Cardiac Arrhythmia Research and Innovation in Ireland

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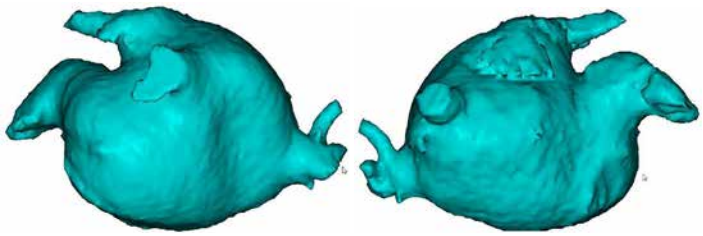
Some cardiac arrhythmias such as ectopic beats in the absence of underlying heart disease are typically benign and in most patients can be safely managed conservatively. Other cardiac arrhythmias such as ventricular tachyarrhythmias in the presence of a cardiomyopathy or inherited ion channelopathy (e.g. Long QT Syndrome) can lead to sudden death and require intervention. Significant progress has been made in recent years at Mater (Heart House), Tallaght (CRY), and Our Lady's Hospital for Children (NCRC) University Hospitals in the screening of families at risk of sudden death through cardiac arrhythmia including Inherited Cardiac Conditions – our understanding of the conditions which can result in such tragic events, their genetic analysis and prevention of further deaths in affected families has been a major step forward and much of this research and development has been achieved at the above centers through charitable donations and public fundraising. These services and research programs are invaluable and can be truly life-saving and should be fully supported.

Research at these centers have included genetic profiling of Inherited Cardiac Conditions in national cohorts and collaborative research between the National Children's Research Center and the Regenerative Medicine Institute (REMEDI) at NUI Galway on skin biopsy samples in patients with Long QT syndrome exploring reprogramming of skins cells to cardiomyocytes with funding from the Irish Research Council. These patient-specific stem-cell derived cardiomyocytes replicate the disease 'in a dish' with multi-electrode array recordings of contracting myocardial tissue similar to ECG's in the same patient. Using CRISPR-Cas9 gene editing technology, novel strategies for disease 'rescue' are being pursued.

At St Vincent's University Hospital our cardiac electrophysiology research program is focused primarily on catheter ablation of atrial fibrillation (afsymposium.com). This is the most common sustained cardiac arrhythmia and is associated with an increased risk of stroke, dementia and slight reduction in longevity and if left untreated in some patients can lead to heart failure. In decades past, it was felt reasonable to leave many patients in atrial fibrillation long-term and to control the heart rate with medication and reduce to the risk of stroke with anticoagulant drugs. More recently there is an increasingly recognized benefit, particularly in younger patients and those with more recent onset AF, to strive towards restoring the rhythm to normal which is primarily achieved by catheter ablation.

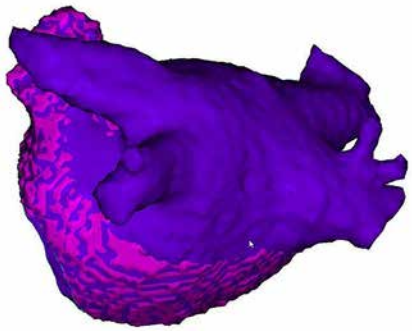
Prior to considering catheter ablation, patients should first address reversible lifestyle triggers which include obesity, smoking, and alcohol excess. There is now compelling data from randomized trials that major weight reduction can bring about a significant reduction in paroxysmal atrial fibrillation burden. Furthermore major weight reduction can facilitate control of hypertension and diabetes both of which can predispose to atrial fibrillation.



In some patients atrial fibrillation is a result of ventricular disease (e.g. heart failure with reduced or with preserved ejection fraction) or mitral valve disease. Depending on the underlying forces, atrial remodeling can be eccentric rather than global which may influence the approach to ablation and when appropriate the underlying condition should be treated prior to atrial fibrillation ablation

Patient empowerment with heart rhythm monitoring by commercially available watches and wearable devices which have the potential to reassure a patient or to provide an indication that further assessment is needed. This can be similar to having a home blood pressure monitor and involves the patient in their own health management. Patients should play an active role on their health care team and should be encouraged to learn about their condition on appropriate patient education websites.

Catheter ablation of tachycardias is conventionally achieved by thermal energy to heat or freeze the culprit cardiac tissue. Catheters are introduced through the blood vessels in the legs and guided to the heart muscle causing rapid or chaotic heart rhythm. While these procedures are quite effective, the risks of a procedural complication range from 1% to 3% depending on the type of rhythm being treated and the general health of the patient.



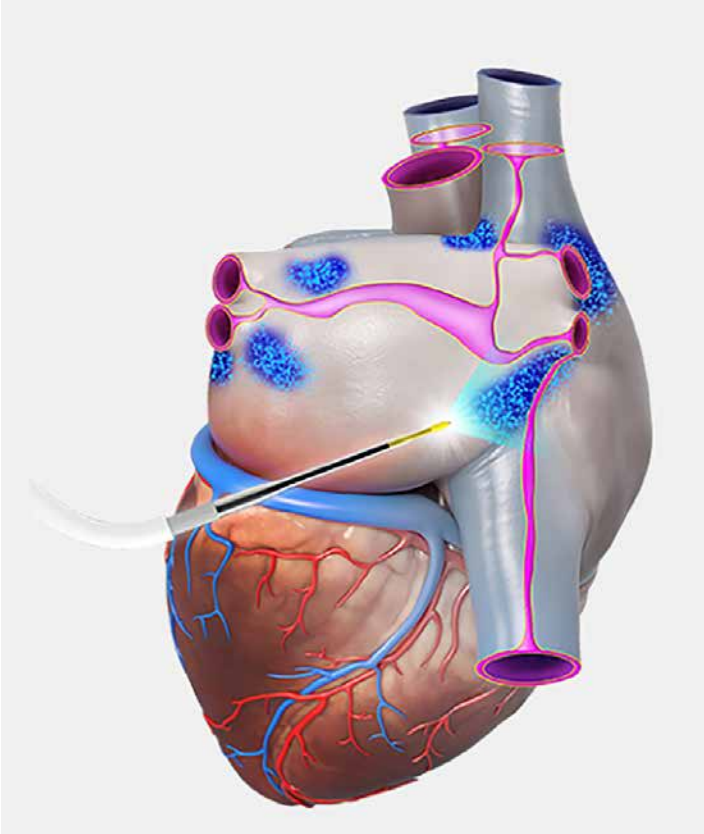
In patients undergoing catheter ablation for persistent atrial fibrillation, the pulmonary veins and posterior left atrial wall (solid purple) are usually isolated prior to consideration of any further ablation.

ECG of atrial fibrillation showing an irregular ventricular rate and variation in atrial cycle length, polarity and morphology.

Following isolation of the pulmonary veins and left atrial posterior wall box, ablation at key sites can result in significant atrial organization as seen above. The top six tracings (white and yellow) are of the surface ECG while the lower seven tracings (cyan) are intra-atrial electrograms.

Pulsed field ablation (electroporation), offers an alternative energy source which may be associated with improved efficacy and potentially reduced risk of complications. By delivering high voltage gradients, micro-perforations in the cell membrane can be induced without causing bara-trauma (arcing) or thermal injury. Currently research is exploring which pulse sequences and electrode configurations may be best suited to treating atrial fibrillation. In-vitro research facilities for electroporation therapy are available in Galway University (NUIG) and in Trinity College Dublin.

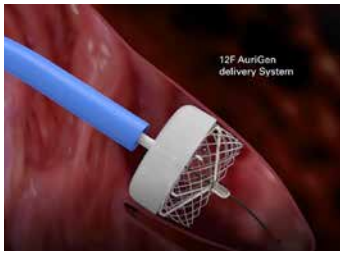
In addition to clinical studies, research and development in Ireland in the field of cardiac electrophysiology has been greatly enhanced by the BioInnovate program in Galway University (NUIG). This program has resulted in many start-ups, three of which are already in an advanced stage of development in the field of cardiac arrhythmias. These include; Atrian; One Projects and Aurigen.



AtriAN' s device for epicardial ablation of ganglionated plexi which play a role in triggering atrial fibrillation.

AtriAN has developed a system to treat the autonomic innervation of the heart by targeting the epicardial ganglionated plexi. The system utilizes pulse field ablation (electroporation) and will be used to prevent post-operative atrial fibrillation in open heart surgery but also will be used minimally invasively using a direct percutaneous approach to the pericardium.

OneProjects are developing VERAFEYE, an endovascular catheter system to increase the efficacy and safety of cardiac ablation. VERAFEYE, utilizes imaging, analytics and a catheter-based sensor system to generate 4D data during the cardiac ablation. In addition to imaging the endocardial shell, the system also images the wall thickness to facilitate titratration of energy settings for ablation. The system also images the lesions created in real-time to guide touch up applications were gaps have been left. This should lower the requirement for repeat ablation procedures. Their system can be utilized with all of the ablative energy sources.



AuriGen's percutaneous implantable left atrial appendage occluder and ablator (electroporation) to prevent strokes and treat patients with long-standing persistent atrial fibrillation.

AuriGen has developed a device which can achieve a combination of (i) percutaneous occlusion of the left atrial appendage (where blood clots tend to form which can lead to stroke) and (ii) ablation of the heart muscle of the left atrial appendage which can facilitate the maintenance of sinus rhythm in patients undergoing catheter ablation for long-standing persistent atrial fibrillation. This ablation is achieved by pulsed field ablation (electroporation). AuriGen Medical won the Global Innovation Award at the International Conference for Innovations in Cardiovascular Systems in Tel Aviv, Israel in 2018.

Eclipse Medical, another independent Irish company, has developed the Omega device for

Omega Left Atrial Appendage Occluder by Eclipse Medical to prevent stroke in patients unsuited to long-term anticoagulation.

percutaneous occlusion of the left atrial appendage for stroke prevention in patients with atrial fibrillation who are not suited to long-term anticoagulant medication. The Omega is CE marked and is currently recruiting patients for its Post Market Study in Europe and will begin commercialization in 2021.

Galenband in Ireland has developed a wristband with multiple sensors for long-term biometric data collection and can monitor heart rhythm continuously for 90 days in addition to other parameters. This should facilitate data collection on the nature of patient's arrhythmia and the efficacy of therapeutic interventions.

Galenband's wristband can provide detailed analysis of patients'arrhythmias.

Boston Scientific's implantable cardiac resynchronization pacing & defibrillator device.

In addition to the above home-grown early stage medical device innovations for the treatment of cardiac arrhythmias, a number of multinational corporations have significant manufacturing facilities for the production of cardiac arrhythmia devices based in Ireland. These include Boston Scientific (implantable cardiac pacemakers and defibrillators) as well as component manufacturing (e.g. Integer and Creganna).

A number of medical device companies avail of the expertise at Tyndall National Institute in Cork for the research and development of integrated ICT hardware and systems including photonics and electronics. Tyndall National Institute is a partnership between UCC, the Science Foundation of Ireland (SFI) and the Department of Enterprise Trade and Employment.

The development of cardiac arrhythmia devices in Ireland has been facilitated by a core of high level engineering graduates, clinical electrophysiologists with a record of innovation and university programs for collaborative research and development, availability of grant support from both national funds (e.g. Enterprise Ireland and the Industrial Development Authority) and European Grants (including EIT and European Development Fund) for research and development. Despite the above platform of multidisciplinary university based research, many meritorious concepts and devices never make it out of the "valley of death" on account of the paucity of interest in equity and venture capital firms in entering funding early in the life cycle of a device prior to first in man studies. Furthermore, if regulatory bodies in Europe and beyond, seek to have longer term clinical follow-up data prior to approval for commercialization without concomitant extension of intellectual property protection the less attractive such long-term investment may become.

Reference websites

nationalchildrensresearchcentre.ie/research-innovation/

nuigalway.ie/our-research/listings/regenerative-medicine.html

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tyndall.ie

CARDIO NEWS

Covid-19 has a Significant Impact on Cardiovascular Health

Members of the European Parliament have called on European and national decision-makers to prevent further damage to cardiovascular health after the Covid-19 pandemic.

This call was made by the MEP Heart Group during an online meeting of European leaders which took place recently.

The MEP Heart Group is a forum which provides MEPs with an opportunity to generate dialogue, outreach and activities at EU and Member State level. It is made up of MEPs who have an interest in promoting measures that will help reduce the burden of cardiovascular diseases (CVD) in Europe and raise CVD as a priority on the EU political agenda. Two Irish MEPs Frances Fitzgerald, and Grace O Sullivan are members of the MEP Heart Group.

The online meeting was organised by the MEP Heart Group, which is coordinated by the European Society of Cardiology (ESC) and the European Heart Network (EHN).

According to the group, even before the outbreak of Covid-19, cardiovascular disease (CVD) was the leading cause of death in Europe and the EU. More than 60 million people live with CVD in the EU and nearly 13 million new cases are diagnosed each year. The pandemic has aggravated this grim scenario, leaving many patients with new cardiovascular health conditions after recovering from Covid-19.

Cardiovascular complications linked to Covid-19 are wide ranging and include cardiac injury, heart attacks, arrhythmia and progressive heart failure. Pre-existing cardiovascular diseases are particularly important predictors of in-hospital complications and mortality in patients hospitalised with Covid-19.

The MEP Heart Group called on European and national decision-makers to put in place a number of measures aimed at preventing further damage to cardiovascular health as a result of the pandemic. These included, the development of separate pathways for the care of cardiac emergencies to reduce the risk of infection.

The group also called for support for clinical activity to prevent, diagnose and treat CVD and support for research on digital health technologies to manage CVD during the Covid-19 pandemic, on treatment options for Covid-19 patients with CVD, or at risk of CVD; and on the mechanisms by which SARS-CoV-2 infections impact the cardiovascular system.

Investment in the collection of Europe-wide data on cardiovascular health was also needed the group said.