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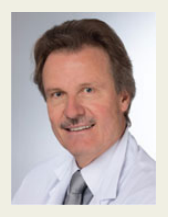
Device therapy in cardiac disease: a success story



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Ever since the development of the external defibrillator by Paul Zoll in the USA[1] and the implantation of the first pacemaker by Ake Senning in Europe in the 1950s,[2] cardiac devices have become a very important part of the therapeutic armamentarium for cardiac patients. The early pioneers were followed by people such as Michel Mirowski, who—25 years later—invented the implantable defibrillator for the prevention of sudden cardiac death.[3] More recently, the biventricular pacemaker was introduced for patients with heart failure.[4,5] All these devices have markedly improved quality of life and survival of cardiac patients, with an excellent cost-effectiveness, if appropriately used according to current guidelines.[6–8]

With the increasing use of cardiac devices, infection appears to be a problem according to current trends. Although a severe complication, it can at times be symptomatically mild, making the diagnosis challenging. Of note, device infections are potentially lethal, and timely diagnosis and early initiation of correct treatment are of the utmost importance for patient outcome. In order to reduce device infections, careful patient selection, preventative measures, and appropriate choice of device types are key.

This issue begins with a timely *Clinical Review* entitled '**Infected cardiac implanted electronic devices: prevention, diagnosis, and treatment**' by Jens Cosedis Nielsen from the Aarhus University Hospital, Skejby in Aarhus, Denmark.[9] The article presents currently available data and a consensus opinion on device infection, and identifies important current practice aspects for future development. Due to their clinical importance, strategies for reducing device infection should be tested in sufficiently powered and well-designed multicentre randomized controlled trials in the future.

Congenital heart defects are the most common birth defects. Such patients are often also in need of cardiac devices, be it pacemakers, implantable cardioverter defibrillators (ICDs),[10,11] or cardiac resynchronization therapy.[12] Major advances in open-heart surgery have led to rapidly evolving cohorts of adult survivors requiring specialized care. As the majority of affected women also now survive to childbearing age, managing pregnancy in grown-ups with congenital heart disease has become an issue. The risk of cardiovascular complications during pregnancy and peripartum depends on the type of the underlying defect, the extent and severity of residual haemodynamic lesions, as well as co-morbidities. The issue continues with a *Clinical Review* entitled '**Pregnancy in women with congenital heart disease**' by Matthias Greutmann from the University Hospital Zurich.[13] The authors note that individualized, multidisciplinary pre-pregnancy risk assessment and counselling, including assessment of risks in the offspring and estimation on long-term outcomes of the underlying heart defect, will enable informed decision-making by the patient. Depending on the estimated risks, a careful follow-up plan during pregnancy as well as a detailed plan for delivery and post-partum care can reduce the risks, and should be made by the multidisciplinary team.

Many patients with hereditary heart disease require cardiac pacing early in life, and hence will repeatedly require new batteries and devices. As pacing leads are difficult to remove, leadless pacemakers have been developed for such patient populations.[14] Furthermore, complications associated with conventional transvenous pacing systems are commonly related to the pacing lead and pocket. Thus, miniaturized devices might be advantageous. In the first FAST TRACK clinical research paper entitled '**Early performance of a miniaturized leadless cardiac pacemaker: the Micra Transcatheter Pacing Study**' by Philippe Ritter from the Hopital Cardiologique du Haut-Lévèque in Bordeaux France, the authors describe the early performance of a novel self-contained miniaturized pacemaker.[15] Patients having a Class I or II indication for VVI pacing underwent implantation of a Micra transcatheter pacing system, from the femoral vein and fixated in the right ventricle using four protractible nitinol tines. Pre-specified objectives were $>85\%$ freedom from unanticipated serious adverse device events (i.e. safety) and a <2 V 3-month mean pacing capture threshold at 0.24 ms pulse width (i.e. efficacy). A total of 140 patients were implanted, 66% for atrioventricular block and 29% for sinus node dysfunction. During the follow-up of $\sim$2 years, the safety endpoint was met, with no unanticipated serious adverse events. Thirty adverse events related to the system or procedure occurred, mostly due to transient dysrhythmias or femoral access complications. One pericardial effusion without tamponade occurred. In 60 patients followed for 3 months, mean pacing threshold was 0.5 V, and no threshold was >2 V, meeting the efficacy endpoint. The average R-wave was 16 mV and impedance was 651 Ohms. The authors conclude that early assessment shows that transcatheter pacemakers can safely and effectively be applied. The long-term safety and benefit of the pacemaker will be further evaluated in the trial.

An **Editorial** by Jagmeet P. Singh from the Massachusetts General Hospital in Boston[16] puts these early findings into perspective and discusses the future of such devices.

In the second FAST TRACK paper, **'Intra-operative defibrillation testing and clinical shock efficacy in patients with implantable cardioverter-defibrillators: the NORDIC ICD randomized clinical trial'**, Dietmar Bänsch from the University Clinic in Rostock, Germany tested the hypothesis that shock efficacy during follow-up is not inferior in patients implanted without defibrillation testing during first ICD implantation.[17] A total of 1077 patients were randomly assigned to first time ICD implantation with or without testing and follow-up for almost 2 years. Intra-operative testing was standardized across all participating centres, and all ICD shocks were programmed to 40 J irrespective of ICD test results. The primary endpoint was the average first shock efficacy for all true ventricular tachycardia and fibrillation episodes. The secondary endpoints included procedural and other serious adverse events, and mortality. The model-based first shock efficacy was found to be non-inferior in patients with an ICD implanted without ICD testing, with a difference in first shock efficacy of 3.0% in favour of the no testing group. A total of 112 procedure-related serious adverse events occurred within 30 days in 18% of the tested and in 14% of the not tested patients. The rate of arrhythmic and sudden unknown deaths was 2% after ICD testing, which was unexpectedly significantly higher than in the no testing group with 0.6%. The authors conclude that defibrillation efficacy during follow-up is not inferior in patients with an ICD implanted without device testing. Defibrillation testing during first time ICD implantation should no longer be recommended. The paper is accompanied by a thought-provoking **Editorial** by Arthur J. Moss from the University of Rochester Medical Center in Rochester, New York.[18]

A small, but important, group of patients often requiring device therapy are those with channelopathies.[19,20] For their diagnosis, genetic analyses are increasingly used. In the third manuscript, '**Rare genetic variants previously associated with congenital forms of long QT syndrome have little or no effect on the QT interval**', Morten Olesen and colleagues from the Rigshospitalet in Copenhagen, Denmark studied whether variants previously associated with congenital long QT syndrome have an effect on the QTc interval in a Danish population sample. Furthermore, the authors assessed if carriers of variants in congenital long QT syndrome-associated genes are more prone to experience syncope compared with non-carriers, and if carriers have an increased mortality compared with non-carriers.[21] All genetic variants previously associated with long QT syndrome were surveyed using the Human Gene Mutation Database. Olesen *et al.* screened a Danish population-based sample of 7031 individuals with available whole-exome sequencing data and genotype array data for putative long QT syndrome genetic variants. In total, 33 out of 1358 variants previously reported to associate with long QT syndrome were identified. Of these, 10 variants were found in >8 individuals. The ECG showed normal QTc intervals in carriers compared with non-carriers. Syncope analysis among variant carriers and non-variant carriers showed that 1.8% and 1.6% of the individuals, respectively, had experienced syncope during follow-up. There was no significant difference in overall mortality rates between carriers (3.2%) and non-carriers (4.7%). QTc data and registry data indicate that 26 long QT syndrome-associated variants did not have any effect on the QTc intervals, or on syncope propensity or overall mortality. Based on the frequency of individual gene variants, the authors suggest that the 10 variants frequently identified, assumed to relate to long QT syndrome, are less likely to associate with a dominant monogenic form of the disease.

Heart failure often occurs as a late stage of an initial ventricular hypertrophy due to pressure overload. A mismatch between adequate angiogenesis and overgrowth of myocytes may be a critical mechanism controlling the transition from adaptive hypertrophy to heart failure. Canopy 2 (CNPY2) was recently identified as a secreted, hypoxia-inducible factor-1α (HIF-1α)-regulated angiogenic growth factor. In the fourth basic science paper, '**Canopy 2 attenuates the transition from compensatory hypertrophy to dilated heart failure in hypertrophic cardiomyopathy**', Ren-Ke Li and colleagues from the University Health Network in Toronto, Canada investigate the role of angiogenic factors in the development of myocardial hypertrophy and the development of heart failure induced by transverse aortic constriction in cardiac-specific transgenic mice that overexpress human CNPY2 in the myocardium.[22] Wild-type mice developed significant ventricular hypertrophy at 4 weeks and severe dilatation and heart failure at 12 weeks after aortic constriction. However, transgenic mice exhibited less severe ventricular dilatation and markedly reduced cardiac apoptosis and fibrosis following aortic constriction. Excess CNPY2 in trangenic mice prevented vasculature loss up to 12 weeks after aortic constriction, resulting in a better local myocardial environment, facilitating myocyte survival and preventing excessive matrix remodelling. Furthermore, trangenic mice expressed less tumour suppressor p53 after aortic constriction, indicating intrinsic activation of the p53-mediated repression of HIF-1α and Cnpy2. Li *et al.* found a correlation between the down-regulation of endogenous mouse Cnpy2 and p53-mediated HIF-1α inhibition during late-stage hypertrophic development. Thus, overexpression of CNPY2 attenuated the transition from compensatory hypertrophic response to maladaptive ventricular dilatation and heart failure, a finding that may stimulate further research and provides a suggestion for a novel therapeutic target to prevent heart failure under conditions of pressure overload.

The editors hope that readers of this issue of the *European Heart Journal* will find the contents of interest.

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