Pioneer in Clinical Cardiac Electrophysiology: Vincenzo Santinelli, MD

“The Guidelines That Currently Say That Asymptomatic Wolff-Parkinson-White Patients Do Not Need Treatment Should Be Changed”

Vincenzo Santinelli, MD, scientific director, Department of Arrhythmology, Maria Cecilia Hospital, Cotignola, Italy, talks to Barry Shurlock, MA, PhD.

By means of nerves, the pathways of the senses are distributed like the roots and fibres of the tree,” wrote the Italian anatomist Alessandro Benedetti, at the end of the 15th century. Many others from that part of the world also helped move science away from animal spirits and towards flesh and blood—and their descendants are still making significant contributions. One of them is Vincenzo Santinelli, MD, scientific director of the Department of Arrhythmology, Maria Cecilia Hospital, Cotignola, Italy, whose main research interests are catheter-based treatment of cardiac arrhythmias and electrical therapy of patients with heart failure. In particular, he has focused on the identification of patients with asymptomatic Wolff-Parkinson-White syndrome who are at risk of sudden death, the use of catheter ablation for atrial fibrillation, and magnetic remote procedures in ablation therapy.

>7000 Electrophysiological Procedures, Including 1000 Radiofrequency Catheter Ablations, 2000 Pacemaker Implants, 250 Implantable Cardioverter-Defibrillators, and 100 Biventricular Pacemakers

Professor Santinelli has a 39 years of experience with cardiac electrophysiology, beginning with his first His bundle recording in 1973. It continues up to the present day with catheter ablation of atrial fibrillation, dramatically advancing the practice of clinical electrophysiology. His clinical experience is enormous, comprising >7000 invasive electrophysiological procedures, including 1000 radiofrequency catheter ablations, 2000 pacemaker implants, 250 implantable cardioverter-defibrillators and 100 biventricular pacemakers. Talking of his work, he says, “The efforts of all electrophysiologists, and doctors in general, must be to aspire to make medicine one of the most humane of the sciences, as its founding fathers intended. We usually perform at least 15 invasive procedures per day, and before each one I give my patients an affectionate pinch of the cheek! What I like best about catheter ablation is that, like surgery, it is a curative approach, and in almost all cases leads to a definitive treatment of symptoms, with an excellent quality of life. The patients, once successfully ablated, do not require repeated visits or chronic drug therapy, and they can then become our friends. The worst aspect of the job is that it takes all of my time!”

Much of Professor Santinelli’s work has been carried out with Carlo Pappone, MD, head of the Department of Arrhythmology at Maria Cecilia Hospital, with whom Professor Santinelli has shown an outstanding knack for writing articles that challenge established opinions and get...
written about in editorials. To take one example: the use of circumferential pulmonary vein ablation for the treatment of atrial fibrillation was initially regarded with some reserve, but it is now widely accepted to be simpler, safer, more rapid, and a more effective method than others, with fewer complications. These events are a tribute to Professor Pappone, whose name has become attached to the approach and a source of pride for Professor Santinelli, whose persistent drive to understand atrial fibrillation has contributed much and has resulted in his former trainee gaining international recognition. In 2004, in a fast-track article in *Circulation*, the 2 Italians—master and pupil—came together to demonstrate that circumferential pulmonary vein ablation has the added advantage of vagal denervation (first experimentally highlighted in 1586 by the anatomist Piccolomini).1

The work demonstrates much about Professor Santinelli’s approach to research and the advice he gives trainee electrophysiologists. He says, “First, it is important to work in well-recognised centres with a high volume of procedures. Even if you think you have done some important work, you must keep on moving forward to new horizons: don’t sit on your laurels! Pioneering studies are difficult to realise and the hardest part is to get the right idea, which for us has come from several years of incessant work in a large number of patients, accurately followed for many years plus advanced technology and a good team, including fellows, technicians, bioengineers, statisticians, and nurses.

Speaking of his studies of the long-term progression of atrial fibrillation,2 Professor Santinelli says, “I am particularly interested in the underlying pathophysiology and natural history of the condition. The most important problem is to identify those patients in which the ablation procedure is effective in eliminating arrhythmia recurrence and progression. It is clearly an invasive procedure, it takes a long time, and there may be complications, so it must be used carefully. We have, for example, shown that many patients with ‘lone’ [uncomplicated] atrial fibrillation do not need treatment, but in those with comorbidities, such as diabetes [mellitus], the disease frequently progresses, so early intervention with ablation may reduce recurrences, progression, and consequences such as stroke.”

In 2011, Professor Santinelli co-authored a study of irrigated-tip magnetic catheter ablation in a series of patients with atrial fibrillation.3 In the heart failure field, he has pursued a number of novel approaches, such as cardiac resynchronisation therapy using multisite pacing and nonexcitatory electrical cardiac contractility modulation.

“By Following Many Asymptomatic Wolff-Parkinson-White Syndrome Patients over Several Years, I Have Shown That They Have Silent or Minimally Symptomatic Life-Threatening Arrhythmias”

A major achievement of Professor Santinelli and colleagues is their role in advancing the knotty story of Wolff-Parkinson-White syndrome. The 3 distinguished cardiologists from both sides of the Atlantic who, in 1930, defined the syndrome—the violin-playing Bostonian Louis Wolff, MD, the shy Englishman John (later Sir John) Parkinson, MD, and the “president’s cardiologist,” Paul Dudley White, MD—would surely be astonished to find that 80 years later, physicians are still arguing about their article on uncontrolled rapid heartbeat.4 And yet, what is possibly the final chapter in the natural history of the Wolff-Parkinson-White syndrome only emerged a few years ago as a result of the seminal studies of the Italian electrophysiologists.

“It turns out that asymptomatic Wolff-Parkinson-White syndrome is not as benign as previously supposed, and the highest risk of sudden death is in the paediatric population,” says Professor Santinelli. The real problem with Wolff-Parkinson-White syndrome is that it is relatively common (about 1 per 1000 population), and in a small minority it is fatal, but how do you find out which patients are at risk?

In a 2012 article in *Circulation*,5 Professor Santinelli and his colleagues concluded that symptomatic patients with Wolff-Parkinson-White syndrome generally have a good outcome, and predictors of malignant arrhythmias are similar to those reported for asymptomatic patients with ventricular preexcitation. The article was accompanied by an editorial titled “Risk of Sudden Death in Wolff-Parkinson-White Syndrome: How High Is the Risk?”6
Professor Santinelli accepts that patients with asymptomatic Wolff-Parkinson-White syndrome are at low risk of sudden death, but he wants to make history of the spectre of young children dropping dead suddenly on the sports field. He explains, “By following many asymptomatic Wolff-Parkinson-White syndrome patients over several years, I have shown that they have silent or minimally symptomatic life-threatening arrhythmias, but I have found the predictors [of sudden death]. So, the guidelines, which currently say that asymptomatic patients do not need treatment, should be changed. “I’ll never forget my first experience of a 7-year-old asymptomatic child who occasionally showed a Wolff-Parkinson-White syndrome pattern on the ECG, with a totally silent malignant arrhythmia of 300 beats/minute throughout 24 hours as documented by a Holter monitoring. Yet, the child had a normal day activity, such as playing soccer, running, eating, and sleeping, without any symptoms.”

In a long-term follow-up study of asymptomatic Wolff-Parkinson-White syndrome patients, Professor Santinelli and his colleagues have evaluated the use of invasive electrophysiological testing for stratifying risk and carried out 2 randomised studies of prophylactic catheter ablation. Both articles were published in the New England Journal of Medicine, and they were accompanied by editorials discussing whether it was time to revisit the guidelines for treating asymptomatic Wolff-Parkinson-White syndrome patients.

Professor Santinelli is passionate about the natural history of asymptomatic ventricular preexcitation, and nothing would make him happier than to hear that electrophysiologists worldwide had supported his views. Asserting the evidence of his many studies, he has several times debated the subject in sessions at international cardiology conferences.

Professor Santinelli was born in Naples, Italy, and is a Neopolitan through and through. He graduated in medicine and trained in the Electrophysiology Lab headed by Giuseppe Critelli, MD, at the University of Naples “Federico II.” He was to spend many years in the southern Italian city, working his way up the ladder, and when his boss moved to the University of Rome, Rome, Italy, in 1986, he took his place and became director of the Centre of Arrhythmology. During this period, he trained Professor Pappone, who was one of his fellows.

He recalls, “At that time he [Professor Pappone] was interested in experimental cardiac metabolism, but during his training in electrophysiology, I immediately realised that I had a talented student. A few years later he moved to Milan as head of the Electrophysiology Lab and Arrhythmology Department of the San Raffaele Hospital, one of the biggest university hospitals in Europe, with thousands of beds and an International Medical Centre of Research. Professor Santinelli followed the same path in 2003 when he was invited to become director of the Strategic Research Programme at the hospital. The move gave him fresh opportunities to team up again in research with his former trainee.

During his career, Professor Santinelli acknowledges the influence of “special persons” or mentors, whom he says by turns gave him “[sound] methodology, criticism, enthusiasm, and positive energy.” He met one of them in 1982 in Dr Critelli’s Electrophysiology Lab in Naples, where he was participating in a research project on transcatheter ablative techniques. This was John J. Gallagher, MD, at one time head of the Clinical Electrophysiology Lab at Duke University Medical Center, Durham, NC. Professor Santinelli recalls, “Six years ago I met up with

Left, The electrophysiology lab rooms at Cotignola Maria Cecilia Hospital. Right, Professor Santinelli and Professor Pappone in Tokyo, Japan. Two years ago, Professor Santinelli and Professor Pappone moved from the San Raffaele Hospital, Milan, to similar positions at the Maria Cecilia Hospital, Cotignola, a private institution that takes ≈3000 electrophysiology patients a year from Italy and elsewhere. Photographs courtesy of Professor Santinelli.
him again at a debate he was chairing during the annual meeting of the Heart Rhythm Society. He still remembered me after 30 years and embraced me as an old friend; he showed me the gold crucifix we had given him in Naples that he still wore around his neck. His human qualities make him an exceptional human being and a wonderful doctor."

From the very beginning of his career, Professor Santinelli, with the support of his many coauthors, has demonstrated that he can carry out research that gets published in the top journals, often with accompanying editorials, and is taken notice of in the electrophysiological world. In 1982 in Naples, he cooperated with Drs Gallagher and Critelli in the world-first closed-chest catheter ablation procedure, and in 2004, he published an account of the first chronic experience in humans of cardiac contractility modulation for congestive heart failure. Other groundbreaking studies he has carried out with the Pappone approach to ablation and associated issues of mortality, morbidity, and quality of life. It seems that electrophysiology and Italy have a special relationship that endures. For his part, Professor Santinelli has a special relationship with Naples and the Amalfi coast of southwest Italy. Here, in the ancient small city of Caserta, he has founded a nonprofit charity Fondazione Casa della Speranza [The House of Hope Foundation] to provide funds for treating cardiac patients. He returns there from Cotignola as often as he can at weekends to spend time by the sea with his wife, whose support he fulsomely acknowledges, friends, and family. Speaking of this and the future, he says, “I have recently acquired a quiet old house in Furore, with panoramic terraces amidst lemon trees. I love gardening and watching things grow. Jazz is another great passion. I have many friends who play jazz. I usually spend my weekends in cultural activities with my friends. I cannot live without them, my parents, and my sea!"

References

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Germany and Norway to Establish and Develop Joint Research Projects

Martin Burger, PhD, full professor of applied mathematics, Westfälische Wilhelms-Universität, Münster, Germany, and Bjørn Fredrik Nielsen, PhD, full professor of applied mathematics, Norwegian University of Life Sciences, Aas, Norway, and adjunct research scientist at the Simula Research Lab, Lysaker, Norway, talk about their DAADppp mobility programme-funded cardiac mathematical modelling to Jennifer Taylor, BSc, MSc, MPhil.

The Deutscher Akademischer Austauschdienst Programme des Projektbezogenen Personenaustauschs (German Academic Exchange Service project-based personnel exchange programmes; DAADppp) (see http://www.daad.de/hochschulen/kooperation/partnerschaft/ppp/05485.de.html) mobility programme Germany–Norway provides funding for short-term visits by scientific staff and groups of researchers to establish and develop joint research projects. The programme, which is funded jointly by Norway and Germany aims to establish and expand the contact between educational and research institutions in the 2 countries and is open to all subject areas and disciplines.

Connecting Inverse Problem Competence in Münster with Heart Modelling Expertise in Oslo

In 2008/2009, a DAADppp mobility programme grant was awarded for the project “Computational Methods for Identifying Ischaemic Heart Disease” to Martin Burger, PhD, full professor of applied mathematics at the Westfälische Wilhelms-Universität, Münster, Germany, and Bjørn Fredrik Nielsen, PhD, full professor of applied mathematics at the Norwegian University of Life Sciences, Aas, Norway, and adjunct research scientist at the Simula Research Lab, Lysaker, Norway. At the time of receiving the grant, Professor Nielsen was a full-time research scientist at the Simula Research Lab. The grant covered travel costs and local expenses for several extended visits of researchers from the collaborating institutions. The involved departments were not asked for financial contributions, but they provided basic facilities such as office space.

Professors Burger and Nielsen applied for the grant to intensify their collaboration on computational methods for the inversion of electrocardiogram/body surface potential map (ECG/BSPM) data. The application process was straightforward, requiring minor paperwork, a 5-page description of previous work, and plans for the project. At the time of writing the project proposal, Professor Nielsen had already...
worked for some years on novel methods for reconstructing transmembrane potentials transmurally from ECG/BSPM recordings and how mathematical modelling could be used to identify ischaemic heart disease. Professor Burger is an expert in inverse problems and started to work on cardiac problems through the collaboration with Professor Nielsen. After moving from Linz to Münster, it was possible for Professor Burger to initiate a strong local collaboration with the Cardiology Department at the University Hospital in Münster. Professor Nielsen’s expertise was important for developing the interdisciplinary collaboration in Münster. Professor Burger’s expertise about inverse problems was beneficial for Professor Nielsen’s research group at Simula Research Lab and strongly contributed to the mathematical understanding of the problem.

In addition to several general aspects of cardiac inversion, a major focus of the joint project was to understand the prospects and pitfalls of inversion for the transmembrane potential in the heart volume. It has become a standard idea to use ECG/BSPM data to invert for the epicardial potential or the epicardial activation sequence. Inverting for the transmembrane potential is a much more ambitious problem, but it turned out that it is mathematically equally difficult as the inversion for the epicardial potential. More precisely, they could show that the instability present in the inversion for the transmembrane potential is exactly the same as the instability in the inversion for the epicardial potential.1

“In order to obtain meaningful practical reconstructions of the transmembrane potential, however, further prior knowledge needs to be introduced in the algorithms; an appealing approach is a representation mainly obtained via the activation sequence,” says Professor Nielsen. “We tried to understand under which conditions it is reasonable to reconstruct such information. During the project, it turned out that the fibre architecture of the myocardium and the location of deficiencies relative to it is crucial.”

Professors Burger and Nielsen and their teams also investigated a novel model-based approach for identifying ischaemic regions from ECG/BSPM data based on the Bidomain model. The inversion algorithm developed in the thesis of Melanie Schröter,2 a student involved in the project, led to interesting results.

“We decided to apply for the grant to strengthen the collaboration between the 2 principle investigators and to allow for mobility of further members of both research groups,” says Professor Nielsen. “This worked out well in the course of the project and led to new joint initiatives. Although we had not published a joint article before, we were awarded the DAADppp mobility programme grant because of the obvious benefits of connecting the inverse problem competence in Münster with the heart modelling expertise in Oslo.”

References

Jennifer Taylor is a freelance medical journalist.
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