Spotlight: Frits Prinzen, PhD, FESC

“Left Bundle-Branch Block Is a Serious Complication of Transcatheter Aortic Valve Implantation”

Frits Prinzen, PhD, FESC, professor of physiology, Department of Physiology, Cardiovascular Research Institute Maastricht, Maastricht University, Maastricht, the Netherlands, traces the origins of a recent article in *Circulation* for which he is the last author, titled “Left Bundle-Branch Block Induced by Transcatheter Aortic Valve Implantation Increases Risk of Death,” back to connections he made via his hobby of running. At a North American Society for Pacing and Electrophysiology meeting in Washington, DC, in 2003, he bumped into cardiologist Albert Meijer, MD, PhD, from the Catharina Hospital, Eindhoven, the Netherlands, who he knew through his Sunday morning running group. Dr Meijer introduced him to his colleagues from the Catharina Hospital, Berry van Gelder, PhD, and Frank Bracke, MD, PhD, who were involved in studies on cardiac resynchronisation therapy (CRT), leading to a collaboration that also included PhD student Patrick Houthuizen, MD. Professor Prinzen recalls, “During one of the lab meetings Dr Houthuizen mentioned that on call during the weekend he saw 2 patients who had developed left bundle-branch block during a transcatheter aortic valve implantation (TAVI) procedure. Knowing the adverse effects of left bundle-branch block from our animal studies, we were surprised that nobody in the TAVI world seemed to worry about this complication. Therefore, we decided to set up a study to investigate this.”

Together with cardiac surgeon, Leen van Garsse, MD, from Maastricht University Medical Center, Dr Houthuizen, MD, convinced 6 other Dutch centres to participate in the study. This provided data for 679 patients going into the TAVI procedure with a narrow QRS complex. One-third developed left bundle-branch block upon TAVI and had a 55% higher mortality rate than patients not developing left bundle-branch block. Professor Prinzen adds, “Of course, we also needed proof that left bundle-branch block was not an expression of a pre-existing worse condition, but this was not the case. Most of the additional mortality proved to be related to excess cardiovascular death, as expected from the adverse effects of left bundle-branch block and from the beneficial effects of CRT in heart failure. We succeeded in pointing out that left bundle-branch block should be regarded as a serious complication of TAVI.” Professor Prinzen says that the increase in mortality associated with TAVI-induced left bundle-branch block is approximately equivalent to the mortality reduction caused by TAVI. “We estimated that left bundle-branch block pretty much neutralises the benefits of TAVI,” says Professor Prinzen. “Therefore, I think this problem should be solved before applying TAVI in a wider population of patients.”

Over the past 3 decades, Professor Prinzen has played a leading research role in cardiac pacing and regional cardiac mechanics, with an emphasis on asynchronous electrical
activation and cardiac resynchronisation. He carried out some of the earliest studies on myocardial deformation by ventricular pacing, proving that it drastically changes local mechanical function as well as perfusion and has performed important magnetic resonance imaging tagging studies.

“A Simultaneous ‘Wow’ Experience. We Saw the Wave of Mechanical Activation Go Over the Ventricles in a Paced Heartbeat”

For Professor Prinzen, it was a case of “love at first sight” with the discipline of physiology when he worked for his PhD at the University of Maastricht from 1978 to 1982 on the relationship between cardiac mechanics, metabolism, and blood flow during ischaemia. Previously, he had completed a master’s degree in medical biology at the University of Utrecht, Utrecht, the Netherlands.

Professor Prinzen then worked as a postdoc and later as assistant professor of physiology at CARIM (see http://circ.ahajournals.org/content/119/7/f37) where he spent half his time teaching physiology in colleges for physiotherapy and occupational therapy alongside his research. He says, “That period was clearly not the typical career of a young investigator, but it helped me in developing didactic skills, which is helpful in many places, including science.”

During this time, he had interesting sabbaticals, one in 1995 at the Department of Biomedical Engineering, Johns Hopkins University, Baltimore, MD, and one in 2004 at the University of Göttingen, Göttingen, Germany. Professor Prinzen feels that some of his most enjoyable research was the magnetic resonance tagging investigation he carried out in Baltimore with Elliot McVeigh, PhD, now chair of Biomedical Engineering, and William Hunter, PhD. It also added a new dimension to his career. He says, “These studies required a full day of experimentation using the magnetic resonance imaging scanner, which was only possible on some Sundays, but people were so enthusiastic that many popped in just to see and help out a bit. Often we were sitting there with >5 people until late Sunday night, eating doughnuts, pizzas, and other unhealthy food.” The resulting article in 1999, which proved, using magnetic resonance tagging, that ventricular pacing redistributes mechanical load throughout the ventricle, is Professor Prinzen’s most cited article. He says, “Dr McVeigh had a complete set-up for doing the measurements and analysis. It took 2 days to ‘contour’ all slices of all frames of a heartbeat to prepare the images for analysis and a night to run the analysis on a big computer. The morning after I finished analysis of the first experiment, Elliot and I looked at the first data and it was a simultaneous ‘wow’ experience. We saw the wave of mechanical activation go over the ventricles in a paced heartbeat. These images have helped to convince clinicians about the serious nature of abnormal conduction and contraction.”

“Cardiologists Said That Such Abnormal Contraction Would Not Occur in Patients With a Ventricular Pacemaker, and We Initially Believed Them. It Took Further Experiments and a Bit More Self-Confidence to Dare to Say That Those Cardiologists Were Wrong”

In 2009, Professor Prinzen was appointed to his current position at CARIM, where he leads the theme “Electromechanics of the Heart,” while continuing to teach physiology. His main research interests are regional cardiac mechanics and long-term structural and functional adaptations to various conditions, with an emphasis on asynchronous electrical activation and cardiac resynchronisation.

Professor Prinzen’s interest first shifted from cardiac metabolism to cardiac mechanics during his PhD and the years that followed. A key defining moment in his career came in the late 1980s when Professor Rob Reneman, MD, PhD, acquired a large programme grant to connect researchers in cardiac metabolism (Professor Ger van der Vusse, PhD), mechanics (Professor Theo Arts, PhD), and electrophysiology (Professor Maurits Allessie, MD, PhD, see http://circ.ahajournals.org/content/124/7/f37).

Professor Prinzen recalls, “During a discussion in the working group, the question arose as to why muscle fibre shortening starts so late in the ischaemic region. One hypothesis was lack of ATP causing passive stretch and subsequent passive shortening. Professor Allessie, however, proposed that the reason was slow conduction in the ischaemic region. To test the latter hypothesis, we performed a control experiment: slow conduction without ischaemia, ventricular pacing. That control experiment turned out to be far more interesting than the initial research question and has kept me busy for 25 years.” This was the first study on myocardial deformation by ventricular pacing, proving that it drastically changes local mechanical function as well as perfusion.
Professor Prinzen reflects on how, in the early days, they studied myocardial deformation by tracking white paper dots glued on the canine left ventricle (indeed like speckle tracking, as it is done nowadays using ultrasound techniques) with a video camera and how it took the most modern computer of the time (with 1 megabyte internal memory) 30 minutes to calculate the deformation of a single heartbeat. Professor Prinzen comments, “The first time we saw the deformation patterns, we did not understand them. They were much more complicated, and worse, than we knew from ischaemic hearts, but we continued to study the mechanics of the paced heart for pure scientific interest. Cardiologists said that such abnormal contraction would not occur in patients with a ventricular pacemaker, and we initially believed them. It took further experiments and a bit more self-confidence to dare to say that those cardiologists were wrong.”

Professor Prinzen’s group subsequently demonstrated in animal studies the importance of the site of ventricular pacing: left ventricular sites being superior to right ventricular sites, and the left ventricular apex being among the best. Their work attracted the interest of paediatric cardiologists because children need ventricular pacing for a significant duration of time and any adverse effect is amplified in the course of a child’s life.

The development of CRT in the mid 1990s to correct pre-existing dyssynchrony such as left bundle-branch block was a “sensational development” for Professor Prinzen because, suddenly, a completely new category of patients qualified for a biventricular pacemaker, boosting support for research in this area. “Due to our previous work, we were ahead of most other centres,” he says. “Although CRT is now a well-recognised therapy, I regard it as still in its adolescence, so many improvements can be made.”

Other important articles on ventricular pacing and ventricular remodelling to which Professor Prinzen has contributed include an article in Circulation in 1998 on how asynchronous electrical activation induces inhomogeneous hypertrophy of the left ventricular wall and an article in the European Heart Journal in 2005 demonstrating “regionally different myocardial remodelling induced by chronic asynchrony.”

Professor Prinzen and his colleagues have now finalised a large multicentre study in collaboration with Professor Jan Janousek, MD, PhD, of the Children’s Heart Centre, Prague, Czech Republic, comparing the effect of the long-term right ventricular and left pacing sites on cardiac function. The article describing this study has recently been accepted for publication in Circulation.

A Series of Articles Using a Computer Model to Analyse Echocardiographic Strain Data and “an Important Step Towards Patient-Specific Modelling”

A number of inspirational colleagues and mentors have helped (and still help) shape Professor Prinzen’s career. Most prominent among them is Professor Reneman from Maastricht, his “promoter and scientific guru.” “He is a great scientist with broad interest and also great in coaching people,” says Professor Prinzen. “He gave me the confidence to continue research through many temporary appointments and triggered me to collaborate with cardiac ‘plumbers’ and ‘electricians.’ Aged 77, he still is a great person to exchange thoughts with.”

Professor Angelo Auricchio, MD, PhD, of Fondazione Cardiocentro Ticino, Lugano, Switzerland (see http://circ.ahajournals.org/content/120/15/f85), one of the first users of CRT, has also proved influential through in-depth discussions. “In those discussions, he added the clinical
perspective: how could we improve selection of CRT patients and how to improve the application of CRT? Through him I came into contact with his extensive network of colleagues and companies, for example, those involved in wireless pacing.”

This link in turn led to further collaborations with the combination of cardiac physiology and computer modelling in Professor Prinzen’s group inspiring Professor Auricchio to start a collaboration with the Department of Computer Sciences at the University of Lugano chaired by Professor Rolf Krause, PhD. This group has access and expertise to run supercomputers and the decision was made to focus that group on cardiac modelling. It started with computer scientists from Professor Krause’s group, medical doctors from the Cardiocentro Ticino of Professor Auricchio’s group, and biomedical engineers (Mark Potse, PhD, and Wilco Kroon, PhD) from Maastricht University, though soon other investigators joined the group, such as Professor Lukas Kappenberger, MD, PhD, and Nathalie Virag, PhD, from Lausanne, Switzerland, and Enrico Caiani, PhD, from Milan, Italy.

In addition, Professor Prinzen reflects on his association with Professor Tammo Delhaas, MD, PhD, who he coached during his PhD period before he went on to become a paediatric cardiologist, while keeping a part-time appointment in physiology and more recently becoming chair of the Department of Biomedical Engineering in Maastricht. “With his broad background and interest to explore really everything, our discussions sometimes lead to ‘crazy’ ideas and fun research,” says Professor Prinzen. “Most of our work is on paediatric pacing and computer modelling for CRT. The latter area, especially, has developed rapidly during recent years and I expect it to continue to do so in the future.” Recently, they published a series of articles where his group used a computer model to analyse echocardiographic strain data, highlighting the benefits of a computer model in the clinical setting and “an important step towards patient-specific modelling.”6

Funding for Professor Prinzen’s work is provided by ZonMW/NWO (the Dutch equivalent of the National Institutes of Health), the Dutch Heart Foundation, and the Centre of Translational Molecular Medicine (a public/private funding initiative) as well as contracts with various companies (primarily pacemaker companies).

In the years ahead, Professor Prinzen plans to continue his work on pacing therapies, both anti-bradycardia pacing and CRT, and also to work to discover novel applications for pacing therapies. He foresees a special role for integration of computer modelling into physiology as well as in clinical diagnosis. However, he believes there is still work to be carried out in this area and that the engineers who develop the mathematical models need a better understanding of physiology for the breakthroughs to be fully effective.

“Models can improve through the input of physiological experiments and, moreover, the models can provide unexpected predictions that can be tested in physiological experiments,” he explains. “A combination of physiology, biomedical engineering, and computer sciences can create great ‘systems biology’ where all the pieces of the puzzle can be fitted together to better understand body functions using hypothesis-driven research.”

References


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For Identification of a Novel Loss-of-Function Calcium Channel Gene Mutation in Short QT Syndrome

Christian Templin, MD, FESC, attending physician in interventional cardiology and acute cardiac care, Andreas-Grüntzig-Catheterisation Laboratories, Department of Cardiology, University Hospital of Zurich, Zurich, Switzerland, talks to Jennifer Taylor, BSc, MSc, MPhil.

Each year the Swiss Society of Cardiology awards a prize for original work in cardiovascular disease carried out by a scientist <40 years of age who is a Swiss citizen or working in Switzerland. The prize money of CHF 30,000 must be used to continue his or her research. In 2011, Christian Templin, MD, FESC, attending physician in interventional cardiology and acute cardiac care, Andreas-Grüntzig-Catheterisation Laboratories, Department of Cardiology, University Hospital of Zurich, Zurich Switzerland (see http://circ.ahajournals.org/content/117/16/f91), received the prize for his work on the identification of a novel loss-of-function calcium channel gene mutation in short QT syndrome.1 “This novel finding has resulted in the sixth type of short QT syndrome,” he says. This scientific work originated from a clinical observation that became an in-depth experimental investigation, which included molecular genetics and electrophysiological and functional analyses.

The short QT syndrome is a channelopathy and can lead to malignant arrhythmias and sudden cardiac death. The study presented for the first time a novel gene mutation in p.Ser755Thr in CACNA2D1, the Cava2d1-subunit of the L-type calcium channel causing a short QT syndrome. Dr Templin explains, “We found a new phenotype with a previously unreported repolarisation pattern in the right precordial leads demonstrating a new variant of this genetic disease. We therefore extended the spectrum of this syndrome and improved knowledge on the pathophysiology of this ion-channel disorder based on a functional and molecular analysis.”

The project was performed by an interdisciplinary team from different institutions and in close collaboration with Professor Firat Duru, MD, head of the Division of Rhythmology, University Hospital of Zurich.

In another aspect of his research, Dr Templin has established a large international multicentre network on Takotsubo cardiomyopathy (see www.takotsubo-registry.com). The aim is to identify the pathogenesis, epidemiological features, and clinical course of this disease. Since launching the registry in January 2011, >20 cardiology centres worldwide have joined the project. “Based on published studies, the International Takotsubo Registry has now become the largest registry worldwide, and we continue to look for new collaborators who would like to participate,” says Dr Templin. He and his group are also performing molecular and experimental studies to determine the mechanism of this complex disease.

Dr Templin began his clinical and scientific career at the Department of Cardiology, Hannover Medical School, Hannover, Germany, headed by Helmut Drexler, MD (see http://circ.ahajournals.org/content/118/14/f79). “I was fascinated by the new field of regenerative cardiology that was still in its infancy,” he says. “It offered promising future therapeutic strategies to replace the loss of myocardial tissue.”

Dr Templin with his mentor Thomas F. Lüscher, MD, FRCP, FACC, professor and chair of the Division of Cardiology, University Hospital Zurich, and editor-in-chief of the European Heart Journal. Dr Templin says, “He inspires me because he is an exceptional, excellent scientist and a clinical cardiologist at the same time.” Photograph courtesy of Dr Templin.

Dr Templin with his colleague Christophe Wyss, MD, during an interventional procedure in the cath lab where Andreas Grüntzig, MD (see http://circ.ahajournals.org/content/116/9/F49), conducted the first balloon angioplasty. “It is a special, often emotional, moment when coronary intervention has been successfully performed, and we show the patient the results before and after intervention.” Photograph courtesy of Dr Templin.
Dr Templin built his own research group and developed novel strategies combining stem and gene therapy to enhance the regenerative capacity of adult stem cells. In his early career, he demonstrated that β-catenin gene transfer leads to immortalisation of bone marrow-derived stem cells, which resulted in an unlimited availability of stem cells. These modified stem cells also showed a pronounced regenerative potential on cardiac function and remodelling after experimental myocardial infarction in mice.

Recently, Dr Templin transplanted, for the first time, induced pluripotent stem cells into a preclinical large animal model of myocardial infarction and demonstrated long-term engraftment by innovative hybrid single photon emission computed tomography/computed tomography imaging of sodium iodide syporter transgene expression.

Dr Templin’s clinical interest lies in interventional cardiology and novel intracoronary imaging techniques. He has validated a novel coronary optical frequency domain imaging technology for stent healing in the cath lab. “The proportion of uncovered coronary stent struts has been identified as a potent risk factor for late stent thrombosis of drug eluting stents,” says Dr Templin. “Our study evaluated the accuracy of coronary optical frequency domain imaging for the detection of uncovered stent struts and suggests that the optical density of optical frequency domain imaging-detected stent strut coverage is different for fibrin versus neointima-covered stent struts.” Dr Templin adds, “The implementation of innovative intracoronary imaging technologies in the daily clinical routine may lead to further optimisation of individual treatment strategies in the future.”

References


