Pioneer in Cardiac Electrophysiology: Maurits Allessie, MD, PhD

“Both Electrical Remodelling and Structural Remodelling, I Believe, Are the Mechanisms Behind the Paradigm That ‘Atrial Fibrillation Begets Atrial Fibrillation’”

Maurits Allessie, emeritus professor of physiology, Maastricht University, Maastricht, the Netherlands, and academy professor of the Royal Netherlands Academy of Arts and Sciences, talks to Mark Nicholls.

Over the past 4 decades, Maurits Allessie, MD, PhD, emeritus professor of physiology, Maastricht University, Maastricht, the Netherlands, and academy professor of the Royal Netherlands Academy of Arts and Sciences has made a number of discoveries and breakthroughs to explain the electrophysiological mechanisms of cardiac arrhythmias.

“I Could Elicit Exactly the Same Rhythm—a Very Rapid Arrhythmia—by a Single Stimulus in the Left Atrium, So Obviously It Had Nothing to Do With the Sinus Node”

“The first breakthrough was in Amsterdam, the Netherlands, as part of my PhD studies. Professor Lennart Bouman, PhD, and Professor Vic Bonke, PhD, were interested in the sinus node and they used the right atrium of the rabbit to investigate the origin of the heart beat,” Professor Allessie explains. Professors Bouman and Bonke found features of abnormal behaviour in the sinus node. They could not explain it, but could not exclude its generation by the atrium itself. They asked Professor Allessie to use the same protocols to examine the left atrium and report back his findings. They expected nothing abnormal.

Professor Allessie recalls, “I was delighted because I had my own experiment and could do the same things they were doing. The abnormal behaviour they observed was the response to an early premature stimulus, which not only reset the clock of the sinus node, but sometimes threw the atrium into a short series of very rapid responses, an atrial tachycardia with a frequency of 400 to 600 beats per minute. I found that I could elicit exactly the same rhythm—a rapid arrhythmia—by a single stimulus in the left atrium, so obviously it had nothing to do with the sinus node. That was quite a thrill for me and a little shock for my colleagues, and it was the start of my own studies on the electrophysiological mechanisms of tachycardia and atrial fibrillation.”

Professor Allessie’s early mapping data of atrial fibrillation.1 Professor Allessie says that Gordon Moe, PhD, had the most effect on his thinking and approach. He explains, “Professor Moe developed a computer model in which he showed that multiple wavelets in the atrium could sustain atrial fibrillation,2 and I was the first to demonstrate that mechanism in vivo. He was my role model, together with Sir Thomas Lewis, FRS, from the United Kingdom. I felt as though I was ‘standing on their shoulders’ and building on the concepts of mapping atrial fibrillation they developed.” Illustration from reference 1, courtesy of Professor Allessie.

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Professor Allessie being presented with his doctorate degree in 1977 by Professor Bouman. He says, “I was a medical student in my third year at the University of Amsterdam when I was scouted by the professor of physiology to become 1 of his junior assistants. Two staff members in the department, Professors Bouman and Bonke, were focusing their research on the sinus node in isolated rabbit hearts using microelectrodes. I found it intriguing, and that started my interest in electrophysiology and cardiology.”

The Department of Physiology was linked by an air bridge to the Department of Cardiology, which had a global reputation for the clinical electrophysiology being developed by Professor Dirk Durrer, MD, and Professor Hein Wellens, MD, at that time. Professor Allessie says, “The 2 things together influenced me in that I became involved in basic science and found that I loved it, but, at the same time, the application to cardiology was important. I have always been involved as a basic scientist in translational research. That was how it started for me. I am a physiologist, and the way my career developed meant that I never became a cardiologist, although I am deeply involved in cardiology but not as a clinical cardiologist.” Photograph courtesy of Professor Allessie.

From this early work using primitive mapping, with only 10 sites at a time, Professor Allessie was the first to discover a rotor in the heart, which at that time he called “the leading circle.” He notes, with some irony, that at present a debate in cardiology is going on about whether atrial fibrillation is sustained by such a rotor. “The funny thing is that I think it is not,” he says, “I was the first to show it in cardiac tissue, and now, at the end of my career, I am debating others who believe that a rotor is the driving force behind the persistence of atrial fibrillation.”

“Mapping Has Survived My Whole Career, From a Small Piece of Isolated Rabbit Atrial Tissue to Patients With Longstanding Persistent Atrial Fibrillation”

At the new Maastricht University in the mid-1970s, Professor Allessie extended his mapping technique, using 256 electrodes for simultaneous recording of numerous sites in the heart. He says, “People thought I was crazy, but I simply believed that mapping is a great technique and was convinced that we needed such a thing. When recording from only a few sites at a time, a complete activation map can only be reconstructed when the arrhythmia is regular and long lasting. To visualise the initiation and termination of an arrhythmia, and irregular arrhythmias such as atrial and ventricular fibrillation, one needs to record from all sites simultaneously. I believe I was one of the first people who developed this technique. I like technical developments, and still write my own software for the analysis of atrial fibrillation. I enjoy developing new technology that allows you to find things that, with the present technology, you cannot find. That is an enjoyable part of my work.”

From the rabbit, Professor Allessie moved on to map atrial fibrillation in isolated canine hearts, thus providing an experimental basis for the multiple wavelets hypothesis of Professor Moe. He then mapped atrial fibrillation in the human heart in the mid-1990s with Karen Konings, PhD, MD, using high-density maps of electrically induced atrial fibrillation in man. He continues to work on this with Natasja de Groot, MD, PhD, from the Department of Cardiology, Erasmus Medical Centre, Rotterdam, the Netherlands. He says, “Last year we mapped patients who had operations for mitral valve disease and longstanding persistent atrial fibrillation. Mapping has survived my whole career, from a small piece of isolated rabbit atrial tissue to patients with longstanding persistent atrial fibrillation.”

“After Only 1 Day of Burst Pacing, Atrial Fibrillation Lasted for 20 Seconds, and After 4 Days, It Continued for Several Hours. In Less Than 1 to 2 Weeks, Atrial Fibrillation Became Persistent”

A milestone in Professor Allessie’s career was the development of the Maastricht goat model and the discovery through it of an important phenomenon of electrical remodelling. At the time, it was considered that the progression from paroxysmal to persistent atrial fibrillation was an expression of the progression of the underlying heart disease. Professor Allessie wanted to know whether atrial fibrillation could change the atria in such a way to promote the easier initiation and perpetuation of atrial fibrillation.

The hypothesis was tested in the goat because a goat heart is similar in size to a human heart, and it was possible to implant electrodes chronically on the atrial epicardium using a small wire through the goat’s neck. Professor Allessie says, “We repetitively induced atrial fibrillation by burst pacing with a weak, 1-second burst that the goat did not notice. In the control condition, these episodes of atrial fibrillation always self-terminated within 5 to 10 seconds.”

The team suspected that after 1 month of continuous burstings and maintaining atrial fibrillation for 24 hours a day, 7 days a week, the duration of atrial fibrillation episodes would increase to >1 minute or maybe even >1 hour. This result would show that “atrial fibrillation itself would beget atrial fibrillation.” Professor Allessie says, “The surprise was that it happened within 24 hours. After 1 day of burst pacing, atrial fibrillation lasted for 20 seconds, and after 4 days, it continued for several hours. In less than 1 to 2 weeks atrial fibrillation became persistent. By maintaining atrial
fibrillation for 1 week, atrial fibrillation became the normal rhythm of the heart. Due to electrical remodeling of the atria, atrial fibrillation rather than sinus rhythm, had now become the preferred rhythm (domestication of atrial fibrillation).10

The electrical remodeling was reversible. Professor Allessie says, “We continued with the goat model and found that if atrial fibrillation is maintained for >1 week—for as long as 1, 2, or 3 months—the atria become structurally remodelled.11,12 Both electrical remodeling and structural remodelling, I believe, are the mechanisms behind the paradigm that ‘atrial fibrillation begets atrial fibrillation’.”

Professor Allessie’s current work mapping longstanding persistent atrial fibrillation in humans has revealed a so far unknown mechanism for the perpetuation of atrial fibrillation. He believes that, instead of a rotor, the end result of the structural atrial remodelling is responsible for maintaining the arrhythmia. The atrial muscle bundles become electrically dissociated, transforming the atrial wall into a double layer of multiple narrow bundles. The fibrillation waves frequently cross over between the endo- and epicardial layer. These breakthroughs provide a constant source of independent fibrillation waves distributed over the entire atrial wall, offering an adequate explanation for the high persistence of atrial fibrillation in patients with structural heart disease.” He explains that the atrium should be considered as a 3-dimensional structure.

“I Wanted to Become a Cardiologist, But It Was Quite Obvious That If I Were to Accept This Offer, I Would Never Become a Cardiologist”

While training for his PhD at the University of Amsterdam, Professor Allessie received an invitation that changed the whole direction of his career. He says, “A new university was starting in Maastricht, and I was invited by one of the founders of the medical faculty, Professor Rob Reneman, to go with Professor Bonke to develop the Department of Physiology. They decided that the whole faculty was to be focused on cardiovascular disease. That was tough because it meant a break point, a point of no return in my life. I wanted to become a cardiologist, but if I were to accept this offer, I would never become a cardiologist. It took me a couple of months to make up my mind, and I decided to do it. So, at the age of 30, I moved as a PhD student to Maastricht to help build up the electrophysiological lab.” He completed his PhD thesis in 1977. At the age of 38, he became professor of physiology, and he became chair of the department 7 years later.

In 1997, Professor Allessie received the Distinguished Scientist Award from the North American Society of Pacing Electrophysiology, and in 1999, he received the Basic Science Award from the European Society of Cardiology. In 2003, he was made Academy Professor of the Royal Netherlands Academy of Arts and Sciences. He has been delighted to receive the Founders’ Lecture Award from the Heart Rhythm Society this year and the Royal distinction of “Knight of the Order of the Netherlands Lion” for his contributions to science.
Funding: International Society for Heart Research, European Section/Servier Research Fellowship

“The Fellowship Helped Me in the Transition From a Postdoctoral Experience in the United States to a More Independent and Stable Position in Italy”

Carlo Gabriele Tocchetti, MD, PhD, research associate, Division of Cardiology, National Cancer Institute, Senator Pascale Foundation, Naples, Italy, talks to Jennifer Taylor, BSc, MSc, MPhil.

In autumn 2008, Carlo Gabriele Tocchetti, MD, PhD, research associate, Division of Cardiology, National Cancer Institute, Senator Pascale Foundation, Naples, Italy, finished a postdoctoral research fellowship at Johns Hopkins Medical Institution, Baltimore, MD, where he worked in the labs of David A. Kass, MD, and Nazareno Paolocci, MD, PhD. He then joined the Department of Clinical Medicine, Cardiovascular and Immunological Sciences, directed by the late Professor Massimo Chiariello, MD, at Federico II University, Naples, Italy where he worked in the lab of Professor Sandro Betocchi, MD, investigating myocardial function in hypertrophic cardiomypathy, and continued his clinical work in the echo lab under the supervision of Maria Angela Losi, MD.

In 2007, Dr Tocchetti presented his data on the molecular mechanisms of the inotropic action of nitroxyl on murine isolated left ventricular cardiomyocytes from Johns Hopkins at the world congress of the International Society for Heart Research in Bologna, Italy, where he found out about the €20,000 International Society for Heart Research, European Section/Servier fellowships for young cardiovascular scientists. He says, “To continue with my research career in Italy, I had to apply for grants, so I applied for this prestigious grant in March 2009.” He was awarded the grant in April 2009 and received it at the joint International Society for Heart Research, European Section/Heart Failure Association of the European Society of Cardiology meeting in Nice, France, in May 2009.

The fellowship started in July 2009 and allowed Dr Tocchetti to assist Professor Betocchi in setting up a new project on oxidative stress in the progression of end-stage hypertrophic cardiomyopathy. Most of all, he was able to progress his studies on nitroxyl as a modulator of myocardial function. A main research topic of the Paolocci and Kass labs at Johns Hopkins is the role of nitric oxide, protein kinase G, reactive nitrogen species, and reactive oxygen species in the modulation of myocardial function. This led to the discovery that nitroxyl donors have potentially clinically relevant cardiac actions.

Dr Tocchetti showed that nitroxyl donated from Angeli’s salt enhances contractility and accelerates relaxation in normal and failing hearts in vivo and in normal cardiomyocytes in vitro by modifying critical cysteines in key excitation–contraction coupling proteins, enhancing Ca$^{2+}$ cycling in the sarcoplasmic reticulum, and inducing myofilament Ca$^{2+}$ sensitisation. These studies provided core data for a patent submission, the creation of a new drug company, and the development of new, purer nitroxyl donor, which is being tested in patients with heart failure.

During the fellowship, Dr Tocchetti and his colleagues aimed to establish whether nitroxyl modifies critical cysteine residues on phospholamban, thereby removing phospholamban functional hindrance on sarco/endoplasmic reticulum Ca$^{2+}$-ATPase 2a activity and accelerating de facto Ca$^{2+}$ re-uptake into the sarcoplasmic reticulum. They wanted to address whether nitroxyl donors retain their positive inotropic and lusitropic actions in failing left ventricular cardiomyocytes obtained from mice subjected to chronic pressure overload (via transverse aortic constriction) that displayed decompenated heart failure and blunted inotropic response to beta agonists. In collaboration with Dr Paolocci, they found that the new and more stable nitroxyl donor CXL-1020 enhanced contractility and Ca$^{2+}$ transients and improved relaxation in failing myocytes.

Selected References


Jennifer Taylor is a freelance medical journalist.
Funding: International Atherosclerosis Society Visiting Fellowship Award

Instrumental in the Acquisition of an Early Career Grant From the Netherlands Organisation for Scientific Research to Integrate PhD and Postdoc Projects

Judith C. Sluimer, PhD, assistant professor, Department of Pathology, Cardiovascular Research Institute Maastricht, University Medical Centre, Maastricht, the Netherlands, talks to Jennifer Taylor, BSc, MSc, MPhil.

After working for a PhD in the group of Professor Mat Daemen, MD, PhD, in the Netherlands, Judith C. Sluimer, PhD, assistant professor, Department of Pathology, Cardiovascular Research Institute Maastricht, Maastricht, the Netherlands, realised that her pursuit of an academic career “would benefit from a postdoctoral fellowship abroad to provide knowledge, technical expertise, an international network of peers and principal investigators, and, hopefully, a good article, all of which are crucial to acquire funding for future research.”

Dr Sluimer’s PhD investigated the association between plaque rupture and hypoxia with dysfunctional angiogenesis.1-3 Hypoxia was prominent in plaque macrophages, but its role in macrophage biology remained unknown. To improve her knowledge, Dr Sluimer therefore applied for a postdoc post in the lab of Professor Ira Tabas, MD, PhD, of Columbia University, New York, NY, the leading expert in macrophage biology. He accepted her application, and together they then pursued funding for the fellowship. As members of the International Atherosclerosis Society, they received an e-mail alert on the call for the 2008 fellowship. They generated the topic and hypothesis together through extensive discussions via e-mail and face to face at a vulnerable plaque colloquium of the Royal Dutch Academy for Sciences in Amsterdam. “Ira would ask questions in such a way that I was stimulated to think one step further without him spelling out the details,” recalls Dr Sluimer. “Finally, we designed the project and wrote the grant proposal in about 2 to 4 weeks.”

The application process was straightforward and not time consuming. It focuses on the quality of the project, the applicant, and the host lab, and the importance for the applicant’s career and projects in his or her home lab. In August 2008, after a 4.5-month review process, Dr Sluimer was happy to hear that she had been awarded the fellowship, providing $8000 to conduct research at Columbia University. After the fellowship, she wrote a 2-page report on her findings and experiences, which was published on the International Atherosclerosis Society website (http://www.athero.org/).

During the fellowship, Dr Sluimer studied a survival pathway in apoptotic macrophages and autophagy in vitro and in vivo models of atherosclerosis. Since her return to the Netherlands, the project has been continued by Xianghai Liao, PhD.

“My postdoctoral research, specifically Ira Tabas, taught me how to manage scientific projects with attention to the mechanistic insight, in vivo relevance, the teleological perspective, innovation, and efficiency,” says Dr Sluimer. She has applied the techniques to new research projects in Maastricht with Professor Erik Biessen, PhD, and Professor Daemen. In addition, Columbia’s active research programme (internationally renowned lecturers, participation in interdisciplinary projects) has broadened her scientific perspective. “I enjoyed the interaction with and learned a lot from the Tabas lab members: Ed Thorp, Tracie Seimon, Xianghai Liao, Gang Li, Connie Woo, Lale Ozcan, and George Kuriakose,” she says. “Also, since our joint postdoc in Ira’s lab, I have been in close contact with Dr Dorien Schrijvers. This has led to technical and theoretical exchanges resulting from several work visits and meetings in our respective home labs in Antwerp, Belgium, and Maastricht.” The fellowship has also been instrumental in acquiring an early career grant (Veni), part of the Innovational Research Incentives (Veni-Vidi-Vici programme) of the Netherlands Organisation for Scientific Research, to integrate her PhD and postdoc projects.

Selected References


Jennifer Taylor is a freelance medical journalist.
The Lefoulon-Delalande Foundation was created in 2000 to provide funding to researchers or teams of researchers, particularly those investigating cardiovascular disease. The foundation falls under the umbrella of the Institut de France, which also houses 5 academies, including the French Academy of Sciences. Each year, the foundation awards postdoctoral fellowships to full-time cardiovascular researchers in France as well as a Grand Prix Scientifique of €500,000 to a world-renowned figure who has made a significant scientific contribution to physiology, biology, or cardiovascular medicine. The members of the foundation’s Scientific Council come from France, Finland, Italy, England, Sweden, Canada, and the United States. Candidates for the Grand Prix Scientifique are nominated by a distinguished scientist, who submits a dossier of evidence to the president of the Scientific Council. The dossier includes a nominating proposal, a 1-page curriculum vitae, description of the candidate’s scientific achievements (2 pages), and a list of 10 major articles.

Based on the Scientific Council’s recommendation, the foundation’s Board of Directors awarded the 2011 Grand Prix Scientifique to Valentin Fuster, MD, PhD, director of the Centro Nacional de Investigaciones Cardiovasculares, Madrid, Spain, and director of Mount Sinai Heart Center, New York, NY (see http://circ.ahajournals.org/content/115/13/f55). Professor Fuster received the prize in recognition of his translational research on atherothrombotic disease and the prevention of coronary artery obstruction, and, specifically, for the following 7 major discoveries:

- Pioneering insight into the role of platelets in atherothrombosis through studies on pigs with von Willebrand factor deficiency and impaired platelet function showing resistance to atherothrombosis.
- Demonstration in dogs and then humans of the role played by platelets in coronary occlusion and the efficacy of aspirin in prevention.
- Demonstration in humans that the rupture of a coronary plaque occurs in paradoxically small and silent plaques during angiography.
- Evidence that rupture of a lipid- and macrophage-rich (vulnerable) plaque is a high-risk factor for thrombosis.
- Identification and characterisation using magnetic resonance imaging of high-risk plaques and their reduction by lipid-lowering drugs such as statins.
- In vivo demonstration of the important role of high-density lipoprotein in the reduction of lipid- and macrophage-rich plaques through studies on rabbits and transgenic mice.
- Demonstration, first through in vitro studies and then in pigs and humans, of the inhibitory action of rapamycin on the migration, proliferation, or development of the extracellular matrix of smooth muscle cells after vascular injury.

Professor Fuster is the only cardiologist to receive all 4 major research awards from the world’s 4 leading cardiovascular organisations (European Society of Cardiology, American Heart Association, American College of Cardiology, and the Inter-American Society of Cardiology). He says, “I will use this prize money to promote young research talent and continue projects on prevention strategies in cardiovascular diseases. I feel proud for what this award represents to my outstanding research colleagues over the years, from the Mayo Clinic to Mount Sinai School of Medicine in New York and lately, Centro Nacional de Investigaciones Cardiovasculares in Madrid. It is a tremendous honour, and I share it with all of them, including Lina and Juan Badimon.”

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