EUROPEAN HOSPITAL

WWW.EUROPEAN-HOSPITAL.COM

CARDIOLOGY 2013

NEWS AND TECHNOLOGY UPDATES FOR CARDIAC CARE

AMSTERDAM • NETHERLANDS 31 AUG - 04 SEP 2013

Turbulence in ultrasound

Ultrasound expands its role in cardiac imaging with disruptive applications. Fasten your seat belt. Cardiac diagnostics is entering a zone of turbulence. Manufacturers of leading systems continue to mine data from the sonic signal that opens new fields for research. *John Brosky* reports

By merging the stunning three-dimensional (3-D) images with traditional X-ray, new systems are providing novel capabilities for diagnosis and navigation. 'I believe that 3-D echo is the cornerstone for the non-invasive diagnosis of cardiac diseases,' says Jose Zamorano MD, head of Cardiology at the University Hospital Ramón y Cajal in Madrid. 'There can be no doubt. You can see the anatomy of the heart, and you can see the function.' He cites as an example the turbulence created by blood flow in the cavities of the heart that is now revealed by technology called vector flow mapping developed by Hitachi-Aloka.

The heart is not a simple pump but a hard-working muscle, twisting, contracting and pushing a pulsing stream of blood. A closer look shows that this flow is not so simple either, swirling and churning in intricate patterns as it encounters resistance.

Nobel Laureate Richard Feynman once described turbulence as the most important unsolved problem of classical physics. It may also be the key to unlocking unsolved problems in cardiac diagnosis.

'It's back to physiology,' Dr Zamorano said. 'From the work in our lab we can now see the vectors and the vortices for normal blood flow, and we have seen the way turbulence is affected by abnormal physiology and different pathologies… What is certain is that this will help in evaluation, and it could become a prognostic indication for the patient. It opens a new area of research to correlate what we are observing with the pathologies of patients.'

Vector flow mapping is an innovative ultrasound application derived from colour Doppler velocity data that adds new mathematical methods to display flow distribution without angle dependency. This quantification tool enables researchers at the University Hospital Ramón y Cajal to visualise, measure and analyse more than a dozen parameters of blood flow distribution.

'Most people think that Doppler ultrasound is an analysis of the blood flow itself, but we need to clarify this understanding, because Doppler only shows velocity,' Dr Zamorano explained. 'With vector flow mapping you truly can see how the blood behaves entering the left ventricle and how it is ejected into the system.'

In the case of an aortic stenosis, he pointed out that the turbulence which appears in the left ventricle outflow is characteristic and 'absolutely different from a normal patient'.

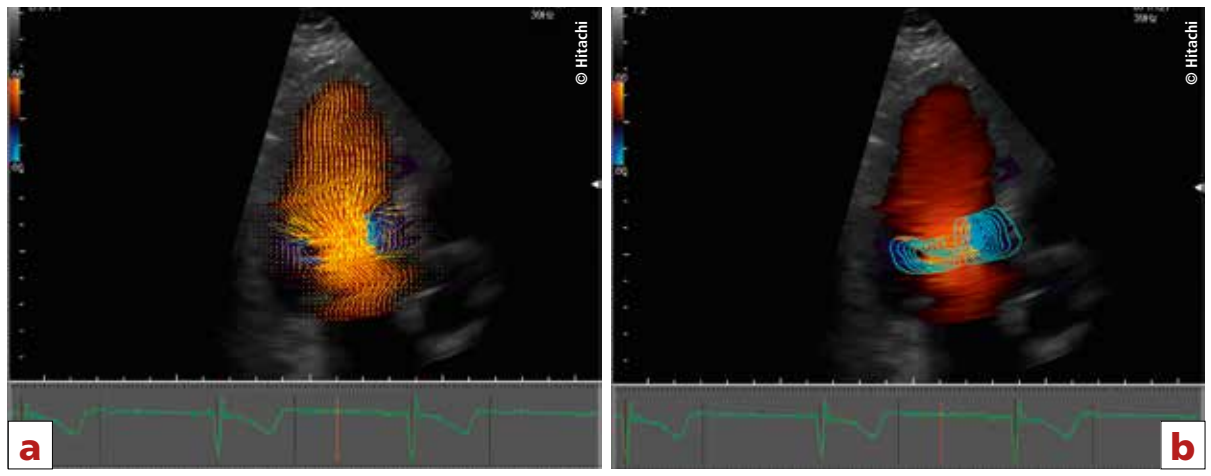
Research is currently being conducted using a two-dimensional ultrasound system and while the technology is not yet ready to show the flow in 3-D, he is confident this product evolution will come.

In early September, at the European Society of Cardiology (ESC) Congress in Amsterdam, Dr Zamorano will discuss the evaluation of valvular heart disease in 3-D with echography. 'Valve anatomy is in three dimensions and 3-D echo assesses the morphology of the valve much more accurately than other modalities,' he explained.

Fusion imaging that combines 3-D echo images with 3-D CT scans today provides a complete picture of the heart for cardiologists. The CT view of the coronary arteries of a patient can help determine if there is a coronary disease and at which level, he pointed out, while 3-D echo displays the abnormal function that is related to that stenosis.

In the cardiovascular research facility in Madrid, he is currently testing a new advance in fusion imaging developed by Toshiba for its CardioVascularFusion (CVI-Fusion) system that creates a revolutionary capability for the assessment of ischaemia. 'At ESC we will reveal a new technique, one that is quite unique, and which no one else is doing,' he promised. 'We will demonstrate the feasibility of using stress echo in fusion imaging, which in my opinion becomes crucial. Stress echo induces ischaemia, but here for the first time we will show the ischaemia. 'By combining these views we can see the stenosis, the location of the stenosis and now how the stenosis impacts on the prognosis.'

Continued on page 12



VFM Vectors: velocity vectors to highlight the flow patterns (a). VFM Vortex: automatic vortices detection (b). The integration and synchronisation of X-Ray images and 3-D ultrasound images provides up to two additional ultrasound views in real time. The ultrasound beam is shown in the live X-ray image and the viewing angles are automatically rotated in a synchronised movement. Placed markers are automatically transferred in an anatomically correct position into the other screens (c). CardioVascularFusion (CVI-Fusion) (d).

Jose Luis Zamorano Gomez MD is the Head of Cardiology at the University Hospital Ramón y Cajal in Madrid. A Fellow of the European Society of Cardiology (ESC), currently he is the Chair of the ESC Guidelines Committee and a past-President of the European Association of Echocardiography of the ESC.
Dr Zamorano is also on the editorial board of many leading journals, including the European Heart Journal and JACC Cardiovascular Imaging.

OPENING A WINDOW ON THE HEART

Recent advances in echocardiography, especially tissue Doppler imaging and speckle tracking, have sharpened the focus on cardiac muscle. Yet, there has not been a link established between the observed blood flow and morphological patterns in the myocardium and cardiac cavities.

Now that link is being observed and quantified using a novel and non-invasive technique developed by Hitachi Aloka called Vector Flow Mapping (VFM). 'With vector flow you really see how blood behaves, which is not something we have seen before,' explained Jose Zamorano MD. Contracting muscle fibres and the chambers of the heart create vortices and turbulence that are specific to patient pathologies, he added.

In his studies using VFM he has documented how the turbulence inside the left ventricle is different and characteristic if the patient presents with a disease such as severely depressed ejection fraction after an infarction compared to a patient with a normal left ventricle but an aortic stenosis. VFM begins with velocity data derived from colour Doppler echography to generate velocity fields on a 2-D image. Engineers at Hitachi Aloka then moved beyond data received in the direction of the beam by applying unique algorithms that enable an estimation of the radial component. Now the flow distribution can be displayed without angle dependency.

In addition to displaying flow distribution through vectors, VFM also provides the mainstream lines. The application can detect and display the intra-cardiac vortices and quantify the different parameters.

Suddenly a window on the heart opens to reveal the intricate interactions at the interface between pulsing blood and cardiac fibres. This data can be visualised, measured and analysed across a complex array of parameters that describe the spatial and temporal distribution of blood flow. In other words, this data can be translated into diagnostic and prognostic information to inform clinical decisions, according to Partho Sengupta MD, lead author of an article entitled, 'Emerging Trends in CV Flow Visualisation,' published in the *Journal of the American College of Cardiology.*

Implanting aortic heart valve prostheses percutaneously will become more common than surgical replacement, according to Dr John Webb

TAVI will surpass heart surgery for aortic valve replacement

Interview: John Brosky

Each year the case grows stronger for transcatheter aortic valve replacement (TAVI). And it is only six years since the procedure was introduced in Europe.

The strongest clinical evidence, which continues to fuel debate, is based on the first-generation of valves and delivery devices. It is also based on a population that was deliberately restricted to the very sickest of patients with an average age of 83 years and suffering from co-morbidities that meant they were unable to undergo traditional surgical aortic valve replacement (SAR).

Today, a new and improved generation of valves and delivery systems has arrived in the clinic. There is greater experience among interventional cardiologists, as well as improved outcomes for patients. Increasingly in Europe the procedure is being performed on 'intermediate risk patients,' those who suffer from a failing heart valve but who are typically younger and better able to withstand the rigors of traditional surgery.

How far are we from a turning point where TAVI will be preferred to surgery? The question is provocative because TAVI remains contentious in the cardiology community. Which patients? Who makes the decision? How reliable are these new valves? What about the high cost?

John Webb MD, from St Paul's Hospital in Vancouver, was a pioneer in the development of TAVI and has performed or supervised over 1,500 procedures worldwide. He is a leading authority on the technique and technology and author on over 300 publications in peer-reviewed journals, including Circulation and the Journal of the American College of Cardiology.

Ahead of the meeting of ESC 2013, we asked Dr Webb for his views and future directions.

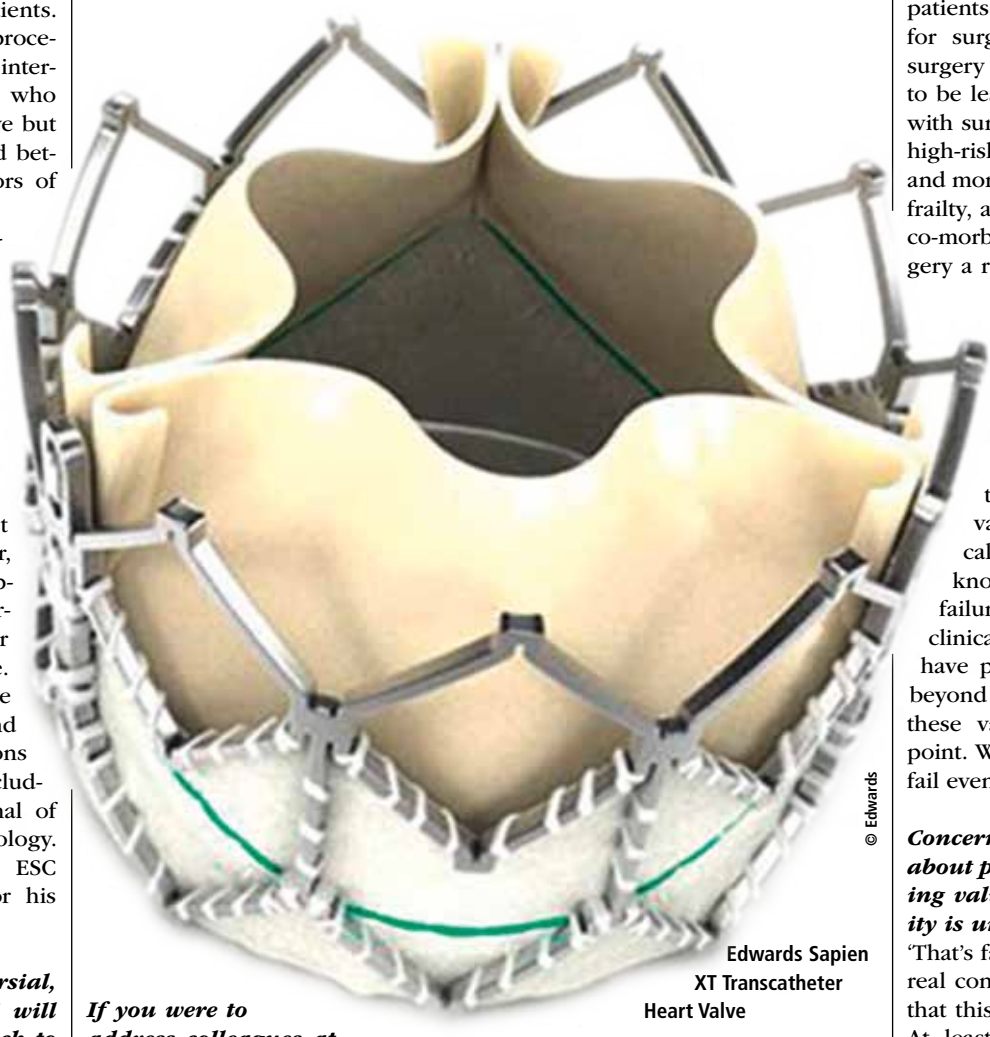
While it remains controversial, you have stated that TAVI will become a dominant approach to aortic valve disease.

Dr Webb: 'I believe so, yes, because as we move into intermediate risk patients with newer devices in experienced centres, the risk of mortality becomes quite low and is competitive with surgery in intermediate risk patients with much less morbidity. Many centres are doing this on awake patients. Early discharges are becoming more common. Certainly patients are mobilised earlier at the hospital stage. Hospital stays are shorter. ICU stays are shorter. And I think the cost of TAVI is going to come down and become competitive with surgery for intermediate risk patients.'

Will TAVI replace open-heart valve replacement surgery?

'There will always be patients who need open-heart surgery. There are obvious advantages to that approach. But I do believe that TAVI will become more common than surgical replacement. There are patients who do not have valves that are suitable for a transcatheter approach, or they have other things that need to be corrected. There are advantages to surgical valves as well for patients who can undergo surgery at relatively low risk.

'In the future, I don't think the issue is going to be whether patients are not candidates for surgery, but just that they would be better off with TAVI. This is the direction we are moving in Canada as well. We are asking who is better off with TAVI. The key message here is that the procedure needs to be done on patients who are going to benefit. This needs to be the focus. Cardiologists need to consider if their patient is going to have a significant improvement in quality of life; that they will live long and prosper.'



© Edwards

Edwards Sapien XT Transcatheter Heart Valve

If you were to address colleagues at the ESC congress in Amsterdam, what would you tell them?

'One of my big concerns about Europe is that this is a procedure that can be done at much lower risk by groups that have a high level of expertise. It is not a procedure that should be performed by low-volume operators. My concern is that there are an increasing number of low-volume centres in Europe and they can do better. There needs to be a balance between availability and ability. If I were to give a number, I'd say that individuals doing less than 50 cases in a year are not at a sufficient volume for expertise.

'Also, there shouldn't be groups competing within a single institution to the point where people who do not have sufficient expertise are performing this procedure. There should be programmes that involve both interventional cardiologists and surgeons who have relatively high volume practices and do high quality work.'

Many cardiologists may scoff at the idea that TAVI should only be performed in consultation with a 'heart team'. Many have never been invited to share in the decision.

'The true heart team is a relatively new concept. Traditionally, surgeons have made up their own minds about whom they will perform surgery on and what kind of surgery they will do. Interventional cardiologists are used to doing the same thing with coronary revascularisation.

But I think that when we have patients who are complex and there are different alternatives, it makes sense for there to be a group discussion about the best choices. 'In the United States this approach has become artificial in some ways because the regulatory requirement is that both interventional cardiologists and surgeons must participate in all procedures. It seems to be overdoing it and may be driven by factors other than the procedure. The main principle to a heart team is that the patient is evaluated by a group with different skills and knowledge. There should be a discussion about which form of valve replacement is better with an evaluation and a discussion of the alternatives available. But the idea of a heart team does not necessarily mean they all need to be in the room doing the chosen procedure.'

Can you compare the development of TAVI in the USA and Europe?

'In the USA the practice is influenced to a much greater degree by the requirements of the FDA, starting with the original trials. For example, in the PARTNER trial patients could only be admitted if they fulfilled very specific criteria and had a very high STS score, a high risk of mortality. Some of these patients are too old, too frail to benefit. So the bar is set perhaps too high in the USA, with the majority of patients at extreme risk for open heart surgery. That bar has been lower in terms of surgical risk for patients in Europe, driven more by the reduction in morbidity in some of the lower risk patients.

'In Europe there has been a more clinically driven approach, which sometimes differs from what was required in the original trials.'

You have asked whether the high-risk patients enrolled in the original trials should be considered for the therapy in the first place.

'That is a problem. Some patients are at such high risk that the benefits may be limited. Where the benefit might be much greater for patients who could be candidates for surgery, but the morbidity in surgery would be high. There tends to be less morbidity with TAVI than with surgery among intermediate to high-risk patients. In Europe, more and more the indication is becoming frailty, advanced age, without major co-morbidities that would make surgery a risk for these patients.'

An open question, especially as Europe moves to younger patients, is how long do these devices last?

'We know that with in-vitro testing, in the lab, the TAVI valves last as long as surgical prosthetic valves. And we know that very, very few valve failures have been seen in the clinical experience to date. We have published our outcomes out beyond five years and failure of these valves is quite rare at that point. We can assume that they will fail eventually, as do surgical valves.'

Concern was expressed in Europe about patients in their 70s receiving valves for which the durability is unknown.

'That's fair enough to say and a very real concern. I guess I would argue that this is not the end of the story. At least with TAVI, valve replacement is a fairly repeatable procedure in that you can place a TAVI valve inside a TAVI valve.

'One of the things people were most interested in (at the Transcatheter Valve Therapeutics event in Vancouver in June, 2013) was the new information on valve-in-valve implants where transcatheter valves are placed inside failed surgical valves. It seemed that in many people's minds this is moving rapidly to a standard of care.

All valves, surgical and TAVI, will wear out in time and repeat surgery is always a higher risk than first-time surgery. Many of these patents, of course, have become older. There are lots of 70-year-old people who received a surgical valve and, as their valve fails, TAVI becomes an attractive option for these older patients.'

What is encouraging about the newer valves produced?

'There are marked improvements in deliverability, profile and sealing with the newer generation of valves. Newer valves are, in general, more easily implanted. The lower profile means they go through smaller sheaths, through smaller arteries with a lowered risk of vascular injury. They tend to be more easily positioned, with features incorporated into the catheter, or in the valve itself, so they tend to be deployed at the correct height and the correct angle in the aortic annulus. So positioning is improving. They tend to have features that reduce paravalvular leak with the better seals.

'In addition to improvements in the valves, there are dramatic improvements in techniques used. Early on, people had a limited idea of where to put the valve and now this is much improved. Early on there was poor understanding about how to pick the correct valve size, and here there have been dramatic improvements in understanding the three-dimensional anatomy in the annulus, which is related to imaging with 3-D CT and 3-D TEE.

'All the new valves need to be proven. To some degree their use can depend on a predicate device. But if there is a dramatic change in how a valve functions, it really needs to be evaluated to see if it is going to be as reliable as a precedent valve.'

John Webb MD is director of interventional cardiology, fellowship training, research at the Centre for Valve Innovation at St Paul's Hospital in Vancouver. He is also an advisor to a number of biomedical companies and the government of Canada and McLeod Professor of Heart Valve Intervention at the University of British Columbia.

Turbulence in ultrasound

continued from page 11

The technique is a non-invasive complement to fractional flow reserve (FFR), which is an invasive procedure, he added.

While FFR is given the highest recommendation in ESC guidelines, the invasive nature of the procedure to assess ischaemia has slowed its adoption.

Dr Zamorano reserved his greatest enthusiasm for advances in ultrasound for the newest arrival in the university hospital, the EchoNavigator from Philips Healthcare: 'I just came from performing two TAVI interventions and can say this system is incredible, very innovative.

'Usually we work with X-ray in a cath lab but now, by superimposing real-time 2-D and 3-D interventional echo on the fluoroscopy, I can see the valves opening and closing… Remember that with X-ray we can't see the valve; we can see only calcium.

Now I can mark exactly where the valve needs to be positioned. Using fluoroscopy I can guide the catheters to that precise position.'

Cardiac disease death rates fall in the EU

Mortality more than halves in many European countries

Report: Mark Nicholls

Death rates from cardiac disease have more than halved in many EU countries since the early 1980s, according to new research published in the *European Heart Journal*. The majority of countries have seen on-going steady reductions in heart disease death rates in both sexes and most age groups, including among younger people – despite increases in obesity and diabetes during this period.

However, heart disease remains a leading cause of death in Europe and the study's researchers say their analysis shows little evidence for the hypothesis that the reduction in deaths from coronary heart disease (CHD) might be beginning to plateau among younger Europeans.

There is significant variation between individual countries, with evidence of a levelling off in some countries and increases in heart disease deaths among some age groups in other countries. 'It's clear that there are some countries in which trends are cause for concern, where overall rates of decrease in CHD mortality do appear to have slowed, and a small number of countries in which CHD mortality rates have begun to increase significantly in recent years in younger subpopulations,' explained Dr Melanie Nichols, a Research Associate from the British Heart Foundation Health Promotion Research Group (BHF HPRG) in Oxford.

'In addition,' she pointed out, 'we should emphasise that cardiovascular disease remains the leading cause of death in Europe, and it is important that we continue to focus efforts on primary prevention, including reducing smoking, improving diets and physical activity levels.'

With her colleagues in the Oxford research group, Dr Nichols looked at trends in deaths from coronary heart disease between 1980 and 2009 in both sexes and four age groups: under 45, 45-54, 55-64 and 65 and over. They found that almost all EU countries had a large and significant decrease in death rates from CHD over the last three decades in both men and women when all ages were considered together. Denmark, Malta, The Netherlands, Sweden and the UK had the largest decreases in mortality for both sexes during this time. The exceptions to these significant decreases were among men in Hungary, Latvia, Lithuania and Poland, where the decreases were small, and in Romania where there was an increase. Among women, decreases were found in Greece, Hungary, Lithuania, Poland, Romania and Slovakia. There was some evidence that the downward trends were beginning to plateau in those aged under 45 among men and women in Italy, Latvia, Lithuania and the UK, among men in Poland and Slovakia, and among women in the Czech Republic and France.

In the 45-54 age group, there was evidence of a possible plateau in both sexes in Latvia and the UK, and also in Lithuania among women and Sweden, Austria, the Czech Republic and Slovakia among men. In Greece, women aged 45-54 showed a significant increase in death rates. Dr Nichols said: 'Overall, across the EU, rates of death from coronary heart disease have continued to fall in most age groups in most countries. There are some exceptions, however, and there remain wide disparities across Europe in both the absolute rates of death from heart disease and the rates of improvement.'

The study authors state that the increase in risk factors for coronary heart disease, such as smoking, obesity and diabetes, could still have an impact on death rates in years to come but felt 'there may still be time for public health policy and action to have an impact on these risk factors.' The team also add that continuing future research is crucial to monitor trends in CHD risk factors and mortality across the EU and to examine the relationships between preventable risk factors and CHD among younger adults.

With funding from the British Heart Foundation (BHF), the study arises from the European Heart Health Strategy II project (EuroHeart II), which has received co-funding from the European Union, in the framework of the Health Programme.

Dr Melanie Nichols joined the BHF HPRG in October 2011 to lead the Oxford work package within the EuroHeart II programme, which aimed to describe and document the burden of CHD across Europe and geographic variations in coronary heart disease trends across the member states of the EU.
She has now returned to Deakin University in Australia as a Research Fellow at the World Health Organisation (WHO) Collaborating Centre for Obesity Prevention at Deakin. Her research interests include the epidemiology of chronic disease risk factors, inequalities in health, the role of communities and environments on lifestyle and chronic disease and evaluation of complex interventions to prevent chronic disease.

Hope or hype in hypertension? Cardiologists remain cautious

Renal denervation

A new procedure may help people with persistent hypertension. By burning or ablating the nerves in the renal arteries, blood pressure levels can be reduced significantly. Can we hope? If true, this promising procedure would mark a breakthrough. The medical and social burden of arterial hypertension is staggering, contributing to two-thirds of all cases of stroke and half of all cases of heart disease. Or is it hype? To date there is no evidence high BP simply disappears by waving a magic wand. Here are two reports on the medical miracle called renal denervation offering the perspectives of clinicians and industry.

Felix Mahfoud, cardiologist at Saarland University Hospital

Report: John Brosky & Holger Zorn

Clinical point of view: Rising tension in hypertension therapy

With two in three over 60-year-olds suffering arterial hypertension, this is among the commonest chronic diseases.

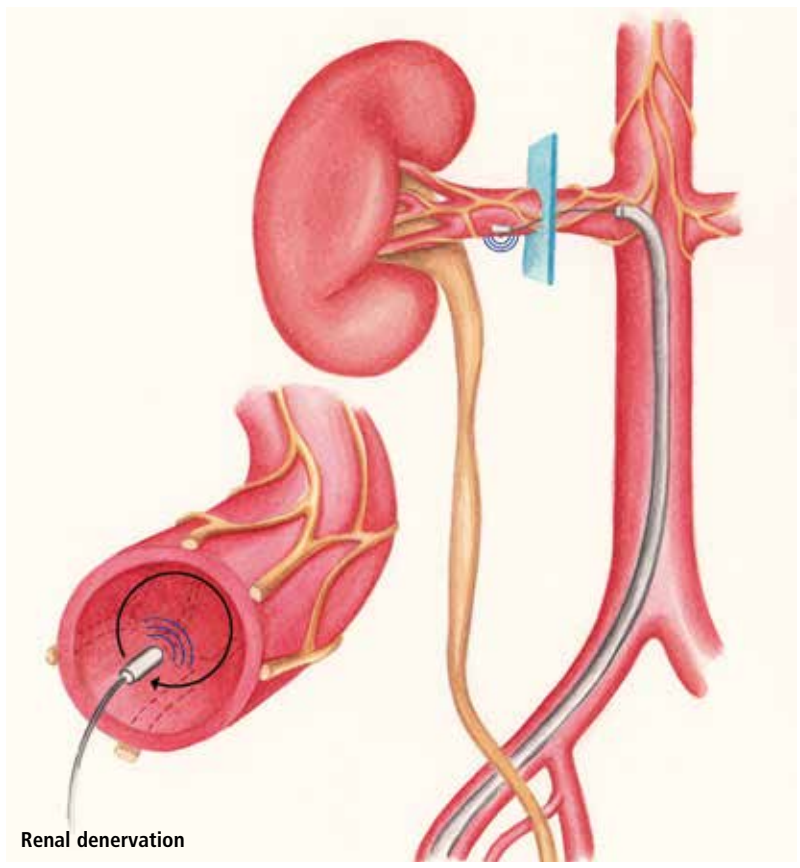
Drug treatment results in only 5-17% of those patients achieving their target levels. However, in about the same percentage of patients conventional treatment fails despite good compliance and the administration of three, five or even more antihypertensive drugs. Their blood pressure (BP) readings often remain much above the level of 140/90 mmHg set in the current ESH/ESC guidelines – an incentive for the development, trial and evaluation of different therapies.

The two most important new developments being discussed are presented below: renal sympathetic denervation and baroreceptor stimulation. While the former is already an established procedure – particularly in Germany where almost half of all interventions are performed – the latter is frequently accompanied by severe adverse effects but is nevertheless considered very promising by many cardiologists.

Renal sympathetic denervation

The debate around renal sympathetic denervation (RDN) is as hot as the procedure itself, which involves heating up the renal arteries intravascularly in several places for a maximum of two minutes focally to up to 70 degrees Celsius to denervate the sympathetic nerves in the adventitia of the arterial walls.

The kidneys not only control the circulation volume but also release a hormone, renin, which affects the constriction of the blood vessels and the heart frequency via the renin-angiotensin-aldosterone system and is therefore a cause of the development and persistence of arterial hypertension. The entire procedure requires just one puncture of the femoral artery, normally takes less than an hour and is carried out under fluoroscopic guidance.



Renal denervation

The European Society of Hypertension (ESH) calls these results 'promising' and has decided to revise its guidelines, which had been jointly developed with the European Society of Cardiology, 'since numerous studies have been published over the last year providing more data about the rationale, therapeutic efficacy and safety of RDN' *(Source: EuroIntervention. 2013 May 22;9 Suppl R:R58-66)*.

Symplicity HTN-1 and HTN-2

The feasibility of the procedure was demonstrated by three Australian and two European hospitals, including the Cardiovascular Centre at the Sankt Katharinen Hospital in Frankfurt and the Jagiellonian University in Krakow, under the direction of Professor Henry Krum at the Centre of Cardiovascular Research and Education in Therapeutics, Monash University, Melbourne, Australia.

Forty-five patients taking an average of 4.7 hypertensives, with a mean BP of 177/101 ±20 /15 mmHg and rated as treatment-resistant, underwent RDN between June 2007 and November 2008. Their mean BP fell by 14/10, 21/10, 22/11, 24/11 and 27/17 mmHg after 1, 3, 6, 9 and 12 months *(Source: Lancet 2009; 373: 1275–81)*. During an extended follow-up observation over a 24-month period BP also did not rise again – reason enough for the authors to believe that once the nerve fibres have been denervated they do not regenerate and no new ones are being formed; the antihypertensive effect therefore works in the long-term *(Source: Hypertension 2011; 57: 911-7)*.

Between June 2009 and January 2010, 106 patients, whose BP remained at a mean of 178/96 mmHg despite the administration of a median of 5.3 antihypertensive drugs, were included in the following, prospective randomised controlled study; 52 of these patients were treated with renal denervation and showed a significant decrease in BP by 32/12 mmHg after six months. Every fifth patient was able to reduce the number or dose of drugs taken. However, BP amongst the 54 members in the control group did not change. Three hypertensive events occurred in the treatment group and two in the control group *(Source: Lancet 2010; 376: 1903-09)*.

In a clinical study at the Saarland University Hospital, 600 patients – the largest cohort worldwide – were examined. Dr Felix Mahfoud, physician at the Clinic for Internal Medicine III, University Hospital, and ardent supporter of the procedure, is convinced that the pathophysiology is correct. 'We do know that the vegetative nervous system is overactive in patients with hypertension. When medication no longer offers a promising option, RSD is an interesting therapy approach. However the patients selected for the procedure have to fulfil certain conditions, as described in the guidelines recently published by the European Society of Cardiology.' According to these guidelines, RSD is indicated for truly resistant hypertensive patients, while patients with organ-related hypertension, impaired renal anatomy, e.g. due to a stenosis or impaired renal function, are excluded. 'The data that are available today, which were collected worldwide, are very promising. We now need further studies that corroborate the initial results,' Dr Mahfoud said. Nevertheless he recommends the procedure for the time being to be limited to medical centres with research capabilities where patients receive systematic follow-up.

The industry: Slowed by hyper-resistant doctors

As fast as the first device for renal denervation received a CE mark in 2010, the pioneering company Ardian was immediately snapped up by medical technology giant Medtronic. With great fanfare the procedure was introduced the following year at EuroPCR, the largest gathering of interventional cardiologists in Europe.

Six million people in Europe suffer from persistent hypertension, unable to bring their systolic BP below 160 millimetres of mercury. Some take three or four different medicines every day, but the condition can resist this drug-based therapy.

The potential for treating such a large population was neither lost on cardiologists nor on other medical technology companies. This year at EuroPCR six new devices for renal denervation were presented, all with the CE Mark, ready to be sold to hospitals.

Yet market leader Medtronic has fallen far short of sales targets. Despite a large footprint covering 70 countries, the company shipped less than half the number of devices it expected to ship. It turns out that physicians are as resistant as the hypertension of their patients. Doctors want to see proof of the claim that charring nerve endings in the renal artery is an effective, safe and sustained treatment for this chronic condition.

Justin Roberts is arguably the point man out on the bleeding edge of this innovation in medical practice. The Senior Director for Renal Denervation Global Market Development for Medtronic, he shared some of the lessons learned in pushing adoption of renal denervation. He commented: 'There are people who believe this is a billion-dollar market; that if they push a magic button patients will suddenly come raining down from the sky,'

The biggest challenge is not the technology, not the next shiny toy, he added, pointing to the growing number of competitors on the exhibition floor at EuroPCR. Instead the challenge is to build clinical evidence to convince very conservative referring physicians.

Medtronic is turning its investment in renal denervation to a clinical programme aimed at building what the company hopes will be a substantial body of evidence.

Enrolment was recently completed in an ambitious pivotal clinical trial in the USA of the Medtronic Symplicity renal denervation system for treatment-resistant hypertension. Data from this trial is expected to be a significant component of an unusual and rigorous parallel review by the USA's Food and Drug Administration (FDA) and the Centres for Medicare & Medicaid Services (CMS) that could lead to approval and reimbursement.

Meanwhile, Justin Roberts believes that companies also need to help build expertise in this new field to win the confidence of referring physicians.

Renal denervation centres capable of appropriately screening patients need to be built, he pointed out. 'Hospitals, even with reimbursement, will continue to operate with very tight budgets. They need to decide if they want to open a service line for renal denervation. These decisions will vary by country, by local guidelines.'

St. Jude is a fast-follower for both technology and clinical trials for renal denervation. More than 5,000 patients will be studied in a robust portfolio of studies in collaboration with a multi-disciplinary physician advisory board as part of the EnligHTN Clinical Evidence Development Strategy. It is the brand name of St. Jude's device for the renal denervation procedure.

The portfolio of related studies represents a significant investment in building clinical evidence that will culminate in EnligHTNment. This landmark work is expected to be the largest randomised renal denervation study ever undertaken with a primary endpoint of major adverse cardiac outcomes and secondary endpoints to include reduction in office and ambulatory BP measures, changes in renal function and cost-effectiveness measures.

Bogged down on the long road to building evidence for renal denervation, Medtronic and St. Jude have lost the first-to-market advantage as more companies roll out new devices.

The technical barriers to entering the renal denervation competition are relatively low. Most companies already have some kind of device for ablation and adapting it to the renal arteries is quickly done.

All the firms will need to conduct clinical studies, but these will be small efforts focused only on proving that their new device is safe for use. For clinical evidence of effectiveness the new players will need only point to the evidence published by Medtronic and St. Jude to win over physicians.

While some new devices are based on follow-the-leaders technology, innovation in the pipeline may prove to make a difference for patients in the long run.

ANOTHER OPTION: BAROREFLEX STIMULATION

Anne Carlsten, a physiologist at the University of Gothenburg, researched the treatment of depression through electric stimulation of the nerves in the carotid sinus and discovered that this also has a cardiovascular effect (source: Act Physiol Scand 1958; 44(2): 138-145).

Baroreflex activation therapy (BAT) stimulates the parasympathetic fibres of the vagus nerve, lowering heart frequency, stroke volume and BP. Electrodes are placed either side of the carotid artery under general anaesthetic and then connected to a pulse generator, which – like a pacemaker – is implanted below the collarbone.

The feasibility study carried out in the Netherlands, Germany, Switzerland, the Czech Republic, Poland and Latvia, under the direction of the Cardiocvascular Research Institute Maastricht (CARIM), included 45 patients with therapy-resistant hypertension whose BP prior to the intervention was a mean of 179/105 mmHg, with a heart frequency of 80/min and a median of five antihypertensive drugs taken.

Three months after the implantation of the Rheos system manufactured by CVRx Inc. of Minneapolis, BP was lowered by a mean of 21/19 mmHg and, after two years, by a mean of 33/22 mmHg in 17 patients who continued with the trial. However, almost every fifth patient suffered severe complications such as stroke, glossoplegia, infection or device displacement (source: J Am Coll Cardiol. 2010;56(15):1254-8).

Although the randomised, placebo-controlled clinical trial of 265 patients did not show a significant acute responder rate in the group receiving baroreflex stimulation, it did show a significant sustained responder rate (source: J Am Coll Cardiol 2011; 58(7): 765-73) – enough potential for future debate.

Heart failure

Remote monitoring in Lorraine reduces hospital re-admissions

Report: Brigitte Dinkloh

About 500,000 people in France people suffer heart failure (HF). In Europe the figure is six million and the same in the USA. While pharmaceutical innovations such as ACE inhibitors, beta blockers and mineralocorticoid receptor antagonists help to decrease mortality in HF patients with reduced ejection fraction, much needs to be done, says Professor Patrick Rossignol, nephrologist and deputy physician at the Inserm Centre d'Investigation Clinique Plurithématique Pierre Drouin (CIC-P) in Nancy, France, because the prognosis remains unfavourable.

The professor is particularly concerned about the high number of hospital re-admissions. 'About 20 percent of all patients with heart failure are re-admitted to a hospital within a month of the initial event and roughly one third of the patients die within a year.' Poor follow-up, he emphasises, is to blame for this dire situation.

Case in point: One year after their discharge many patients receive the same medication without dose optimisation as upon their discharge. While international guidelines recommend disease management programmes (DMP) for HF patients, Patrick Rossignol points out, many patients are either not included in such a programme or it does not follow harmonised standards.

In the Lorraine region, the 'réseau lorrain des insuffisants cardiaques' (ICALOR – Lorraine network for cardiac insufficiency patients) was introduced in 2006, a DMP unique in France because it covers an entire region and currently includes 3,000 patients. Each patient is closely monitored at home by nurses, on top of the usual out-patient follow-up by physicians. Results are collected in a patient record that can be accessed by the patient and hospital-based and/or office-based physicians.

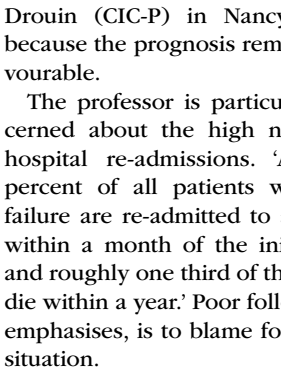
The programme results are very encouraging: the implementation of the ICALOR programme was associated with a reduction in HF hospitalisations in Lorraine, estimated by an absolute difference between the number of hospitalisations observed in the Lorraine region, and than expected had it been similar to that observed in the whole country of -7.19% in 2010. The estimated annual hospital cost saved by ICALOR was €1,927,648 in 2010. (REF). Nevertheless, Professor Rossignol stresses, much remains to be done to ensure that the course of HF is less dramatic: 'Hospital re-admission is a severe event for the heart failure patient because at that time cardiac function is already seriously compromised. The alarm signs indicating deterioration of the pump function must be recognised earlier.'

Together with Professor Faïez Zannad, who heads the Heart Failure and Hypertension Unit in the Department of Cardiology, Nancy University Hospital, Patrick Rossignol developed a new procedure for telemedical monitoring of heart failure patients. All the patients need do is introduce a drop of blood every day into a box that assesses a set of renal and cardiac biomarkers. The data are encrypted and forwarded to a telemedical monitoring centre. When the values show signs of deterioration, the primary physician is informed who can initiate a therapy adjustment, with the help of a dedicated decision support system. 'The extremely simple procedure for patients is based on the same principle as blood sugar monitoring in diabetics. It's a response to the problem of frequent re-hospitalisation of cardiac insufficiency patients.'

Currently being piloted, the first prototypes of the device are expected to become available later this year. Application will then be made for the CE mark.

Next year, a clinical study with several hundred patients throughout is planned and Prof. Rossignol is confident this may prove that the device helps reduce follow-up complications in HF patients. The project, which was awarded funding of €1.9 million from the Lorraine region and the European Regional Development Fund (ERDF), is carried out by a consortium headed by Cardiorenal Diagnostics, a company founded by Professors Rossignol and Zannad with Gerard Houis.

* Ref: Agrinier N, Altieri C, Alla F, Jay N, Dobre D, Thilly N, Zannad F. Effectiveness of a multidimensional home nurse led heart failure disease management program-A French nationwide time-series comparison. Int J Cardiol. 2013 Jun 25



Nephrologist **Patrick Rossignol MD PhD** is Professor of Therapeutics at the University of Lorraine, France. Since 2007, he has been deputy physician at Nancy University Hospital's Inserm Clinical Investigation Centre, headed by Professor Faïez Zannad, and an Inserm UMR_S1116 researcher, as well as being a consultant at the University Hospital Heart Failure and Hypertension Unit and haemodialysis clinics. The professor's research priorities are clinical trials and biomarker studies in the context of heart failure, chronic renal insufficiency, hypertension, and vascular diseases such as abdominal aortic aneurysms.

The time machine

While the benefits of extracorporeal membrane oxygenation (ECMO) as a temporary respiratory support for adult patients are still debated, it is undisputed that for many infants ECMO is the only chance to survive, because it provides them with time to strengthen their lungs, says EH correspondent *Holger Zorn*

If a baby's lungs are not properly unfolded upon birth they can be supported mechanically for a few days, as Dr Robert Bartlett of Orange County Medical Centre in California (cf EH 2/13 p. 15) showed almost forty years ago. In extracorporeal membrane oxygenation (ECMO) the blood is drained from the body and pumped into an artificial system. In a membrane carbon dioxide is removed and oxygen is added before the blood is returned to the body (Fig. 1). Dr Bartlett was aware of the poor outcomes in adult patients: A national study had been discontinued after 92 patients, due to a mortality rate of 90% in both the ECMO and the control group.

Despite those results, he continued to use ECMO after his initial successful treatment of a neonate and he achieved survival rates of 75% in neonates and infants – clinically speaking quite a success, scientifically far from a validated procedure.

The problem was less of a technical one than an ethical one. How can a study with neonates be designed in which one group receives the treatment that needs to be validated, while the control group is refused this potentially life-saving procedure? Dr Bartlett went for a unique study design: 'Play the winner'.

Following his medical studies and the completion of his doctoral degree at the University Tübingen, Germany, **Dr Thomas Schaible** received specialist training at the Paediatric University Hospital Ulm. In 1996 he joined the Intensive Care Unit of the Paediatric Clinic of the University Mannheim.

The first patient has a 50/50 chance to receive either ECMO or the conventional therapy. If the patient survives, the next patient receives a chance at ECMO and the rate would be 2:1. If this second patient dies the chance to receive ECMO treatment decreases to 1:2. The result was convincing: the first patient received ECMO and survived; the second patient received conventional treatment and died. The third patient now has a 3:1 chance to receive ECMO. The patient did receive ECMO and survived. The study was halted after twelve patients: eleven neonate patients had received ECMO and survived, only one patient – the second – had not received ECMO and had died *[source: Pediatrics. 1985 Oct;76(4):479-87]*.

ECMO prevailed and today more than 50,000 ECMO therapies have been registered with Extracorporeal Life Support Organisation (ELSO) in Ann Arbor, Michigan, USA. Two thirds of these therapies were performed on neonates (Fig. 2). The types of lung failure that are being treated with this technology have different causes: hypoplasia, meconium aspiration syndrome, sepsis and pneumonia, but also congenital diaphragmatic hernia (CDH).

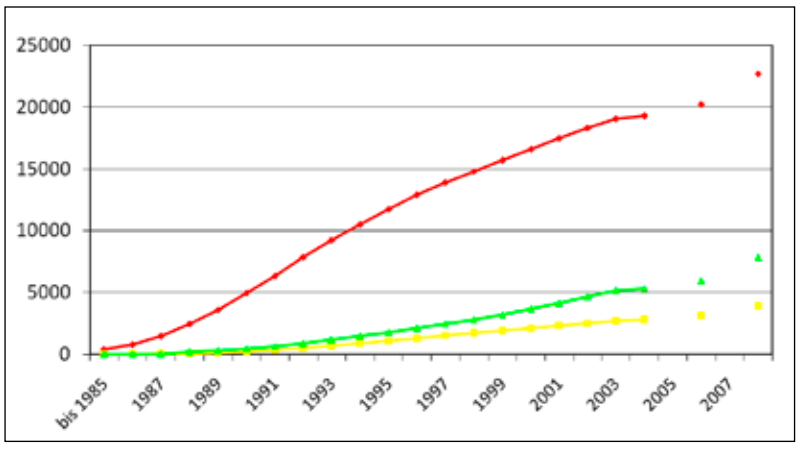


Fig 2: ECMO cases with respiratory indication in neonates (red) and paediatric patients (1 month to 18 years – yellow) as well as cardiac indication in children of 0 to 5 years (green) were reported worldwide with the ECMO register of Extracorporeal Life Support Organisation (ELSO) in Ann Arbor, Michigan

In Europe one of the biggest ECMO centres is at the University Hospital Mannheim, where 500 neonates were treated since the centre's opening in 1987. Dr Thomas Schaible, head of the children's ICU says: 'ECMO can be initiated as a temporary respiratory support measure when ventilation and other additional measures did not yield the desired outcomes. Most acute ECMO cases are to be found in neonatology; when lung failure occurs in children, ECMO is not necessarily the immediate option. For example if the oxygen concentration cannot to be reduced to less than 80 percent after five days of ventilation, ECMO comes in. Thus ECMO is a safety net in all critical ventilation situations and yields a survival rate of at least 70 percent.'

Moving a patient to an ECMO centre requires complex transport logistics that provide all intensive care options. If necessary, the transport can be done with ECMO running – in adult patients this is a routine procedure, but in neonates, with their small and fragile vessels, cannulation and ECMO should only be initiated by an experienced team in a safe environment.

The success of ECMO is also evident on the international level: ELSO, which has been maintaining its register since 1990, recorded a mere 83 participating hospitals and 1,644 cases in the first year. In 2012 a total of 200 centres reported 3,545 cases. Altogether, 53,190 ECMO cases are documented in the non-mandatory register, of which 32,043 were neonates. ECMO therapy, which usually lasts only a few days, secured the survival of 32,303 patients, of whom 21,900 were neonates (source: ELSO).

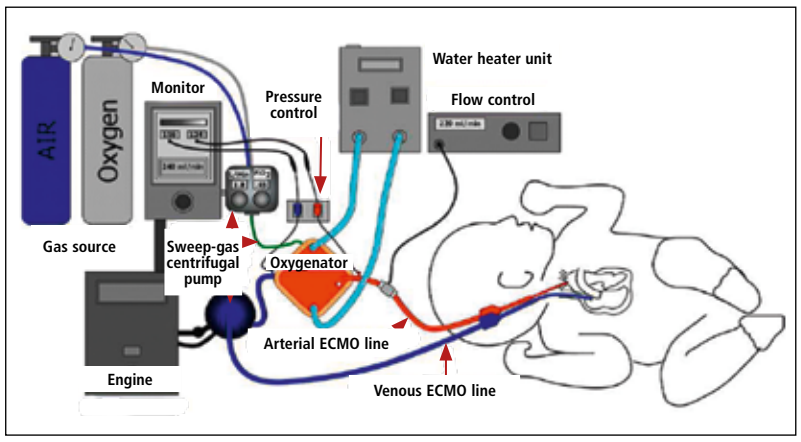


Fig 1: Veno-arterial ECMO circuit with neonate

Cardiovascular medical technology

Berlin's Biotronik celebrates 50th anniversary of quality and innovation

A little over five years ago, when Frank Busch began to work for leading cardiovascular technology manufacturer Biotronik, he noticed certain changes in the way the company carried out its business. 'Instead of being cost-driven, suddenly I was working in an environment that was people-driven, with a focus on developing new, cutting edge technologies of the highest quality. Before, business was just about downsizing.

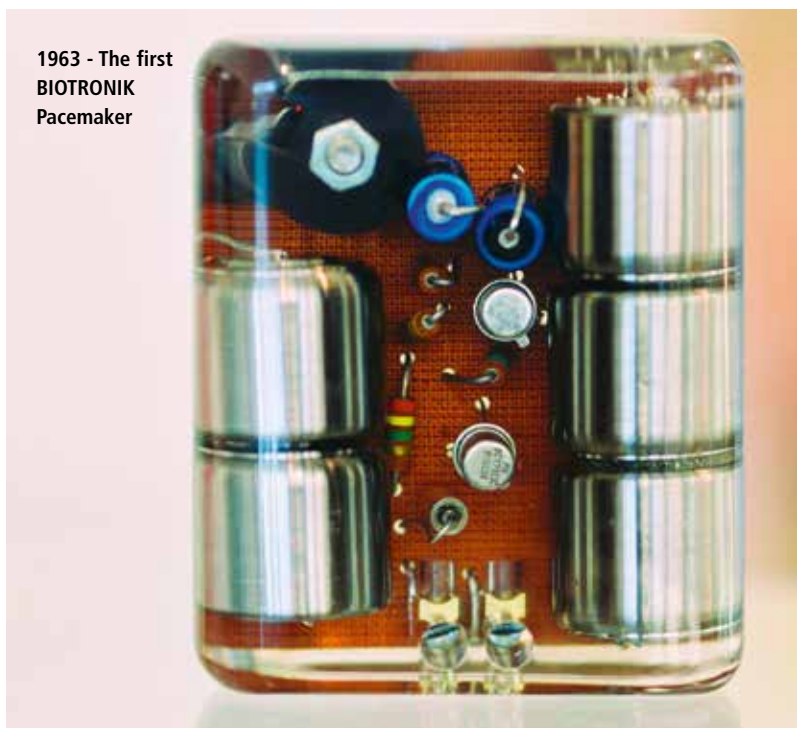
Now, with Biotronik, it's all about growth.' As manufacturing director Frank Busch can certainly speak from experience. The office where he sits is only temporary, built until a more permanent one can be constructed. In other words, the firm is expanding faster than it can find space. 'Good news for a company that can look back proudly on 50 years of excellence, quality, and innovation since 1963,' Biotronik points out.

Back then, physicist Max Schaldach and electrical engineer Otto Franke started a biomedical engineering revolution when they developed Germany's first implantable pacemaker. Today, Biotronik specialises in three business areas: cardiac rhythm management, electrophysiology and vascular intervention, with a focus on in-house research and development. Continuous innovation keeps the firm at the forefront of patient care, says Frank Busch: 'We make sure that people still understand the company's ethos, because everyone needs to know what it means in his or her daily work to be consistently living up to the highest quality standards.'

In the last decade the firm has implemented a number of technological solutions to ease physician-patient interaction and ongoing care. For example its ProMRI technology has been used in cardiac devices and leads since 2010, enabling patients with a cardiac implant to safely undergo MR scans. Indeed, it is the world's only company which allows ICD, IPG and heart failure patients access to those scans.

In 50 years, Biotronik has been able to grow tremendously while remaining true to its early pioneering spirit, the company points out. 'Today, it is represented in more than 100 countries worldwide, and has 5,600 employees.

Importantly, the focus is on patients, as Frank Busch explains: 'I like keeping up the awareness in everybody's mind that they are working on implants for actual people…and one of those people could be their grandmother.'



1963 - The first BIOTRONIK Pacemaker

Cardiology drives innovation

A leading Austrian professor commends scanner advances

Report: Michael Krassnitzer

'Cardiology is one of the most innovative medical disciplines. Many modern technologies, such as catheterisations or imaging procedures, were triggered by cardiology,' declared Professor Gerald Maurer MD, Head of the Department of Cardiology at Allgemeines Krankenhaus Wien (Vienna's General Hospital) and Director of the University Clinic Internal Medicine II at Medical University Vienna. In our EH interview, held during the annual meeting of the Austrian Cardiology Society in June, Prof. Maurer outlined the most recent technological developments in cardiology.

'MRI images of heart structures are becoming increasingly precise and with increasing resolution,' he said. This includes the late enhancement, contrast MRI technique, where the contrast agent Gadolinium-DTPA provides detailed information on the metabolism and status of heart muscle cells, supporting tissue differentiation and allows a more precise diagnosis of the cell vitality. The cardiologist can see whether a sub-endocardial infarction occurred where the necrosis, due to a lack of perfusion, is limited to the innermost layer of the heart muscle while the outer layer of the heart muscle is not involved. With myocarditis late enhancement has become the most important diagnostic indicator.

Today in cardiac ultrasound, so-called strain imaging provides new functional information. In 2-D imaging the speckle tracking technology tracks several points in the heart muscle throughout the entire heart cycle and can thus look at the deformation (strain) of the myocardium.

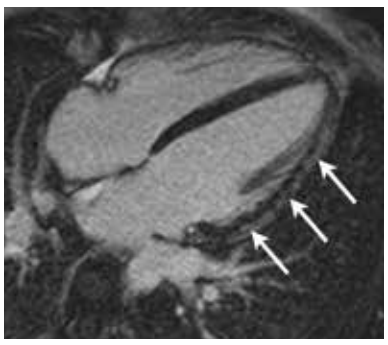
This is particularly relevant in patients with heart failure (HF) with preserved ejection fraction (HFPEF). For a long time cardiac insufficiency was thought to be solely associated with the lack of the heart's contraction ability. However, around 50% of cardiac failure patients show normal ejection fractions. While some of these patients show a diastolic dysfunction, systolic abnormalities can also contribute. In those patients the myocardial longitudinal shortening is inadequate – a dysfunction that can be detected in strain imaging. 'In an aging population HFPEF is a growing public health problem,' Prof. Maurer points out.

He believes that cardiac computed tomography (cardiac CT) will also play an increasingly important role. Cardiac CT visualises the coronary vessels well and helps determine the calcium or Agatston score, an important indicator of a coronary disease. 'While this method does not replace the catheter, it allows the exclusion of significant coronary heart disease with high probability,' he explains, adding that a further development is the measurement of cardiac profusion with contrast-enhanced CT.

In the area of cardiac implants, bio-absorbable stents are an important innovation. 'One of the problems with conventional stents is the fact that in young patients they may be associated with long-term risks. In an 80-year-old patient this is not that much of an issue, but there are many patients between 20 and 40 years of age who suffer CHD and need an implant.'

While conventional stents remain intact for several decades, bio-absorbable stents, which are made from polylactide, dissolve within two to three years – with water and carbon dioxide absorbed by the body. In most cases the endothelium fully recovers and the patient receives a conservative therapy with cholesterol and BP medication and anticoagulants. Large long-term studies are currently being conducted but final results are not yet available.

CMR image of a patient with myocarditis; the lighter coloured lateral wall (arrows) is caused by late enhancement



Professor Gerald Maurer MD, who has headed the cardiology department at AKH (General Hospital) in Vienna since 1993, is also Director of the University Clinic Internal Medicine II at Medical University Vienna. He gained his medical degree and doctorate at Vienna's medical school and completed his specialist physician training in the USA (American Board of Internal Medicine; Subspecialty Board, Cardiovascular Disease). He became a professor at the University of California (UCLA), Head of Non-invasive Cardiology and Interim Head of Cardiology at Cedars-Sinai Medical Centre in Los Angeles before returning to work in Austria. Prof. Maurer is Member of the Board of the Austrian Cardiology Society (ÖKG) and currently Editor-in-Chief of the European Heart Journal – Cardiovascular Imaging.

Cardiac magnetic resonance imaging

The potential of cardiac magnetic resonance imaging (CMRI) is still largely untapped. One novel application might be ablation follow-up. The first MRI-guided cardiac interventions were performed at Herzzentrum Leipzig, but, as far as coronary imaging is concerned, MDCT remains superior to MRI

The diagnostic potential of CMRI has not yet been fully explored. 'Myocardial tissue differentiation – the detection of inflammation, fibrosis and scar tissue – will be further improved and objectified,' says Professor Matthias Gutberlet (Fig. 1). The Director of the Department of Diagnostic and Interventional Radiology at Herzzentrum Leipzig and professor for cardiovascular imaging at the University Leipzig expects MRI to play an increasingly important role in prognostic evaluation of patients with infarction, cardiac myopathy or inflammation.

'Another big issue in CMRI application will be therapy follow-up in rhythmology and the evaluation of pathological cardiovascular haemodynamics with 4D flow,' he points out (Fig. 2). While MRI is already the method of choice for volumetric and functional analyses no single cardiac imaging procedure, Prof. Gutberlet says, has or will have a monopoly. More likely, hybrid imaging procedures, such as MR/PET or PET-CT and image fusion technologies, will prevail (Fig. 3). 'No single modality will be able to offer one-stop shopping capabilities,' the radiologist predicts.

With regard to coronary imaging, the professor is sure that multi-detector computed tomography (MDCT) will retain its advantage (Fig. 4 a). 'Unlike MDCT, MRI has not advanced significantly in the past few years,' he explains, and he doubts it will gain substantial ground soon. However, CMRI may well conquer image-guided cardiac interventions. 'In our institution, together with the rhythmologists we quite successfully performed MRI ablations in 10 initial patients with atrial fibrillation (Fig. 5). The rhythmologists are so excited that we will definitely continue our cooperation,' he confirms.

Rhythmologists consider CMRI particularly promising because the length of the ablation procedure is accompanied by high radiation exposure. Moreover, fluoroscopy does not provide sufficient anatomical detail. 'MRI offers clearly enhanced visualisation of the substrate pre- and post-intervention (Fig. 4 b, c and Fig. 5 b, c). Although we are far from routine use, we made huge progress in terms of feasibility and were quite surprised how well the procedure worked – albeit in a rather simple intervention,' he reflects optimistically, and underlines that the foremost aims are the reduction of radiation exposure followed by enhanced visualisation of anatomy and the arrhythmogenic substrate, as well as therapy success generally.

MRI despite a pacemaker?

Patients with implants, such as a pacemaker or ICD, require particular attention prior to MRI examination. 'These patients are not per se excluded,' Prof. Gutberlet says. 'They can well undergo MRI even if they do not have a so-called MR conditional device.' While the manufacturers continue to develop MR-safe devices, most of those available are not suitable for MR. 'Before an MRI exam, the device has to be checked by a cardiologist and set to a certain mode,' the professor explains. The patients must be informed that a certain risk remains due to the antenna effects of the ventricle electrodes. These are mostly thermal effects that might damage the device. MR conditional implant or not – one major problem remains unsolved: artefacts created by the device or the electrodes (Fig. 6). A pacemaker that is implanted on the left side causes artefacts right where the heart sits and the lead in the right ventricle can provide misleading information in imaging (Fig. 6).

*Reprint from 'RöKo HEUTE 2013', the official publication of the German Radiology Congress

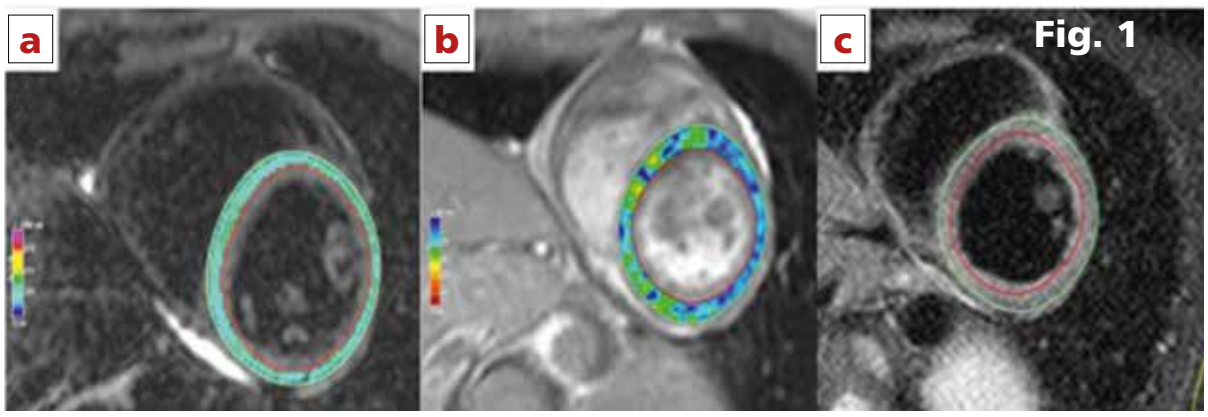


Fig. 1

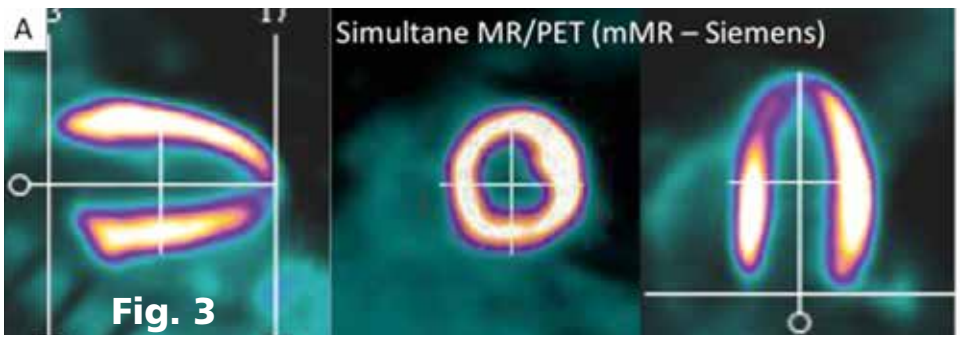


Fig. 3

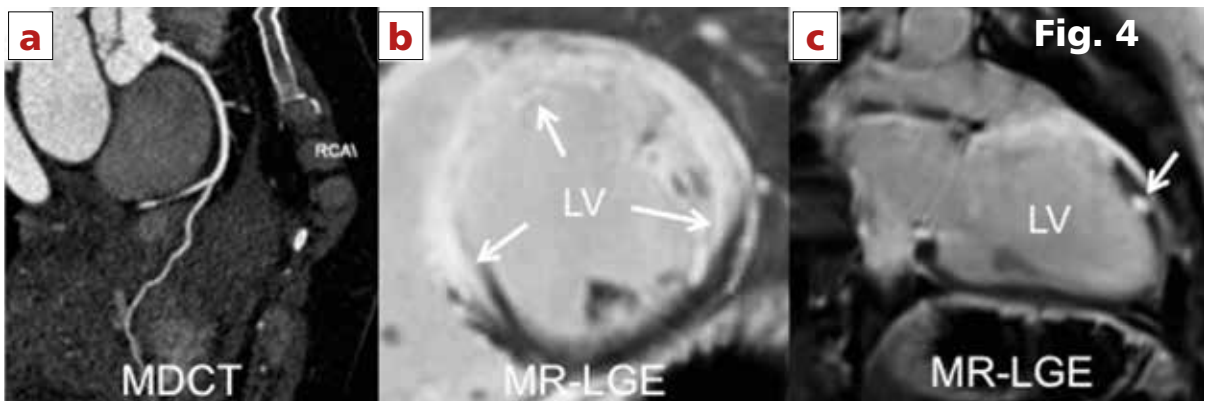


Fig. 4

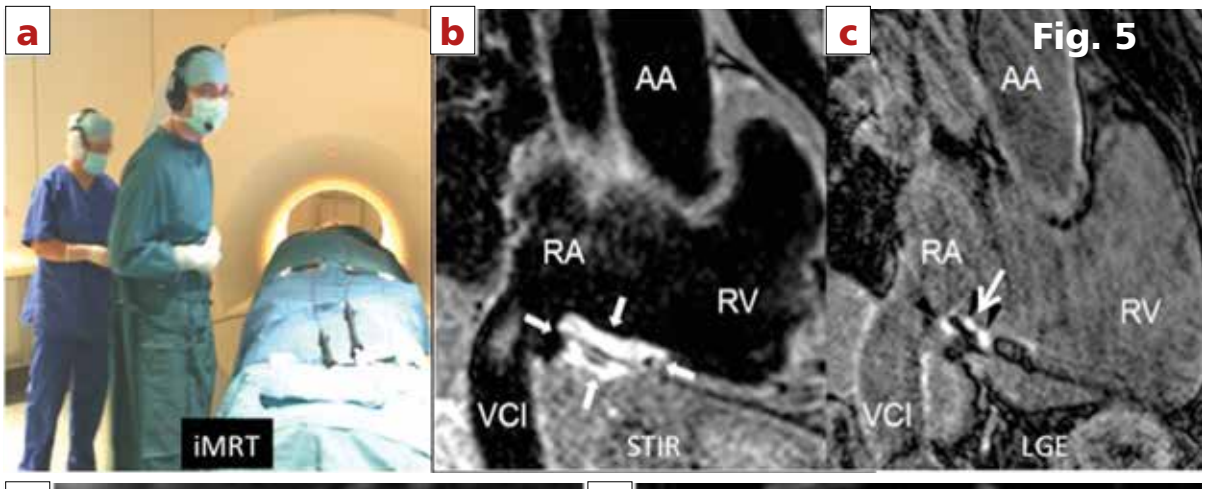


Fig. 5

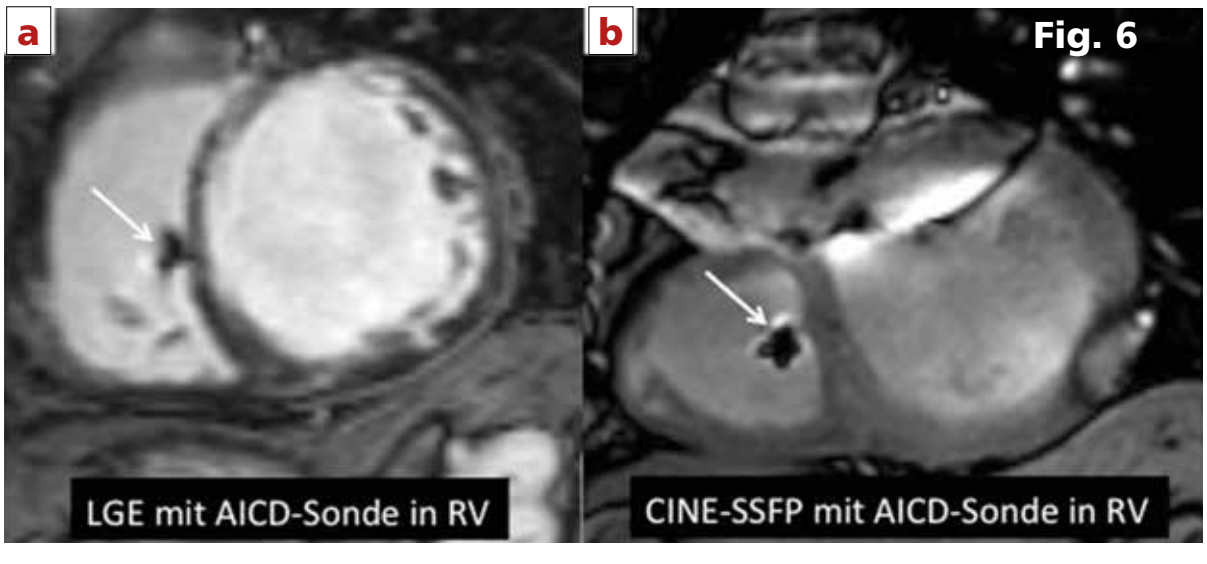


Fig. 6

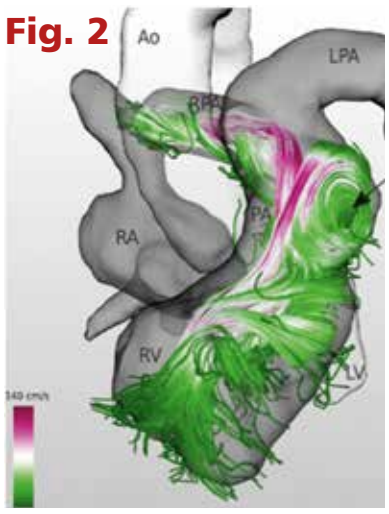


Fig. 2

Fig. 1: (a) T1 mapping after CM, (b) T2 mapping with focal elevation in the lateral wall area and (c) oedema ratio (here increased at 2.5) from STIR sequence in a 29-year-old patient with suspected acute myocarditis (T1 and T2 mapping created with CVI42 using WIP sequences by Philips and Siemens)

Fig. 2: Visualisation of the turbulent flow (arrow) in reconstructed RVOT with aneurysm in a patient with repaired tetralogy of Fallot. (Image from: S Born, M Pfeifle, M Markl, M Gutberlet, G Scheuermann. (2013), IEEE Trans Vis Comput Graph. Jun;19(6):900–912)

Fig. 3: (a) Enhancement of the volumetric and functional analysis as well as vitality and inflammation diagnostics with simultaneous MR/PET with MR/PET overlay (images created with Corridor 4DM) and (b) systemic diseases with cardiac involvement, such as sarcoidosis. (Images: Prof. O Sabri, Prof. T Kahn and Prof. M Gutberlet – Leipzig University)

Fig. 4: (a) Exclusion of CHD with MDCT (here Curved MPR of the RCA) in a 41-year-old patient with ventricular tachycardia. (b) Late Gadolinium Enhancement (LGE) (PSIR image (arrows)) in the short and (c) long axis of the same patient shows clear subepicardial to transmural LGE following myocarditis with scar tissue. In electro-anatomical mapping the vital muscle bridge (arrow) was identified as rrhythmogenic substrate and was ablated. (Images: PD C Piorkowski, Prof. G Hindricks, PD M Grothoff, Prof. M Gutberlet – Leipzig University)

Fig. 5: (a) Setup of interventional MRI (iMRI) for MR-guided ablation of atrial flutter at Herzzentrum Leipzig. (b) Result of the ablation of the cavotricuspid isthmus in patient with atrial flutter in edema visualisation (STIR sequence) and (c) LGE with scars successfully visualised (arrow) (Images: Priv.-Doz. Dr C. Piorkowski, Priv.-Doz. Dr M. Grothoff, Prof. G. Hindricks and Prof. Gutberlet – University Leipzig)

Fig. 6: Patient after Dor procedure and AICD implant. (a) IR-GRE sequence to visualise scar with LGE and RV probe (arrow) shows only few artefacts compared to the CINE-SSFP sequence (b).

Professor Matthias Gutberlet MD has directed the Department of Diagnostic and Interventional Radiology at the Herzzentrum (Heart Centre) of Leipzig University since 2007. His research and teaching priorities are Doppler ultrasound and cardiac CT and MRI, above all in patients with congenital heart defect, cardiomyopathies, myocarditis and coronary heart disease (CHD).
The professor studied medicine at Marburg and Berlin, where he submitted his habilitation thesis on diagnostic radiology on *MRI in patients with congenital heart disease*. In 2012 and 2013, jointly with Professor Holger Thiele, he was scientific director of the German Cardiac Diagnostics Symposium in Leipzig.

Computed tomography

CT will remain an imaging heavyweight

Computed tomography (CT) is the modality of choice for many diagnostic issues. Whilst currently its major strength is the visualisation of anatomical detail, future technological improvements may also reduce radiation exposure.

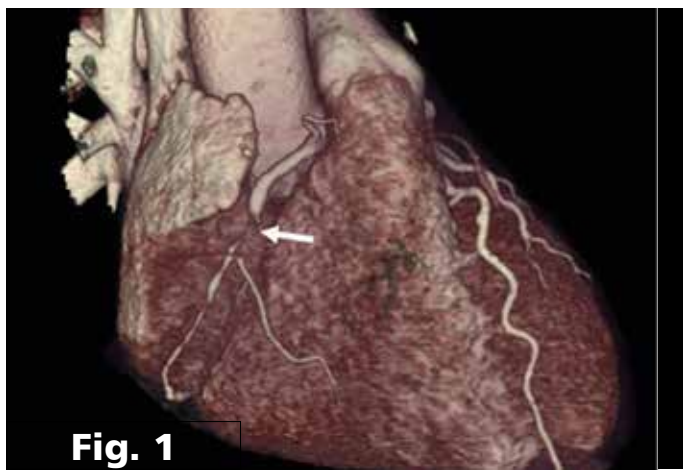


Fig. 1

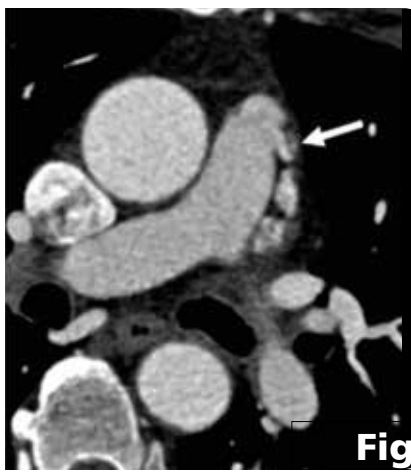


Fig. 2

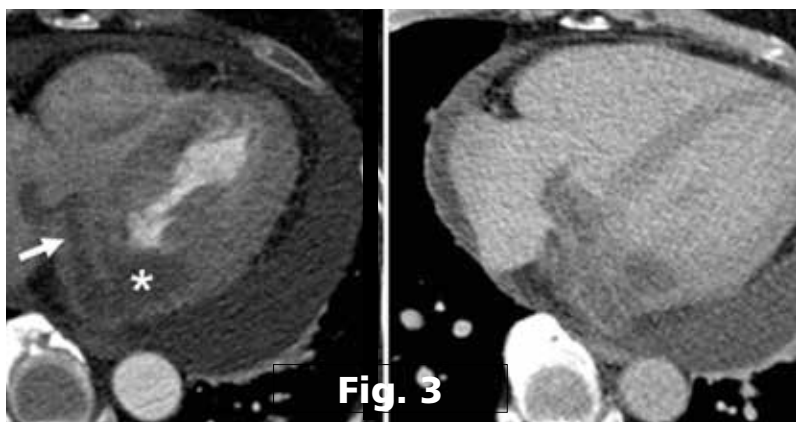


Fig. 3

Professor Gabriele A Krombach MD studied medicine and specialised in radiology at Aachen medical school, later receiving her teaching certification for diagnostic radiology in 2003. In 2006 she became chief senior resident at the Radiological Diagnostics Clinic at Aachen University Hospital and was appointed adjunct professor in 2008. Two years later she became Director of the Diagnostic and Interventional Radiology Clinic at University Hospital Giessen, where cardiac imaging, MRI, interventional radiology and pulmonary imaging are her research priorities.

Fig.1: CTO (chronic total occlusion) of the right coronary artery
Fig. 2: Fistula between left coronary artery and pulmonary artery
Fig. 3: Tumour infiltration (bronchial carcinoma) with tumour thrombus in the coronary sinus (arrow)
(Image courtesy of Christian Schneider MD, chief senior resident, Clinic of Diagnostic and Interventional Radiology, University Hospital Giessen)

FREQUENT INDICATIONS FOR CT

- Patients for cardiac surgery not involving the coronary arteries, such as valve replacement or cardiac tumour resection
- Patients with intermediate risk who should not undergo a coronary angiography
- (Suspected) coronary anomalies
- Evaluation of bypasses (problems: calcification of the native vessels, evaluation of the anastomoses), also in case of repeat surgery to visualise existing bypasses
- Method of choice for percutaneous valve replacement
- Visualisation of cardiac veins prior to the implementation of a bi-ventricular pacemaker
- Visualisation of the pulmonary veins prior to ablation with arrhythmias
- Visualisation of the pulmonary veins post ablation (suspected stenosis)
- Anomalous pulmonary venous connection

'Today, computed tomography is the best imaging modality to detect stenoses in patients with intermediary pre-test probability where a coronary angiography is not immediately indicated,' according to Professor Dr Gabriele A Krombach, Department Director at the Clinic of Diagnostic and Interventional Radiology at University Hospital Giessen and Marburg (UKGM). The degree of anatomical detail, she adds, is much better in CT than in magnetic resonance imaging (MRI). 'In malignant variations of the descending artery, where the coronary artery is compressed between aorta and pulmonary artery, CT is currently the diagnostic method of choice.'

CT is also the modality of choice for visualising coronary stenoses. With low-risk patients without suspected coronary stenoses who require cardiac surgery, e.g. to remove a cardiac tumour, a CT scan can provide valuable information on possible coronary stenoses and help predict surgical outcome.

A further important indication for CT is the visualisation of plaque to risk-stratify patients with medium pre-test probability, Dr Krombach adds. 'With an asymptomatic patient who has a risk of 10 to 20 percent to develop coronary heart disease over the next ten years, quantification of coronary calcification with CT in indicated.' However, with higher risks CT is not indicated and the patient has to undergo an invasive angiography right away. Similarly very low risk (below 10 percent) asymptomatic patients do not need a CT. 'In such a cases,' she explains, 'we simply wait and see.'

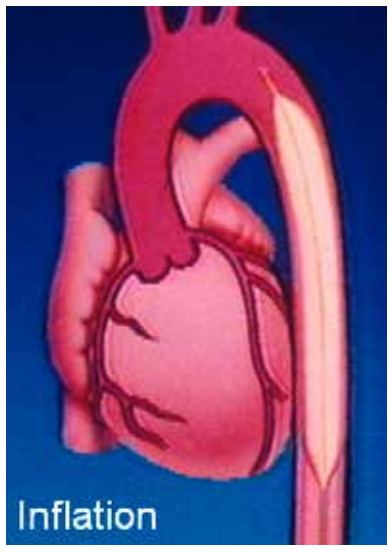
The radiologist particularly appreciates CT in percutaneous aortic valve replacements (TAVI), recently experiencing a veritable boom. According to the *Herzbericht 2010* by Dr Ernst Bruckenberger, the number TAVI procedures increased from 93 in 2006 to more than 4,800 in 2010. 'When planning a percutaneous aortic valve replacement the diameter of the ring and the distance of the coronary artery ostia to the valve have to be determined – this is done best with CT,' Dr Krombach explains. As a radiologist she does not expect CT to fall into obscurity any time soon, primarily because no single modality can do everything. The coronaries, for example, cannot be visualised in echocardiography. Additionally, technological progress in CT might open access to new patient groups. The alpha and omega of CT development is the reduction of radiation exposure and indeed new kinds of detectors are being designed that aim to decrease radiation to submillisievert level.

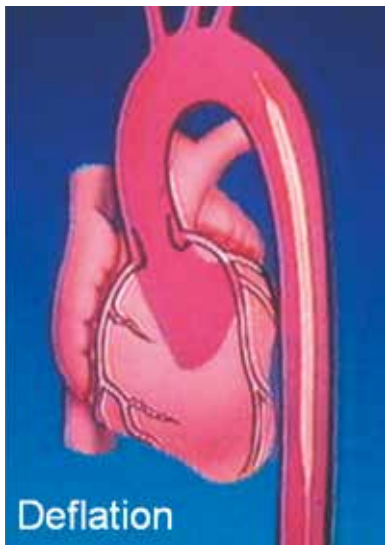
'If we could realise dose reduction in CT by using the different spectra of X-rays, we could also examine younger patients, such as those with congenital heart defects' – patients who today undergo MRI, she stresses.

Counterpulsation: The

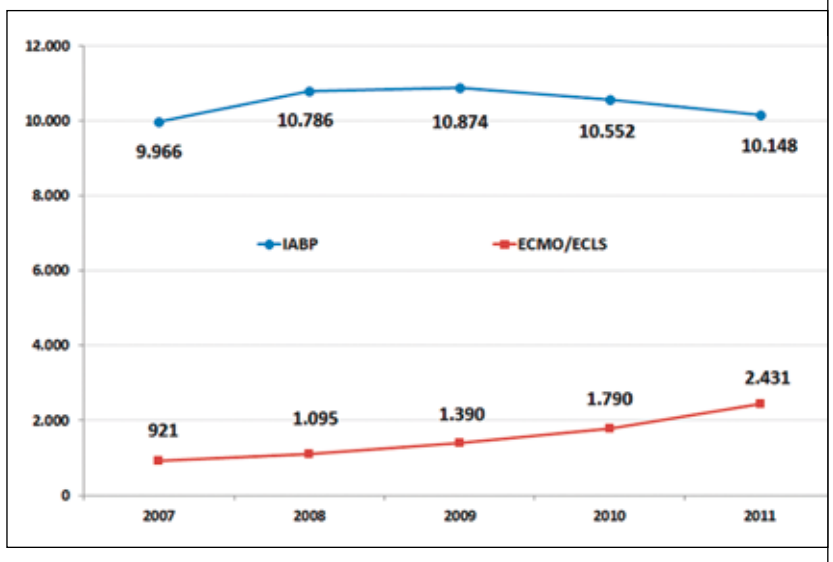
'The report of my death was an exaggeration,' Mark Twain precisely commented in the New York Journal in June 1897. That quote could be applied to those that have appeared in some places since, at last year's European Society of Cardiology gathering, the demise and funeral of the counterpulsation procedure were reported. Along with intra-aortic counterpulsation, an established procedure (the benefit of which is sometimes disputed), there is now also extra-aortic and even external counterpulsation. Having discussed the subject with cardiologists, cardiac and vascular surgeons and manufacturers, in the following three sections *EH Correspondent Holger Zorn* reports that speaking about a funeral would be a 'exaggeration'.

Intra-aortic balloon pump pros & cons





Left: The balloon is quickly inflated immediately after the left ventricle ejects blood into the aorta, thus blocking the aorta and increasing blood flow to the coronary arteries, improving blood supply to the cardiac muscle, which at this point is relaxed. Right: Milliseconds before the next heartbeat the balloon is quickly deflated, reducing pressure and helping the heart to eject blood



IABP vs. ECMO/ECLS in Germany. The number of patients receiving an IABP peaked in 2009 and has since been slightly decreasing. At the same time, the use of extracorporeal systems has increased constantly; in 2007 the ratio was 10:1, in 2011 this fell to 4:1. *[Own presentation based on data from the DRG statistics of the German Federal Statistical Office (Destatis)]*

Since cardiac surgeon Adrian Kantrowitz, of the Maimonides Medical Centre, Brooklyn, first introduced intra-aortic balloon pulsation (IABP) into clinical practice in 1967 *(Surg Clin North Am. 1969 Jun; 49 (3) :505 -11)*, the technique has been considered the method of choice for short-term mechanical cardiac support following a heart attack.

The principle is impressively simple. Connected to a helium pump, a cigar-shaped balloon is ECG triggered, folded and inserted into the femoral artery in the groin and pushed into the descending aorta to the point where the tip rests just under the aortic arch. After the left ventricle has ejected its blood into the aorta, the balloon is quickly inflated. The aorta is blocked, blood cannot flow out peripherally and so flows into the coronary arteries improving blood flow in the now relaxed cardiac muscle. Milliseconds prior to the next heartbeat the balloon is abruptly drained, creating a slight vacuum effect and making it easier for the heart to eject the blood.

The procedure had already received a class 1 recommendation in the treatment guidelines. However, only every fourth patient in cardiogenic shock is treated with this method and there is some doubt as to its effectiveness. The recommendation was recently downgraded to class 11a.

In August 2012, a randomised multicentre study was presented at the European Cardiology Congress in Munich. Out of 600 patients with cardiogenic shock (CS) after acute myocardial infarction (AMI) 301 received IABP and 299 did not. Both groups received percutaneous coronary intervention (PCI).

After 30 days, 119 patients (39.7%) in the IABP group had died and, in the control group, 123 patients (41.3%) had died. 'The use of intra-aortic balloon counter pulsation did not significantly reduce 30-day mortality in patients with cardiogenic shock complicating acute myocardial infarction, for whom an early revascularisation strategy was planned,' said Professor Holger Thiele, cardiologist at the Heart Centre at the University of Leipzig, representing the authors of the SHOCK-II-Trial *(N Eng J Med. 2012 Oct 4;367 (14) :1287-96)*.

Some experts were surprised, others not – i.e. those who had not necessarily been following the class I recommendation unconditionally. Maybe simple semantics could help here. Where nothing pulsates, i.e. during cardiogenic shock, there is nothing to counter pulsate.

Meanwhile, a further study was published that examined a different patient population and collated long-term data. This study came to a different conclusion. Out of 301 patients with impaired cardiac function and severe coronary disease, 151 received high risk PCI with IABP, and 150 without. Mortality data for the entire cohort were available after a median 51 months. Overall, 100 patients (33%) died, with 42 of those in the group that had received IABP and 58 in the group that had not.

Dr Divaka Perera, cardiologist at St. Thomas' Hospital, London, explained: 'Elective IABP use during PCI was associated with a 34% relative reduction in all-cause mortality compared with unsupported PCI' *[Circ. 2013 Jan 15;127 (2):207-12]*. Professor Marco Tubaro, cardiologist at the San Filippo Neri Hospital, Rome, put it this way: 'Even if a reduction of mortality has not been demonstrated with IABP in association with primary PCI, the bulk of evidence and everyday clinical practice are in favour of IABP use as haemodynamic support in patients with AMI complicated by cardiogenic shock non-immediately responsive to volume expansion and inotropic stimulation.'

Professor Andreas Markewitz, Lieutenant Colonel in the German medical corps and cardiac surgeon at the German Armed Forces Hospital in Coblenz, sees another aspect. Out of all patients in the SHOCK-II-Trial only a little over a third (38%) were completely revascularised. 'IABP is only of benefit if the heart is given a chance to completely recuperate,' Prof. Markewitz believes. Additionally, in patients with multi-vessel disease this is often not achieved with PCI; coronary bypass surgery (CABG) is the superior procedure here.

The professor therefore believes that IABP should continue to be considered very important for cardiac surgery. 'Soon,' he said, 'there will be a new, interdisciplinary S3 guideline that will confirm this.

Since 2010, **Colonel Professor Andreas Markewitz, MD** has directed the Department XVII, at the Cardiovascular Surgery Clinic, German Federal Armed Forces Central Hospital, Coblenz. He gained his medical degree and specialist training in surgery at the University of Tübingen. In 1994, he wrote his habilitation and a year later he became a senior consultant at the Coblenz hospital. He qualified as cardiac surgon in 1996. The professor is very active in the German Society for Thoracic and Cardiovascular Surgery, the German Cardiac Society and the German Interdisciplinary Association for Intensive Care and Emergency Medicine.

After gaining his medical degree at the Free University of Berlin, **Professor Holger Thiele** specialised in internal medicine at the Leipzig Heart Centre and the German Heart Institute in his home town, Berlin. Following a research period alongside Professor Mohan Sivananthan in Leeds, UK, he became a consultant and, in 2006, senior consultant under Professor Schuler at the Leipzig Heart Centre. Since 2009 Prof. Thiele has held an extraordinary professorship at the University of Leipzig.

Extra-a counte

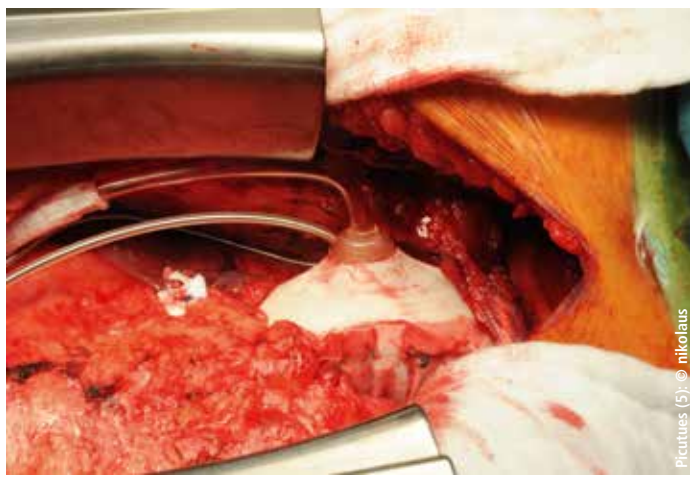
The C-Pulse, manufactured by Australian-American company Sunshine Heart, Inc. is neither a pulsatile artificial heart nor one of the well-known non-pulsatile left heart support systems *(EH 5/2006 p.23 and 3/2011 p.3)*.

However, the device appears to be suitable to help slow down or even stop symptoms in patients with moderate chronic heart failure. The technology is innovative: the principle of counterpulsation (CP) is not applied intra-aortically but extra-aortically. A cuff is placed around the ascending aorta and triggered by an ECG-electrode attached to the left cardiac apex epicardially (image 1, 2). When the left ventricle contracts and the blood has been ejected into the aorta, the balloon inside the cuff is blown up and compresses the aorta slightly so that more blood is retained and flows into the coronary arteries, directly improving the heart's oxygen supply. Draining the balloon just before each contraction of the ventricle temporarily also lowers resistance in the aorta and alleviates work for the heart.

The device was first used in humans in May 2005 at Auckland City Hospital in New Zealand. Dr William S Peters, the system's inventor, has been implanting the C-Pulse in Australia since 2010 *(source: J Heart Lung Transplant. 2010;29:1427-32)*.In May 2013 he oversaw the first European implantation of the system at the German Heart Institute Berlin (DHZB). Professors Roland Hetzer and Thomas Krabatsch, of the DHZB, and Dr Holger Hotz, of the Cardio-Centrum Berlin, have now fitted three patients with the C-Pulse (image 3) who had not responded to prior cardiac resynchronisation therapy (CRT) in the context of a pan-European, multicentre study. Prof. Krabatsch sees two advantages: 'The system does not come into contact with the patient's blood circulation; therefore there is no need for permanent anticoagulation therapy. Moreover, the patient can turn the system off temporarily or even disconnect it – for example, to take a shower. Of course, this is not possible with other pumps that are fitted intra-aortically.'

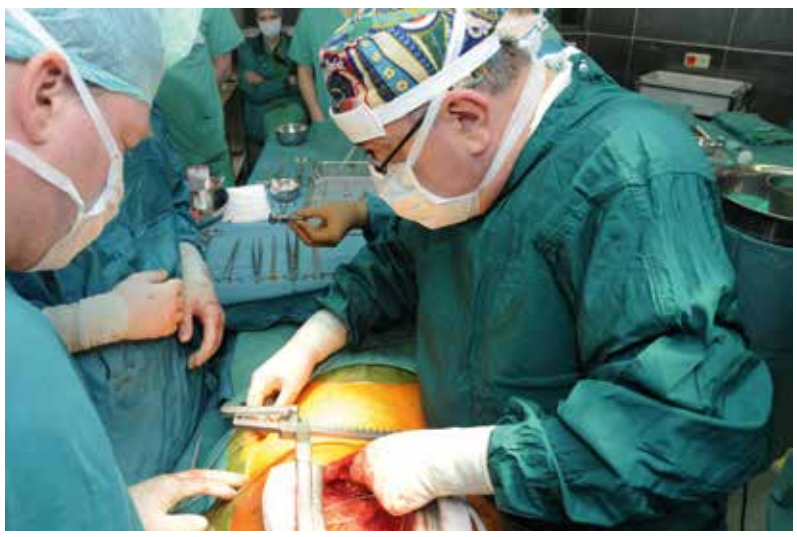
The operation can be carried out without using a heart-lung

condemned live longer



Picutues (5): © nikolaus

ortic r pulsation



Prof. Roland Hetzer (right) and Dr Holger Hotz (left) during the implantation

machine and takes less time than the implantation of a classic blood pump whilst still being technologically complex. 'The aorta has to be completely exposed so that it can be correctly covered by the cuff, Prof. Krabatsch pointed out, adding: 'The ECG-electrode also has to be attached to the heart from the outside, most often at just the point that's furthest away from surgical access, i.e. the sternotomy.'

Failing hearts in which drug treatment has been unsuccessful do not tolerate such manoeuvres haemodynamically without some restrictions. One patient required a Ventricular Assist Device (VAD) just a few days after the intervention.

These VADs are usually only implanted when patients are in a state of terminal heart failure, as bridge-to-transplant devices or destination therapy. But the C-Pulse has a different approach: The implantation at an early stage either at least delays or possibly completely removes the need for the implantation of a VAD. Dr Peter Göttel, Medical Director for Europe at Sunshine Heart, added: 'The C-Pulse system bridges the gap between CRT-Non-Responders and the indication for an LVAD within the therapeutic range. It's important that cardiologists who treat these types of patients mostly as out-patients are aware of the existence of new, less invasive methods of cardiac support such as extra-aortic counterpulsation. The C-Pulse alleviates patients' symptoms with minimal impact on quality of life. In the future, we will also offer a fully implantable version. As the system does not require an implantable buffer battery, this technological advance will be possible soon.'

Studies involving 20 patients in Canada and the USA, and 50 patients in 11 hospitals across Europe, will now test the results gathered so far. These include, in Germany (alongside the DHZB), hospitals in Hannover, Duisburg, Düsseldorf and Erlangen in Britain a hospital in Glasgow, the Royal Brompton in London and Harefield Hospital, Middlesex; in Italy, hospitals in Milan, Padua and Turin.

Professor Thomas Krabatsch gained his medical degree at the Humboldt-University of Berlin and trained as a cardiac surgeon at Berlin's German Heart Institute. He has been Consultant for Thoracic & Vascular Surgery since 1999. In 2002 he wrote his habilitation on 'Examinations of the clinical relevance and underlying mechanisms of transmyocardial laser revascularisation'

Personal shear rate therapy

In 1839 Richard Thoma was the first to observe that arteries respond to flow: he identified a fundamental relationship between blood flow and arterial calibre. This important physiological mechanism currently has a renaissance in vascular medicine: Enhancing arterial flow and flow velocities rather than pressure is an important activating mechanism in the growth of biological bypasses (arteriogenesis). This can be achieved non-invasively by externally compressing arteries after a systolic pulse wave in such a way that a diastolic augmentation is achieved.

This involves fitting cuffs around the calves, lower and upper thighs and buttocks, which are then inflated and deflated by a compressor. Whereas researchers believed that the haemodynamic changes in blood pressure would be the underlying mechanism of clinical improvement, it is now shown that this mechanism is far more complex, according to Dr Ivo Buschmann, a specialist in vascular medicine at the Charité Clinic in Berlin: 'The effect of blood volume redistribution is probably overestimated, however blow flow is accelerated, in a similar way to what would happen during a gentle run, without a significant increase in heart rate. The objective of this personalised shear rate therapy is the induction of arteriogenesis – a rescue mechanism of the vascular system during occlusion or stenosis. It stimulates pre-existing but not fully developed collateral vessels across the entire coronary circulation to grow.

In a prospective study, 23 patients aged 61+2.5 years with stable coronary disease (CHD), and at least one haemodynamically relevant stenosis, were split into two groups. Sixteen patients in the therapy group received 35 one-hour treatment sessions of external counterpulsation over seven weeks; the seven patients in the control group did not. In the therapy group, the collateral flow index (CFlp) increased from 0.08 + 0.01 to 0.15 + 0.02 and the fractional flow reserve (FFR) also increased significantly from 0.68 + 0.03 to 0.79 + 0.03; P = 0.001; however, no change was observed in the control group [source: Eur J Clin Invest. 2009;39:866-75].

Tailored treatment

'The extent of volume shift from the legs towards the heart is not really that important,' Dr Buschmann explained. This also might be the reason why Cochrane and the FDA do not recommend an older system such as enhanced extracorporeal counterpulsation (EECP). Potential risks, in particular due to high pressures, can be harmful. However, it is not the compression ratio in the cuffs that is decisive, but the velocity impulse which results from the inflation of the cuffs. This impulse changes the flow profile in the blood vessels. The flow not only increases, but also the shear rate across the arterial walls. This sets off morphological and biochemical processes and eventually leads to a proliferation of the vessels [source: Development 2010].

That impulse is shown graphically on a novel vascular ultrasound 'tachometer' to measure blood flow, volume and pulse rate being developed in connection with the Herzhose® (literal translation heart pants – describing the cuffs system) which serves as a basis of calculation for the correct setting of this personalised shear rate therapy. Each treatment is individually adapted to the patient.

Given one-hour training sessions, the heart requires three to six weeks to develop the growth of natural bypasses sufficiently. This period of time depends largely on the individual blood flow acceleration of each individual patient, Dr Buschmann explained, adding: 'We now know that the effect lasts for around a year, so repeated training is needed – an ideal passive addition to active cardio exercise.

Health insurers in Germany have started to cover this personal shear rate treatment, but not all; it has neither NUB (new examination and treatment procedures) status nor does it qualify for an additional reimbursement. Meeting the costs is always negotiated on an individual basis.

However, there is considerable interest. Apart from the Charité, another 20 clinics – in Germany, Austria and Switzerland – plan to offer this patent protected personal shear rate treatment this year.

The procedure is suitable to treat stable CHD and particularly diffuse CHD, i.e. patients who cannot be revascularised interventionally or surgically. In addition, patients with peripheral vascular disease (PAD) also benefit from the treatment, especially if they are also diabetics. Several clinical trials are currently being initiated to confirm the beneficial effects in larger patient cohorts.

The system can also be used to treat erectile dysfunction, a disease estimated to affect every other male over the age of 40 and which can frequently be a precursor of systemic vascular disease.

Ivo Buschmann fits a patient with a personal shear rate therapy system. Inflatable cuffs are placed around the calves, upper and lower thighs and pelvis, then connected to a computer-controlled compressor via a pneumatic hose

© Funke

PD Dr Ivo Buschmann studied medicine at the University of Hamburg, where he also began his career in the cardiology department with Professor Thomas Meinertz. Awarded a Max Planck Society scholarship he moved to Prof. Wolfgang Schaper's group, where he participated in several high impact papers in the field of therapeutic arteriogenesis. With a grant from the Volkswagen Foundation's excellency programme (2000 – 2006) Dr Buschmann continued his research at the Albert Ludwigs University of Freiburg. In 2004 his research group initiated the Richard Thoma Laboratories (RTL) for Arteriogenesis at the Charité Berlin in the Centre for Cardiovascular Research (CCR). The focus of the RTL is the generation of molecular experimental data and translation of the latter into clinical practice.
Clinically, Dr Buschmann directs the interventional angiology at the Charité Berlin (Campus Virchow) and is a founding member of ESVM – the European Foundation for Vascular Medicine.

Cardiology & therapy

Healing hearts 1: Bioresorbable stents

Cardiologists believe they can restore coronary arteries thanks to a new generation of stents that help the body to strengthen collapsed vessels. Elsewhere, patients' own stem cells are being programmed to rebuild cardiac muscle in HF patients. John Brosky reports

Not every patient needs to be cut open to replace or bypass clogged coronary arteries. Some 30 years ago we learned arteries could be reopened with a balloon in a minimally invasive procedure. More recently interventional cardiologists learned they could keep the artery open by inserting a metal tube.

Unfortunately, the body does not agree and fights this foreign object. Patients with metal stents face a risk of the artery closing again inside the tube. Thousands of patients today are being treated with an innovative stent made of biocompatible materials that holds the artery open long enough for the body to heal the vessel naturally, and then dissolves into the blood.

The results from clinical trials are so good that cardiologists are speaking for the first time about 'healing' coronary arteries. Dozens of these new stents are being pushed through product pipelines by companies specialising in cardiovascular technology.

In May of this year, at Europe's largest gathering of interventional cardiologists, the combination of solid evidence from the clinic and new product announcements from companies reached what is called an inflection point, a moment when the tide turns.

'We have reached the point of no return,' said Patrick Serruys MD, stopping in his tracks on the way to speak at a scientific session devoted to these revolutionary devices, which he calls bioresorbable vascular scaffolds (BVS).

Christoph Naber MD, of St. Elisabeth Hospital Essen, Germany, has personally implanted 200 of the new scaffolds

The Editor-in-Chief of the journal *EuroIntervention*, and recognised as a co-developer of metal-based drug-eluting stents (DES), Dr Serruys has been preaching the need for this new technology.

'Seven years! It's like a biblical time to wait, but now it's here,' he said, clearly enthusiastic about the cascade of good news during the EuroPCR congress in Paris. 'I will have to check, but I have the impression that bioresborbables were used in half the live sessions this week.'

'We are calling it vessel restoration therapy (VRT),' said Dr Serruys, a professor of Interventional Cardiology at Erasmus University (Rotterdam, the Netherlands), where he is also the Director of Clinical Research in the Catheterisation Laboratory. Bioresorbable scaffolds are revolutionary, disruptive for a coronary revascularisation market that is expected to reach $10 billion annually by 2016.

Because DES scaffolds are made of metal, no matter how thin, or how carefully coated with a therapeutic drug, they continue to irritate arterial tissue creating a risk of blockage, or restenosis. BVS are made with magnesium or various combinations of synthetic copolymers derived from amino acid l-tyrosine, such as polycarbonates and poly L-lactic acid (PLLA). Medical imaging studies show these bio-friendly materials hold their form reinforcing an arterial lesion for four to six months as the tissue repairs itself, and then they begin to degrade until absorbed by the body and almost completely disappear at 24 months.

Abbott Vascular's advanced bioresorbable vascular scaffold

Christoph Naber MD, from St. Elisabeth Hospital in Essen, Germany, said he has personally implanted 200 of the new scaffolds and colleagues at his hospital have used more than 400 each. 'This is the first generation and we need to watch for any safety concerns, anything to show that this therapy is a problem,' he said. 'But, so far, with something like 10,000 devices implanted, there have been no signals of concern.'

A leading cardiac interventionalist, Dr Naber was a panelist for the Great Debate during EuroPCR and spoke for other panelists when he concluded, 'the principle to treat and leave nothing behind is the way to go'. Co-chair of the Great Debate, Michael Haude, from the Städtische Kliniken in Neuss, Germany, noted that BVS are now moving out of simple lesions with more advanced designs. He also introduced a note of caution saying that, while safety data is proving to be 'very good, we need long-term data to show these scaffolds have a superiority to the established standard of care, which remains new generation drug-eluting states (DES)'.

Doctors Naber and Haude both agreed with a conclusion during the Great Debate that DES will continue to be the predominant stent used, but that in 10 years it will be replaced by BVS as the standard of care. 'Yes we all agreed with that in the discussion to be polite,' Dr Naber told *European Hospital*, 'but internally at my hospital, everyone believes it will be more like five years.'

Bioresorbable scaffolds are being developed by all major players, with Abbott Vascular the most advanced, but followed by major competitors Medtronic and Boston Scientific. Smaller companies introducing more novel devices include Kyoto Medical Planning (Japan), Biotronik (Germany), Elixir Medical (USA), Reva Medical (USA), Arterial Remodelling Technologies (France), Amaranth Medical (USA), OrbusNeich (Hong Kong), Huaan Biotechnology Group (Laiwu, China), and Xenogenics/MultiCell Technologies (USA).

Healing hearts 2: Stem cell cocktails

Nothing new has been invented in heart failure in the last 15 years, according to Christian Homsy, CEO of Belgian-based Cardio3 Biosciences. This explains the excitement surrounding an emerging treatment among cardiologists, patients and investors.

The innovative technique for turning stem cells into cardiac muscle was developed at the celebrated Mayo Clinic in the United States.

One of the first cardiologists to get caught up in the excitement over this new approach was William Wijns MD, from the Cardiovascular Centre Aalst in Belgium. In 2007, Wijns and Homsy founded Cardio3 BioSciences in order to license the technology and bring this American innovation to patients suffering chronic heart failure. 'Dr Wijns is totally out of his element when it comes to questions about the market potential of this new procedure,' Christian Homsy explained. 'He's 120% dedicated to treating patients and the expertise he brings is knowing the outcome needed for patients and how to test it with patients.'

However, investors in Life Sciences businesses, which are very much focused on market potential, also caught the excitement. Homsy was able to gather €60 million in several financing rounds to bring the science out of the laboratory and into the long process of experiments and clinical trials.

Following a successful Phase II study with 45 patients, the company boldly went public in July 2013, raising a further €23 million on the NYSE Euronext stock exchanges in Brussels and Paris. Homsy said this fresh funding will allow Cardio3 to complete its European Phase III study, the final step in an intensive clinical development programme before seeking the regulatory approval that will finally make the treatment available to patients.

The treatment is only available in Europe. With successful results in the Phase III clinical trial, Cardio3 will be able to discuss with the USA's Food & Drug Administration (FDA) the start of a clinical trial there. Millions of people are waiting, some who may not live long enough to see this therapy arrive in the hospital. In Europe alone, 3.6 million people are diagnosed each year with HF, a very serious condition in which a damaged heart cannot pump enough blood to meet the body's need. This number is expected to double over the next 10 years. One patient in three who is diagnosed with HF will die within the year.

Called C-Cure, the new therapy is a three-step process. First, cells are harvested from the patient's bone marrow in the hip, using a catheter and performed using local anaesthesia. These cells are sent to Cardio3's processing centre where they are re-engineered with the 'cocktail' invented at the Mayo Clinic. Called Cardiopoiesis, the reprogramming process takes 30 days, teaching the new cardiac progenitor cells to behave like those cells that have been lost to heart disease. This highly personalised batch of cells is frozen and sent to the hospital where it can be injected through a minimally invasive procedure into the patient's heart muscle using a specialised catheter developed by Cardio3.

'We believe C-Cure has the potential to go beyond symptom relief towards healing heart tissue and could mark a significant step forward in treatment for heart failure patients, Homsy says in the cautious language required before the results of the Phase III trial are known.

In June 2013, the first patients were enrolled in the CHART-1 trial (Congestive Heart failure Cardiopoietic Regenerative Therapy). This is a prospective, multi-centre, randomised, blinded study, comparing treatment with C-Cure to a sham treatment. More than 240 patients with chronic advanced HF of ischemic origin will be enrolled. The primary endpoint of the trial is a composite result at nine months after treatment that includes mortality, morbidity, the Six Minute Walk Test, quality of life, and left ventricular structure and function.

The result from the Phase II trial that generated the excitement behind C-Cure, said Homsy, is that the heart became smaller for treated patients. In chronic HF, the heart progressively becomes larger to keep up with the body's needs until finally it fails. Among patients in the Phase II trial, 'it was as if the heart had regressed back to an earlier stage in the disease history, at a moment when the patients were less sick than they are now,' he explained. In terms of heart function, the heart's ability to pump blood, measured as the left ventricular ejection fraction, improved by 25% after six months. The improvement in a patient's physical capability was an increase of 77 metres during the Six Minute Walk Test.'This progress has not been seen before in a chronic disease,' said Homsy. 'We have results out to two years now and this can be considered long-term results for patients who had a 12-month life expectancy. It is not a guarantee of success for the CHART-1 trial, but it points in the right direction.'

Christian Homsy, CEO of Cardio3 Biosciences

William Wijns MD, Cardiovascular Center Aalst

'What is important here, what makes this unique are these results combined with the physical remodelling of the heart,' he said.

The name of the product, C-CURE derives from the full description of Cardiopoietic stem Cell therapy in heart failURE and, despite its hopeful sound, Homsy cautioned that the therapy it is not a cure. 'Cure means you become healthy again, that your heart has been reconstructed in its entirety,' he said. Small animal trials showed that C-Cure could do that, but bringing the treatment into humans is a completely different case. 'Heart failure in humans is a complex disease,' he said. 'We have shown that C-Cure can regress the disease by remodelling the heart. But to heal a patient completely? We are not there yet.'

EUROPEAN HOSPITAL
EUROPEAN HOSPITAL Publisher,
Theodor-Althoff-Str. 45,
45133 Essen, Germany
Phone: +49 (0)201 87 126 850
Fax: +49 (0)201 87 126 864
E-mail: info@european-hospital.com
www.european-hospital.com

Editor-in-Chief: Brenda Marsh
Art Director: Olaf Skrober
Managing Editor: Brigitte Dinkloh
Senior Writers: John Brosky, Michael Reiter
Executive Director: Daniela Zimmermann

Correspondents
Austria: Michael Kraßnitzer, Christian Pruszinsky. **France:** Annick Chapoy, Jane MacDougall.**Germany:** Anja Behringer, Annette Bus, Bettina Döbereiner, Jennifer Eletr, Jörg Raach, Walter Schäfer, Susanne Werner, Holger Zorn. **Great Britain:** Brenda Marsh, Mark Nicholls.
Malta: Moira Mizzi. **Poland:** Pjotr Szoblik. **Russia:** Olga Ostrovskaya, Alla Astachova. **Spain:** Eduardo de la Sota.
Switzerland: Babara Steinberg, Dr. André Weissen. **USA:** Kerry Heacox, i.t. Communications, Jacquie Michels

UK editorial address
55 Wey Meadows,Weybridge, Surrey KT13 8XY
Subscriptions
Janka Hoppe, European Hospital, Theodor-Althoff-Str. 45, 45133 Essen, Germany
Subscription rate
6 issues: 42 Euro, Single copy: 7 Euro.
Send order and cheque to:
European Hospital Subscription Dept
Printed by: WVD, Mörfelden-Walldorf, Germany
Publication frequency: bi-monthly
European Hospital ISSN 0942-9085

Representatives
China & Hongkong: Gavin Hua, Sun China Media Co, Ltd, Room 802, 15th Building, BinJiang Residential Quarter, Dongyuan Road, Futian District, Shenzhen, Guangdong, China, Code: 518031
Phone: +86-0755-81 324 036
E-Mail: gh@european-hospital.com
Germany, Austria, Switzerland:
Ralf Mateblowski, Hintergasse 1, 55234 Hangen-Weisheim, Germany
Phone: +49 6735 912 993
E-Mail: rm@european-hospital.com
France, Italy, Spain: Eric Jund, 2264 Chemin de Sainte Colombe, 06140 Vence, France Phone: +33 493 58 77 43
E-Mail: ej@european-hospital.com
GB, Scandinavia, BeNeLux: Simon Kramer, Willem Alexander Plantsoen 25, 2991 NA Barendrecht, The Netherlands
Phone/Fax: +31 180 6200 20
E-Mail: sk@european-hospital.com
Israel: Hannah Wizer, International Media Dep. of El-Ron Adv. & PR Co., Ltd., 7, Leteris street, Tel-Aviv 64166, Israel
Phone: +972-3-6 955 367
E-Mail: hw@european-hospital.com
South Korea: CH Park, MCI, Room 103-1011, Brown Stone, 1330, Baekseok-dong, Ilsan-Ku, Goyang-si, Gyunggi-do, Korea 410-360
Phone: +82 2 730 1234
E-Mail: chp@european-hospital.com
USA & Canada:
Hanna Politis, Media International, 8508 Plum Creek Drive, Gaitherburg, MD 20882, USA
Tel: +1 301 869 66 10 E-Mail: hp@european-hospital.com