardiovascular Center, Aalst, Belgium, and professor of cardiac pathophysiology at the VU University Medical Center, Amsterdam, the Netherlands, talks to Barry Shurlock, MA, PhD.

One day in 2004, Attila Borbély, MD, a Hungarian research fellow working on isolated cardiomyocytes in the Department of Physiology at the VU University Medical Centre, Amsterdam, the Netherlands, consulted his supervisor, Walter J. Paulus, MD, PhD, associate director of the Cardiovascular Center, Aalst, Belgium, and professor of cardiac pathophysiology at the VU University Medical Center, with concerns that his study of isolated cardiomyocytes was bedeviled by an artefact. He was investigating the direct effects of nitrates on cardiomyocytes of patients with heart failure by carrying out resting force and sarcomere length measurements on biopsy samples taken before and after treatment. The problem was, he thought, that, although cardiomyocytes from patients with systolic heart failure stretched in a normal manner, those from patients with diastolic heart failure had a high resting force and were unusually stiff. His boss greeted his findings with delight. Since the late 1970s, Professor Paulus had been aware that diastolic heart failure differed from its systolic twin, probably as a consequence of the stiffness of the heart muscle. At last, he had proof at the cellular level.

Since then, Professor Paulus and his team at the VU University Medical Center have taken the story further. He says, “By carrying out force/extension measurements with single cells, we have shown that cardiomyocytes have a high passive tension, reflecting the overall phenotype of the heart. Moreover, we have shown that this stiffness can

be reversed in vitro with protein kinases. The stiffness in the cardiomyocyte is known to be due to a single protein, titin, which is the largest polypeptide known. It is an extremely complex molecule with 224 individually folded protein domains and acts like a bidirectional spring.

“Titin covers the complete sarcomere in cardiac muscle, and we have been the first to show that in diastolic heart failure a lack of titin phosphorylation renders the cardiomyocytes stiff.¹ Both protein kinase A and protein kinase G can phosphorylate titin. The ability of protein kinase G to do this explains our earlier work showing that nitric oxide (NO) increases diastolic distensibility because protein kinase G sits in the NO cascade. Also, working with myocardial biopsy material of patients with diastolic heart failure, we have shown that active protein kinase G needs a cofactor, cyclic guanosine monophosphate (GMP). Cyclic GMP is produced by soluble guanylate cyclase, whose activity is controlled by NO. As a result of low NO bioavailability, cyclic GMP is 8 times lower in the myocardium of patients with diastolic heart failure. The low bioavailability of NO is related to high oxidative stress associated with obesity or diabetes. Excess free radicals in the presence of high oxidative stress inactivate NO, reducing cyclic GMP and leading to diastolic heart failure.

“These ideas are exciting, but we still have to establish the link with obesity. Essentially, we regard diastolic heart failure as a consequence of obesity-induced endothelial

On other pages...



Spotlight: Sanjay Prasad, MD, FRCP, FESC, FACC

Dr Prasad, honorary senior lecturer, National Heart and Lung Institute, Imperial College London, London, England, is investigating heart failure using cardiovascular magnetic resonance. **Page f4**



Funding: Marie Curie Intra-European Fellowship for Career Development

Ana Belén Cerezo López, PhD, from Spain, is a Marie Curie postdoctoral researcher, Institute of Food Research in Norwich, England. **Page f6**



Left, Professor Paulus with his longstanding clinical collaborator, Jean Bronzwaer, MD, PhD, in the isolated cardiomyocyte lab of the VU University Medical Center, Amsterdam, the Netherlands, where Professor Paulus has been professor of physiology since 2003. The university (above) was founded in 1880 by the Calvinist politician Abraham Kuyper, who was the Dutch prime minister between 1901 and 1905, and has ≈27,000 students in all faculties. Photographs courtesy of Professor Paulus.

dysfunction. There is still no effective treatment, but it seems clear that approaches that need to be examined include risk factor control, use of the appropriate antioxidative agents (results with vitamins A and E have been frustrating), measures to prevent the breakdown of the cofactor cyclic GMP (perhaps with sildenafil), and reassessment of the use of angiotensin-converting enzyme inhibitors because they have NO-releasing properties.”

“This Article Demonstrated a Continuous Decline of Left Ventricular Pressure During Diastole and Supported the Notion That the Resting Phase of the Cardiac Cycle Was Dynamic”

Professor Paulus’s study of cardiac cells began >30 years ago when he was at medical school in his hometown of Antwerp, Belgium. He says, “I was fortunate to work with the distinguished physiologist Professor Dirk L. Brutsaert, MD, PhD (see <http://circ.ahajournals.org/content/124/11/f61.full.pdf+html>). He was extremely stimulating, and in my first year asked any undergraduate who was interested in doing some research to contact him. So I did, and I worked in the lab on isolated muscle strips, 2 days a week during term time and even more in the holidays. This chance encounter with Dirk Brutsaert shaped my entire career, and it still does.”

After studying internal medicine, Professor Paulus worked as a cardiology fellow. By age 28, his research had made him first author of 3 articles published in *Circulation Research*. Then in 1979, he became a Fogarty International Fellow to Brigham and Women’s Hospital, Boston, MA. He says, “I benefited from the tail end of the Marshall Plan (European Recovery Programme) brought in after the war and funded by the National Institutes of Health. At Harvard, my mentor was Bill (William) Grossman, MD, who was director of the cardiac catheterisation lab. He was already aware that in diastolic heart failure contraction is normal, but a dysfunction in cardiac muscle makes the heart stiff. I was not yet an accredited cardiologist, so I worked as a research fellow and a clinical fellow. It was an incredibly stimulating place to be. Eugene Braunwald, MD, and Tom Smith, MD, were both there. The group of cardiology fellows I was with have all gone on to hold major positions, such as Peter Libby, MD, Marvin Konstam, MD, Marc Pfeffer, MD, Samuel Goldhaber, MD, Richard Nesto, MD, Morton Kern, MD, and John Horowitz, MD. In retrospect, although the research was important, perhaps the most

important thing about such a fellowship is that you establish a network of people in the same field.”

The research in the United States did, however, result in an article that Professor Paulus considers to be 1 of his most important, albeit as second author, namely, a demonstration of improved diastolic function and systolic performance in hypertrophic cardiomyopathy after administration of the calcium channel blocker nifedipine.² He says, “This article demonstrated a continuous decline of left ventricular pressure during diastole and supported the notion that the resting phase of the cardiac cycle was dynamic.”

“We Increasingly Realised That Diastolic Heart Failure Is Related to Type 2 Diabetes Mellitus, Obesity, and Hypertension”

After his fellowship, Professor Paulus was offered a position in San Francisco, CA, but he says, “I had to give up my American Dream and serve for 14 months as a lieutenant at a military hospital in Brussels, working as a cardiologist” because military service in Belgium was obligatory under agreements with the North Atlantic Treaty Organisation. Professor Paulus was then invited to take up a position as a cardiologist at the newly formed Cardiovascular Center on the campus of the Onze-Lieve-Vrouwziekenhuis at Aalst, where he continued with his research on diastolic heart failure while taking on a heavy clinical load of routine cardiology and interventional procedures. Since 1984, he has been associate director of the division, which is now the second largest cardiac centre in Belgium.

In 1994, Professor Paulus published another landmark article, which showed that NO has acute effects on left ventricular relaxation and diastolic distensibility.³ This finding was to be better understood as his research unfolded the mechanisms of diastolic heart failure. He says, “Rather than regarding diastolic heart failure as an unusual form of heart failure, different, for example, from postmyocardial heart failure, we increasingly realised that it was prevalent and related to type 2 diabetes mellitus, obesity, and hypertension. The latest statistics from the Mayo Clinic (Rochester, MN) show that it accounts for ≈50% of all heart failure and is increasing every year.

“Diastolic heart failure is clearly a consequence of affluence and ‘overindulgence’ in Western countries, and there is a suspicion that it is correctable and reversible. There is some evidence in this direction, but we still have



Left, Professor Paulus and his wife, Jackie, enjoy sailing in the sea arms of the southern Netherlands. Right, The MEDIA study group at the kickoff meeting held in Amsterdam at VU University Medical Center on January 18, 2011. Photographs courtesy of Professor Paulus.

to prove it. Recent work has shown, for example, that you can alleviate diastolic heart failure with an exercise training programme. This is an important message because heart failure overall is 1 of the most frequent reasons for hospitalisation and is a huge economic burden. Lifestyle changes will probably be effective, but we need to note that there are subtle differences in the consequences in terms of macro- and microvascular complications of unhealthy habits. In diastolic heart failure, the microvascular changes are most significant. This explains why diastolic left ventricular dysfunction correlates with erectile dysfunction.”⁴ He adds, “Recent evidence from Italian workers suggests that sildenafil is beneficial for diastolic heart failure.”⁵

In 2003, Professor Paulus took up an additional appointment as professor of cardiac pathophysiology at the VU University Medical Center in Amsterdam, 200 km from Aalst (Dutch is his native language, although he also speaks French, English, and German). In this role, he is coordinating the Metabolic Road to Diastolic Heart Failure (MEDIA) research project involving 18 centres throughout the European Union to unravel the links between “lifestyle” and the epidemic of diastolic heart failure in elderly people, which has received funding of €12 million from the European Commission’s Seventh Framework Programme (see <http://circ.ahajournals.org/content/123/25/f145.full.pdf+html>). He says, “In 2009, the European Commission called for proposals for a large project on diastolic heart failure. I contacted people around Europe, and we met at Schiphol Airport (Amsterdam) to put together a proposal to be coordinated from the VU University Medical Center, which we submitted in November 2009. It was accepted the following March, signed off in December, and started in 2011 with the first tranche of 3 million Euros. The rest of the funding will be provided in stages based on our reports of ‘deliverables.’ It is important that we establish an animal model of diastolic heart failure to prove that metabolic factors are causal. We also need to find more firm diagnostic criteria. We are therefore looking for biomarkers in the blood that reflect oxidative stress, low NO bioavailability, or other determinants of myocardial stiffness. Finally, we have to come up with a comprehensive treatment programme.” Professor Paulus and colleagues from Portugal (University of Porto) and Hungary

(University of Debrecen) have already shown that diabetes mellitus worsens diastolic left ventricular dysfunction in aortic stenosis by altering the structure of the myocardium and increasing cardiomyocyte stiffness.⁶

Professor Paulus’s other professional activities have included serving on the board of the Heart Failure Association of the European Society of Cardiology and as chair of the European Society of Cardiology Working Group on Myocardial Function. Together with Otto Smiseth, MD, PhD from Oslo, Norway (see <http://circ.ahajournals.org/content/122/4/f19.full.pdf+html>), and the late Cees Visser, MD, from Amsterdam, he organised numerous postgraduate courses on “diastology” at the European Society of Cardiology Heart House in southern France. However, Professor Paulus is probably best known as the European lead editor of the textbook *Cardiology*.⁷

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Contact details for Professor Paulus: Laboratory of Physiology and Institute for Cardiovascular Research VU (ICaR-VU), VU University Medical Center, Van der Boechorststraat 7, 1081 BT Amsterdam, The Netherlands. Tel: 31 20 4448110. Fax: 31 20 4448255. E-mail: wj.paulus@yumc.nl

Barry Shurlock is a freelance medical journalist.