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CARDIOLOGY

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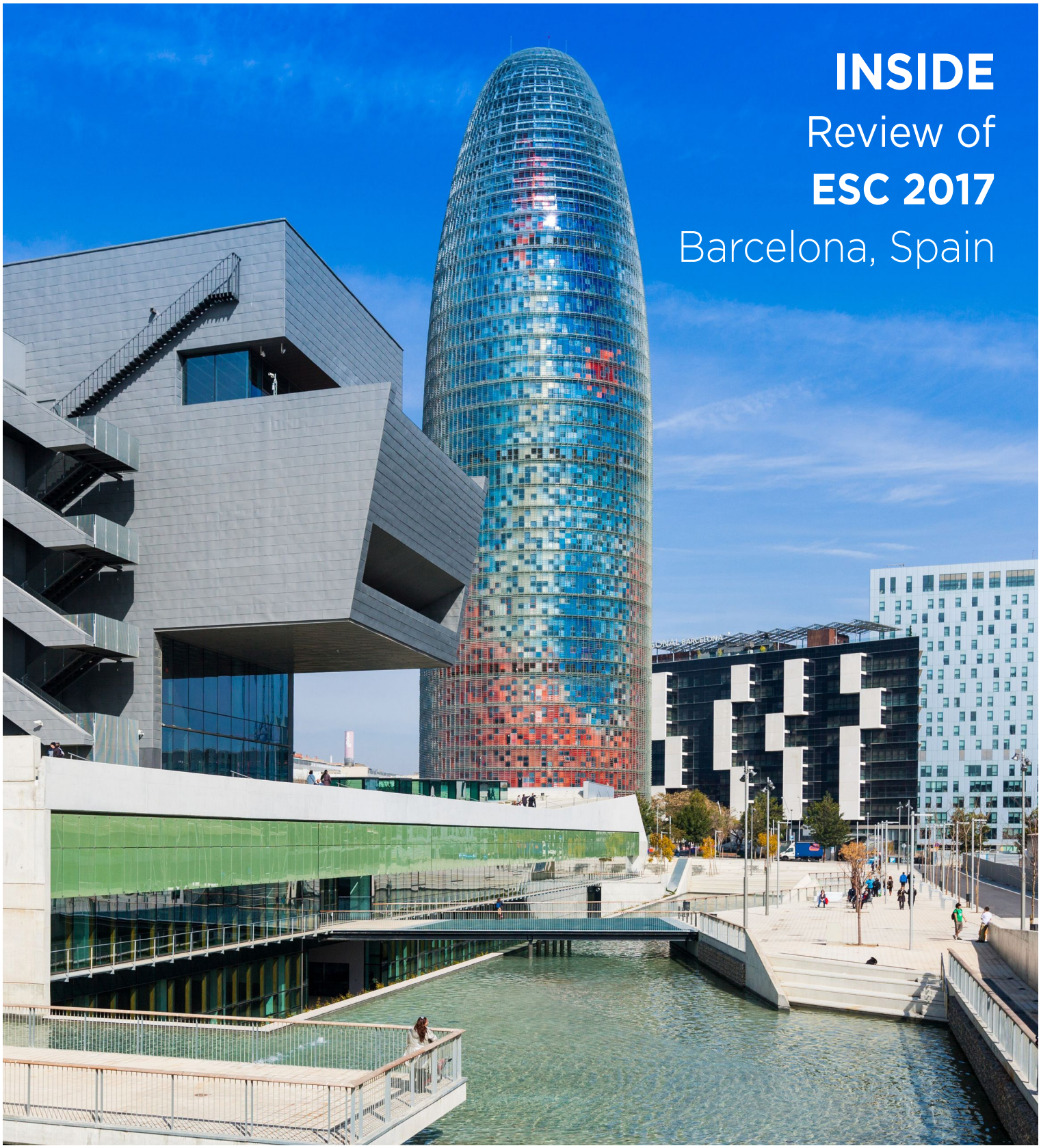

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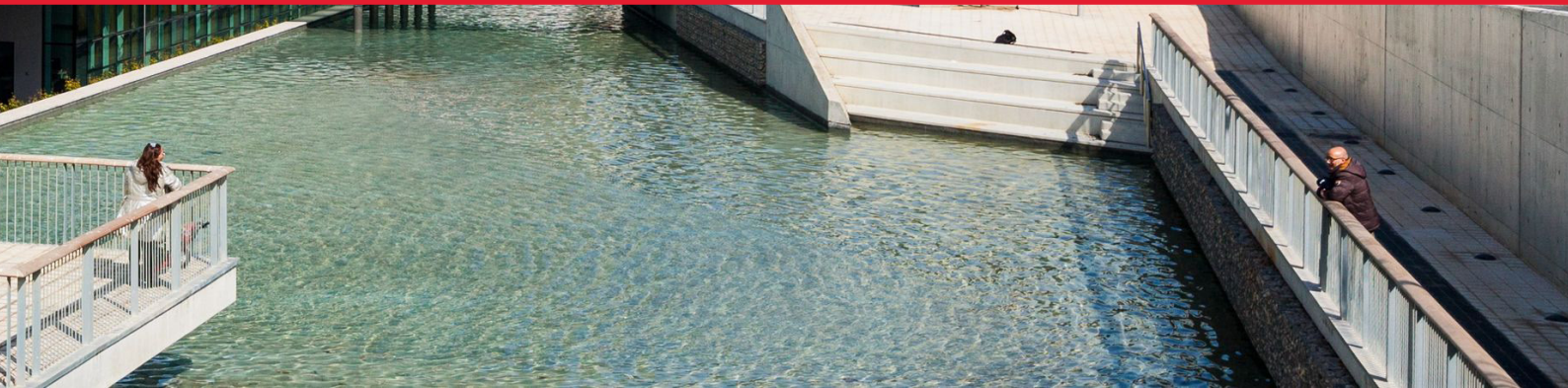

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CARDIOLOGY 5.1
OCTOBER 2017

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Welcome

Greetings and welcome to the 2017 edition of *EMJ Cardiology*. Inside, you will find copious amounts of exciting, new research, including some fantastic highlights from this year's European Society of Cardiology (ESC) annual congress. This event is the world's largest for this therapeutic area and featured >4,500 abstracts provided by leading researchers from around the world. With a variety of peer-reviewed articles, abstracts, and congress highlights enclosed, *EMJ Cardiology 5.1* has something to offer everyone.

> "With researchers striving to improve knowledge surrounding the cardiology field, new insights are constantly being reported. *EMJ Cardiology 5.1* promises you some fascinating, novel examples of exactly that."

The ESC congress 2017, which took place in Barcelona, Spain, had >31,000 people attend throughout the 5-day event. The Congress Review section of this eJournal gives you an overview of some of the intriguing advances in cardiology medicine reported at the event, from the latest results of clinical trials, to a significant insight into open heart surgery. We also bring to you comprehensive interviews with numerous cardiology experts, all highly experienced members of our Editorial Board, who have shared their opinions and experiences from the field. On top of this, you will also find several abstracts by authors describing their recent research findings following their abstract presentations at the ESC congress 2017.

With researchers striving to improve knowledge surrounding the cardiology field, new insights are constantly being reported. *EMJ Cardiology 5.1* promises you some fascinating, novel examples of exactly that. One such article, by Goel et al., provides an extensive review of the advances in the use of bioresorbable coronary scaffolds. Although originally aimed at overcoming the complications associated with traditional stents, bioresorbable coronary scaffolds possess their own difficulties. Goel et al. expand on these, as well as discussing what lies ahead for bioresorbable coronary scaffold use.

For those of you with a particular interest in molecular biology, Luyten and Schoenberger have provided a report that emphasises the relevance of molecular imaging in cardiac disease diagnosis and management. With the ultimate aim of improving patient care, the authors present extensive evidence supporting the need for molecular imaging to further our growing mastery of the human heart.

With all of this and more, we truly hope that you enjoy this year's edition of *EMJ Cardiology* and come away from your reading feeling refreshed in the knowledge that cardiology therapeutics are progressing every day. We are all counting the days until next year's ESC congress in the picturesque city of Munich, Germany, where we eagerly anticipate further inevitable breakthroughs in this fascinating therapeutic area.

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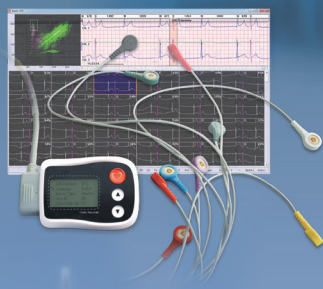

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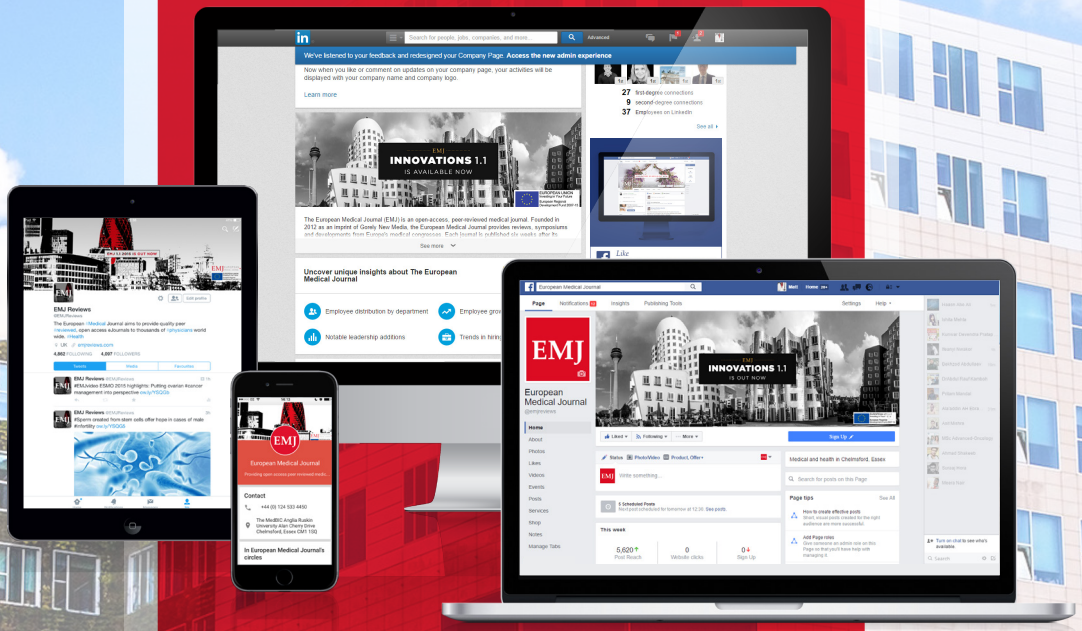

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Foreword

Dr Çetin Erol

Ankara University, Turkey

Dear Friends and Colleagues,

It is with great pleasure that I present to you the latest edition of *EMJ Cardiology*, including a compilation of expertly written peer-reviewed articles detailing the very latest advances in this exciting field. Also featured is an independent summary of the European Society of Cardiology (ESC) congress 2017, which I am sure some of you were lucky enough to attend and to take advantage of the fantastic networking opportunities on offer with cardiologists from across the world.

This year held in Barcelona, Spain, the ESC congress 2017 featured a complex scientific programme with an abundance of symposia, oral presentations, and expert sessions for all to enjoy. The Congress Review section of this eJournal contains not only an account of some of the ground-breaking news revealed at the congress, but also a hand-picked selection of the original research on show, summarised by the presenters themselves.

I would also like to turn your attention to the collection of Editorial Board interviews within *EMJ Cardiology 5.1.* This is an inspiring section of the journal in which you can learn the thoughts and opinions of some of my colleagues, including what enticed them to pursue a career in cardiology, as well as their hopes for the field in the future, which I am sure you will all be able to relate to.

This new edition also contains a compendium of insightful, high-quality articles based on a variety of hot topics from the field of cardiology. Simpson et al. have provided a comprehensive review of premature atrial and ventricular contractions, highlighting to the physician when these ectopic beats warrant significant treatment. Also on the theme of treatment, Nappi et al. have described the current understanding of the pathophysiology of ischaemic mitral valve prolapse with a focus on the implications for surgical treatment. For those of you with an interest in the role of inflammation in cardiology disorders, Kurup and Patel have summarised the importance of neutrophils in acute coronary syndrome, specifically the inflammasome-mediated release of inflammatory cytokines from neutrophils in disorders such as myocardial ischaemia and atherosclerosis. Lastly, it is my pleasure to direct you to our Editor's Pick for this edition, namely the paper penned by Krone. This fascinating article reviews the vital role of collaboration between cardiologists and oncologists in the protection of the heart in cancer patients. Understanding the impact of cancer regimens on the heart and developing methods to prevent heart damage will ultimately ensure a better quality of life for patients.

With something for everyone to enjoy, I am certain the material within *EMJ Cardiology 5.1* will be a worthwhile read and provoke engaging discussions amongst friends and colleagues.

Kind regards,

Çetin Erol

İbn-i Sina Hospital, Faculty of Medicine, Department of Cardiology, Ankara University, Ankara, Turkey.

EMJ EUROPEAN MEDICAL JOURNAL

EMJ Interventional Cardiology 5.1 2017 Available Now

Includes a selection of the latest abstract reviews, articles, interviews, and a full review of EuroPCR 2017.

Featured inside:

CONGRESS REVIEW

Review of the Annual Meeting of the EuroPCR Congress, held in Paris, France, 16th–19th May 2017

INTERVIEWS

With *EMJ Interventional Cardiology* Editorial Board

ABSTRACT REVIEWS

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Editor's Pick: Current Status of Fully Automated Software with Three-Dimensional Echocardiography for the Quantification of Left Ventricular Function

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Stent or Scaffold Thrombosis: Past, Current, and Future Perspectives

- Hideki Wada et al.

Repair of Congenital Heart Defects: Essentials for the Adult Cardiologist

- Andrew H. Constantine et al.

Is There an Optimal Duration of Dual Antiplatelet Therapy After Drug-Eluting Stent Implantation?

- Bernard Cheung et al.

Drug-Coated Balloons and Coronary Bifurcation Lesions

- Alessandro Durante, Pietro Leonida Laforgia

Percutaneous Coronary Intervention for Chronic Total Occlusion, a Review of Indications, Techniques, and Complications

- Maria-Cruz Ferrer-Gracia

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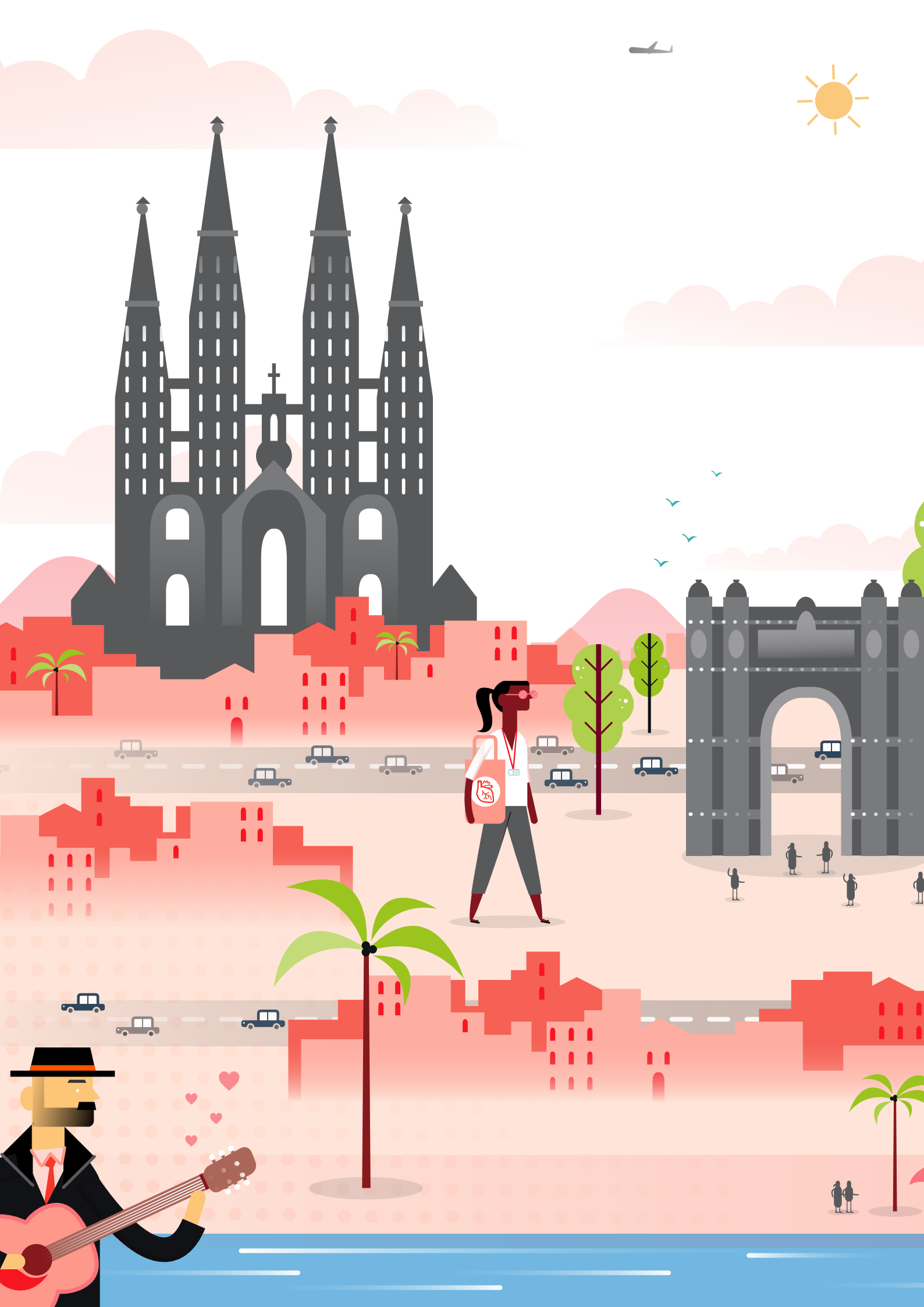


ESC ANNUAL CONGRESS 2017

FIRA BARCELONA
BARCELONA, SPAIN
26TH–30TH AUGUST 2017

Welcome to the European Medical Journal review of the Annual Meeting of the European Society of Cardiology

Citation: EMJ Cardiol. 2017;5[1]:12-27. Congress Review.

The glorious city of Barcelona, Spain was resplendent in the summer sun this August, as cardiologists from all over the world flocked to take part in the European Society of Cardiology (ESC) annual meeting. Bursting with history and culture, the Catalan capital was the ideal location for a congress that promised to carry the field of cardiology forward into the digital age. However, in order to look to the future, one must first understand the past, and this year's congress was deeply intertwined with the discipline's roots, honouring the 40th anniversary of Andreas Grüntzig's pioneering balloon angioplasty. With millions of angioplasty procedures now performed every year, this landmark event in 1977 changed the face of cardiology forever, catapulting the discipline into the future. Today, with the rapidly evolving world of technology, this year's ESC congress sought to modernise cardiology and once again bring it to the forefront of medical innovation, as Grüntzig did almost half a century ago.

The opening ceremony was an excellent introduction to the event, with its focus on education, innovation, and collaboration. Remarking on the attendance, the ESC President, Prof Jeroen Bax, said: "Nowhere else in the world can you find cardiovascular professionals from >140 countries coming together like this. This is unique. Yes, we are called the ESC, but this is a profoundly global organisation. From our very beginning, 67 years ago, we recognised that our diversity is our strength. And that philosophy has never been more important than it is today." Prof Bax then introduced Prof Eric Topol, Scripps Research Institute, San Diego, California, USA, to discuss cardiology in the digital age. Prof Topol spoke at length about modernising many of the seemingly archaic aspects of cardiology, for example, the stethoscope, which has been largely unchanged for >200 years. He spoke of the rising role of technology, from big data to neural networks and artificial intelligence, but noted the paramount importance of retaining human compassion in a digital world. The ceremony concluded by honouring the field's best and brightest for their impressive career achievements. Dr Anthony DeMaria (USA) and Prof William Wijns (Belgium) were presented with ESC gold medals for their contributions to cardiology and, in an emotional presentation, Prof Bax honoured Sir Magdi Yacoub for his lifetime of humanitarian work, saying: "Thank

you for all the good work you are doing for this world. I don't know anybody who is doing so much good work like you."

The congress was attended by >32,000 people from >140 countries, breaking the previous year's record and making it the largest cardiology event in the world. A further record was broken with regard to the number of abstracts submitted, which totalled around 11,000, of which >4,500 were selected for presentation. The meeting's programme was incredibly vast, featuring a huge range of symposia, late breaking clinical trials, keynote lectures, demonstrations, and 'Live in the Box' sessions, where clinical cases and interventional procedures were broadcast directly to the congress audience. In keeping with its theme of cardiology in the digital age, the congress also featured a corresponding mobile app, which allowed visitors to plan their itinerary in detail as well as to interact directly with speakers via a live voting system.

> "...we are called the ESC, but this is a profoundly global organisation. From our very beginning, 67 years ago, we recognised that our diversity is our strength. And that philosophy has never been more important than it is today."

With so much research on offer, it surely comes as no surprise that our following Congress Review section is packed with highlights that will be of interest to a huge range of medical professionals. We include a selection of abstract summaries, written by the presenters themselves, as well as bringing you the results from the most important clinical trials, including the revolutionary, paradigm-shifting CANTOS trial on treating inflammation in patients with cardiovascular disease.

Whether you attended this incredible meeting and wish to revisit the material, or are coming to this review with fresh eyes, we hope that it provides you with all the information needed to spark lively debate amongst colleagues and guide future research. We hope you enjoy reading and we look forward to seeing you at next year's ESC congress, held in Munich, Germany.

Long-Awaited Results of CANTOS Trial Revealed

PIVOTAL research has revealed the potential of inflammation-reducing drugs in drastically lowering the risk of both cardiovascular disease and lung cancer. Described in a ESC press release dated 27th August 2017, results of the CANTOS trial showed that lowering inflammation, independent of cholesterol, reduced cardiovascular risk, a vital finding for the 50% of heart attack patients who do not experience high cholesterol.

> “...the use of inflammation-reducing drugs was described as the beginning of a new era of preventative cardiology.”

Principal investigator, Dr Paul M. Ridker, Center for Cardiovascular Disease Prevention, Brigham and Women’s Hospital, Boston, Massachusetts, USA and his team focussed their attention on the human monoclonal antibody, canakinumab, which suppresses inflammation by neutralising interleukin-1β signalling. The study involved patients who had experienced a heart attack in the past and had a high degree of inflammation, indicated by elevated levels of high sensitivity C-reactive protein. The 10,061 participants were treated with aggressive standard care and were additionally randomised to subcutaneous canakinumab (50, 150, or 300 mg) or placebo treatment, once every 3 months.

Following ≤4 years of monitoring, the trial investigators observed that patients who were given 150 or 300 mg doses of canakinumab experienced a reduced risk of the primary endpoint by 15% (hazard ratio [HR]: 0.85; 95% confidence interval [CI]: 0.74–0.98; p=0.021) and 14% (HR: 0.86; 95% CI: 0.75–0.99; p=0.031), respectively, defined as the first occurrence of non-fatal myocardial infarction, non-fatal stroke, or cardiovascular death. The secondary endpoint was also the first occurrence of any of the above as well as the requirement of hospitalisation for unstable angina needing urgent revascularisation and was reduced by 17% in the 150 mg (HR: 0.83;

95% CI: 0.73–0.95; p=0.005) and 300 mg canakinumab (HR: 0.83; 95% CI: 0.72–0.94; p=0.004) groups.

After statistical analysis, the authors concluded that a significant reduction in the occurrence of primary and secondary endpoints was evident in the participants who received a 150 mg dose of canakinumab. Furthermore, exploratory analyses showed dose-dependent reductions in the rates of cancer death, particularly those due to lung cancer. Although replication of these results is required, the use of inflammation-reducing drugs was described as the beginning of a new era of preventative cardiology.

Upstream Therapies Improve Sinus Rhythm in Arterial Fibrillation Patients

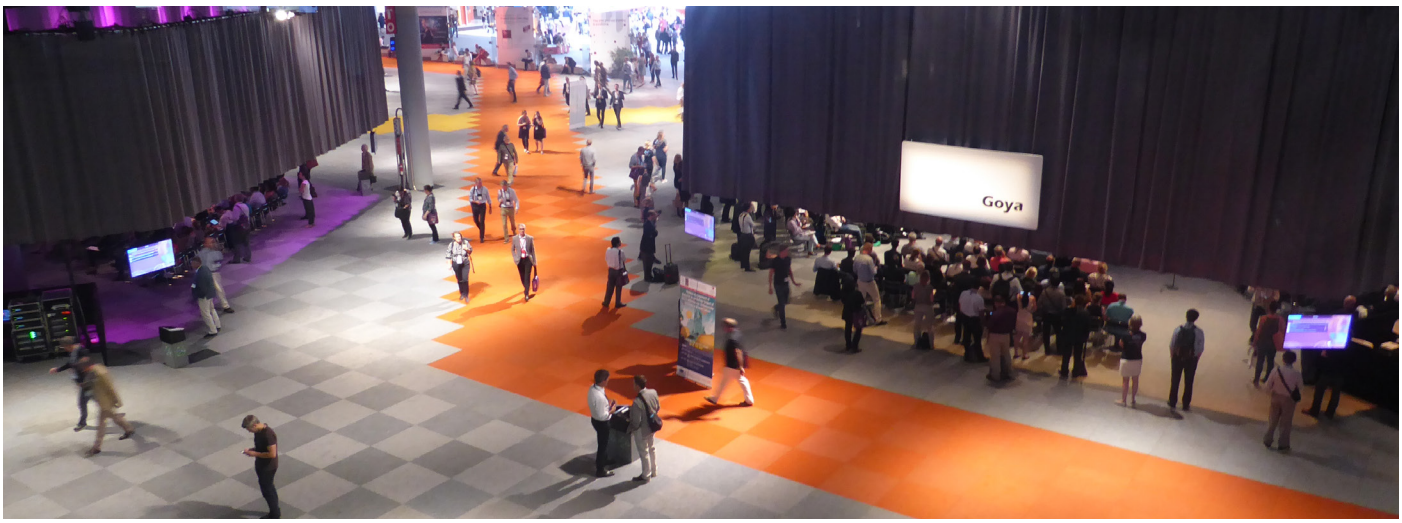
IMPLEMENTATION of four risk factor-driven upstream therapies could improve sinus rhythm in patients with atrial fibrillation (AF) and early, mild-to-moderate heart failure, according to RACE 3 trial results presented at this year's ESC congress and reported in a ESC press release dated 27th August 2017.

"AR is the most common sustained cardiac arrhythmia and affects millions of people in Europe," said principal investigator Dr Michiel Rienstra, University Medical Centre Groningen, University of Groningen, Groningen, Netherlands. Symptoms include palpitations, shortness of breath, and an impaired tolerance to exercise, and Dr Rienstra explained patients: "...have poor quality of life and are at increased risk of stroke, heart failure, or death."

Typically caused by comorbidities such as hypertension, heart failure, and obesity, AF is a progressive disease with a problematic long-term maintenance of sinus rhythm. The progression and onset of AF are caused by structural remodelling of the left atrium, and it was thought that upstream rhythm control may help prevent AF onset and progression. The RACE 3 trial was conducted to assess this hypothesis and determine whether upstream therapies were superior to conventional therapies for the maintenance of sinus rhythm.

This multicentre trial recruited 250 patients with symptomatic early persistent AF and early, mild-to-moderate heart failure. All patients received causal treatment and were subsequently split into two treatment groups, one to only receive conventional rhythm control and the other to receive rhythm control alongside four risk factor-driven upstream therapies. The upstream therapies included cardiac rehabilitation (involving physical activity, dietary restrictions, and regular counselling on drug adherence), mineralocorticoid receptor antagonists, statins, and angiotensin-converting enzyme inhibitors and/or angiotensin receptor blockers.

> "Upstream rhythm control, including meticulous treatment of risk factors and change of lifestyle, is effective, feasible, and safe in improving maintenance of sinus rhythm..."



At the 12-month follow-up, 89 of the 119 participants (75%) in the upstream therapy group presented with sinus rhythm, compared to 79 of 126 participants (63%) from the control group (p=0.021). Between the two groups, there was no difference in the number of electrical cardioversions or antiarrhythmic drug use. Dr Rienstra concluded: "Upstream rhythm control, including meticulous treatment of risk factors and change of lifestyle, is effective, feasible, and safe in improving maintenance of sinus rhythm in patients with early, short lasting AF and early, mild-to-moderate heart failure. The upstream therapies also improved treatment of cardiovascular risk factors."

Positive Results from the CASTLE-AF Trial

CATHETER ablation was found to produce improved outcomes in the treatment of left ventricular dysfunction and atrial fibrillation in the CASTLE-AF trial presented at this year's ESC congress. The results were reported in a ESC press release dated 27th August 2017 and showed that catheter ablation produced lower rates of both mortality and hospitalisation for worsening heart failure when used to treat atrial fibrillation in comparison to conventional drug treatment.

The trial in question, co-led by Prof Nassir F. Marrouche, Comprehensive Arrhythmia Research and Management (CARMA) Centre, University of Utah, Salt Lake City, Utah, USA, and Prof Johannes Brachmann, II Med. Hospital Klinikum Coburg, Coburg, Germany, enrolled 397 patients from >30 clinical centres worldwide. Patients all had symptomatic paroxysmal or persistent atrial fibrillation and heart failure with ejection fraction <35%, and each had implantable cardioverter defibrillators with Home Monitoring™ features to allow continuous observation of atrial fibrillation. The primary endpoint of the study was the composite of all-cause mortality and unplanned hospitalisation for worsening heart failure; secondary endpoints were all-cause mortality and heart failure hospitalisation.

Patients were randomised to receive radiofrequency catheter ablation or conventional drug treatment recommended by the American Heart Association (AHA) and ESC, and at a median of 37.8 months follow-up it was found that the primary endpoint was significantly lower in those receiving ablation (28.5%) compared to the control group (44.6%) (hazard ratio [HR]: 0.62; 95% confidence interval [CI]: 0.43–0.87; p=0.007). This trend continued for the secondary endpoints, with catheter ablation associated with all-cause mortality of 13.4% compared to 25.0% with conventional treatment (HR: 0.53; 95% CI: 0.32–0.86; p=0.011). Furthermore, those treated with catheter ablation had a 20.7% rate of hospitalisation due to heart failure compared with 35.9% in the conventional treatment group (HR: 0.56; 95% CI: 0.37–0.83; p=0.004).

> "This study has the potential to change the way physicians manage many patients suffering from heart failure and atrial fibrillation."

Prof Marrouche commented on the results: "We found that compared to those receiving conventional treatment, patients receiving catheter ablation were 38% less likely to experience the primary endpoint, 47% less likely to die, and 44% less likely to be hospitalised with worsening heart failure. A significant number of patients undergoing the ablation treatment were still in normal rhythm at the end of the study."

It was seen as a limitation to the study that all the patients had an implantable cardioverter defibrillator, which could have affected mortality across both groups. Regardless, Prof Marrouche was positive about the impact of the trial, and commented: "Until now, we had no evidence that ablation, arrhythmia medications, or any other treatment was superior to another in saving lives and reducing hospitalisation," adding: "This study has the potential to change the way physicians manage many patients suffering from heart failure and atrial fibrillation."

New Treatment for Patients with Peripheral Artery Disease

A REDUCTION in major adverse cardiovascular and limb events in patients with peripheral artery disease (PAD) can be achieved by adding rivaroxaban to aspirin as a therapeutic option, according to results from the COMPASS trial, as reported in a ESC press release dated 27th August 2017. Globally, PAD is believed to affect 200 million people and these individuals are at a heightened risk of heart attack, stroke, death from cardiovascular causes, and limb-threatening ischaemia. Currently the standard antithrombotic therapy used is aspirin; however, this is only moderately effective.

> "This is an important advance for patients with peripheral artery disease."

Researchers in the COMPASS trial investigated two potential therapeutic options for protection against major adverse cardiovascular and limb events in 7,470 patients with PAD of the lower extremities and carotid artery disease recruited from 33 countries (e.g. severe limb ischaemia and amputation): rivaroxaban and rivaroxaban plus aspirin. Patients in the rivaroxaban group received two daily doses of 5 mg rivaroxaban, patients in the rivaroxaban plus aspirin group were given 2.5 mg rivaroxaban twice daily and 100 mg aspirin once daily, while the aspirin group received the standard aspirin therapy of 100 mg once per day. The trial's primary endpoint was a combination of stroke, myocardial infarction, or cardiovascular death.

It was found that patients in the rivaroxaban arm had reduced major adverse limb events when compared to those in the standard aspirin therapy arm but no reduction in major adverse cardiovascular events. When cardiovascular and limb events were taken together, rivaroxaban alone was not more efficacious than aspirin. However, in the rivaroxaban plus aspirin arm, there was a 31% reduction in major adverse cardiovascular or limb events compared to the aspirin arm. This translated to a 46% reduction in limb threatening ischaemia (including amputation) and a 28% reduction in the risk of cardiovascular death, stroke, or heart attack.

Speaking about the impact of these findings, the leader of the PAD component of the COMPASS trial, Prof Sonia Anand, Department of Medicine, McMaster University, Hamilton, Canada, declared: "This is an important advance for patients with peripheral artery disease." She went on to explain: "To now have a therapy that reduces major adverse cardiovascular events and major adverse limb events by one-third is going to be a great benefit for these high-risk patients."

Blood Pressure Lowering Efficacy of Renal Denervation

BLOOD PRESSURE of uncontrolled hypertensive patients is significantly lowered following treatment with a renal denervation procedure, according to a ESC press release dated 28th August 2017. By applying the lessons learnt from the SYMPLICITY HTN-3 trial, scientists designed the SPYRAL HTN-OFF MED study to test the safety and blood pressure lowering efficacy of the multi-electrode Symplicity Spyral renal denervation system (Medtronic, Minneapolis, Minnesota, USA).

Patients were selected based on having uncontrolled hypertension, defined as a systolic blood pressure measuring 150–180 mmHg and a diastolic blood pressure >90 mmHg, as well as a 24-hour mean systolic blood pressure of 140–170 mmHg. Blood pressure was noted at baseline and participants were assigned to either a revised procedure for renal denervation treatment involving the main renal arteries and branches, or a sham procedure.

> This is particularly important as even small reductions correlate to significant reductions in death, stroke, and overall cardiovascular risk.

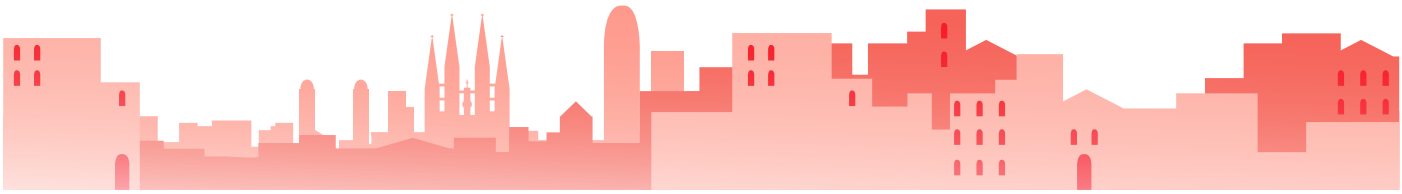
The 3-month results, presented at this year's ESC congress, described the blood pressure measurements after treatment of the first 80 patients, including 38 who received renal denervation and 42 from the sham procedure group. There was no significant reduction in the systolic and diastolic blood pressure in participants from the sham procedure arm; however, participants who received renal denervation treatment experienced a significant decline in both their systolic and diastolic blood pressures, which were lowered by 10.0 mmHg ($p<0.001$) and 5.3 mmHg ($p=0.008$), respectively. This correlation was also reflected when 24-hour ambulatory blood pressure was compared to baseline; the systolic and diastolic blood pressure of patients decreased by 5.5 mmHg ($p=0.04$) and 4.8 mmHg ($p<0.001$), respectively, following renal denervation, whereas there was no significant difference in blood pressure data from participants who underwent the sham procedure.

These statistically significant results were suggested by the authors as being due to both the new procedural approach and the inclusion of uncontrolled hypertensive patients. When summarising the results, co-principal investigator, Prof Michael Boehm, University of Saarland, Homburg/Saar, Germany, commented: "This is particularly important as even small reductions correlate to significant reductions in death, stroke, and overall cardiovascular risk."

Sildenafil Worsens Clinical Scores in Residual Pulmonary Hypertension Patients

SILDENAFIL administration should be avoided when treating valvular heart disease patients with residual pulmonary hypertension, according to the SIOVAC trial presented in a press release from this year's ESC congress, dated 28th August 2017. With valvular disease predicted to become the next cardiac epidemic due to its strong association with age, and the rapidly ageing global population, establishing an effective treatment is essential. Repair or replacement of the dysfunctional valve is the only established treatment; however, symptoms often remain or reappear later.

"Residual pulmonary hypertension is the most important risk factor for death and disability after successful correction of the valvular lesion," commented principal investigator Dr Javier Bermejo, Hospital General Universitario Gregorio Marañon, Madrid, Spain. Pulmonary hypertension is caused by increased blood pressure in the pulmonary artery; in patients with long-standing valvular disease, it causes the high pressure in the left side of the heart to be transmitted backwards, which results in thickening of the lung vessels. Valve treatment may not result in a reversal of this process, which leads to persistent pulmonary hypertension.



It was thought that using the potent vasodilator, sildenafil, would help reduce the pulmonary hypertension pressure. Sildenafil, commonly used to treat erectile dysfunction, showed discrepant results in previous trials for pulmonary hypertension but was believed to be well tolerated. During the SIOVAC trial, 200 patients from 17 public hospitals were randomised into two groups, including one group that received 40 mg sildenafil three times daily, and a placebo group. The double-blind study set out to test the potential of sildenafil in improving long-term outcomes of patients with residual pulmonary hypertension after correction of a valvular lesion.

> “We found that in patients with residual pulmonary hypertension after successful corrected valvular heart disease, 6-month treatment with sildenafil leads to worse clinical outcomes than placebo.”

The 6-month results were unexpected; 33% of the sildenafil group had worse composite clinical scores (composite of all-cause death, hospital admission for heart failure, worsening exercise tolerance, worsening self-assessment score) than at the beginning of the trial, whereas 15% of the placebo group had worsened scores (odds ratio for improvement: 0.39; 95% confidence interval: 0.22–0.67; p<0.001). Sildenafil patients also experienced more hospital admissions, with the overall risk of requiring hospital treatment double for the sildenafil group. Three sildenafil and two placebo patients died during the trial (p=0.63). Dr Bermejo commented: “We found that in patients with residual pulmonary hypertension after successful corrected valvular heart disease, 6-month treatment with sildenafil leads to worse clinical outcomes than placebo.” He concluded: “Long-term usage of sildenafil for treating residual pulmonary hypertension in patients with valvular heart disease should be avoided.”

PRECISION Findings Supported by PRECISION-ABPM Trial Results

ADVERSE cardiovascular events, including increased blood pressure, have long been linked with the use of non-steroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen; however, until recently, data were lacking on the impact from specific drugs. In a late-breaking results presentation at this year’s ESC congress, the results from the PRECISION-ABPM trial showed that ibuprofen was associated with an increase in blood pressure and hypertension in osteoarthritis or rheumatoid arthritis patients when compared with celecoxib.

As reported in a ESC press release dated 28th August 2017, investigators enrolled 444 patients from 60 sites across the USA who had either osteoarthritis (n=408, 92%) or rheumatoid arthritis (n=36, 8%) and were either at an increased risk of, or diagnosed with, coronary artery disease. An alteration from baseline in 24-hour ambulatory blood pressure at 4-month follow-up was the primary endpoint of the prospective, double-blind, randomised, non-inferiority trial, designed to determine the effects of selective cyclooxygenase-2 inhibitor celecoxib in comparison with the non-selective NSAIDs, naproxen and ibuprofen.

> “...clinicians need to weigh the potential hazards of worsening blood pressure control when considering the use of these agents.”

Patients were randomised 1:1:1 to receive celecoxib (100–200 mg twice daily), ibuprofen (600–800 mg three times daily), or naproxen (375–500 mg twice daily) with matching placebos. Results showed that both ibuprofen and naproxen increased average systolic blood pressure by 3.7 mmHg and 1.6 mmHg, respectively, when measured over 24 hours, whereas celecoxib decreased this

measurement by 0.3 mmHg. Investigators reported a significant difference between celecoxib and ibuprofen at -3.9 mmHg (p=0.009). In addition, the team looked at how many patients developed hypertension when they previously had normal baseline blood pressure, equating to 23.2%, 19.0%, and 10.3% for ibuprofen, naproxen, and celecoxib, respectively (odds ratio: 0.39; p=0.004 for celecoxib; odds ratio: 0.49; p=0.03 for ibuprofen and naproxen).

Principal investigator Prof Frank Ruschitzka, Department of Cardiology, University Hospital, Zürich, Switzerland, commented: "PRECISION-ABPM clearly demonstrates that NSAIDs, particularly ibuprofen, may be not as safe as previously thought. Patients with osteoarthritis and arthritis should continue to consult their doctor before taking NSAIDs or coxibs and clinicians need to weigh the potential hazards of worsening blood pressure control when considering the use of these agents. Since decreasing systolic blood pressure by just 2 mmHg lowers stroke mortality by 10% and ischaemic heart disease mortality by 7%, increases in systolic blood pressure associated with NSAIDs as observed in PRECISION-ABPM should be considered clinically relevant."

Protection of the Brain in Open Heart Surgery

A SIGNIFICANT reduction in the risk of brain infarctions and stroke after heart surgery can be achieved by closing the left atrial appendage, according to the results of the LAACS study, which were presented in a ESC press release, dated 28th August 2017. It is well-known amongst cardiologists that atrial fibrillation is a common occurrence following heart surgery and that this leads to an increased risk of stroke. This is a particular issue as patients may be asymptomatic, meaning they do not undergo prophylactic oral anticoagulation treatment and therefore remain at risk of blood clotting. The lead study author, Dr Jesper Park-Hansen, Department of Cardiology, Bispebjerg/Frederiksberg University Hospital, Copenhagen, Denmark, explained why it was crucial to protect the brain, announcing: "A stroke following open heart surgery can have devastating consequences for patients and their families."

> Based on the LAACS study, it would be advisable to systematically add surgical closure of the left atrial appendage to planned open heart surgery.

As blood clots tend to develop in the left atrial appendage, it is common practice amongst some heart surgeons to protect against stroke by closing the left atrial appendage. However, this was the first study to date to provide evidence showing that closure of the left atrial appendage during open heart surgery resulted in a reduced risk of brain infarctions and stroke.

One hundred and eighty-seven patients referred for open heart surgery (coronary artery bypass grafting, valve surgery, or both) were enrolled in the study and randomised to either surgical closure of the left atrial appendage (n=101) or no closure (n=86). The study's combined primary endpoint was the incidence of transient ischaemic attack/stroke or silent cerebral infarction. This endpoint was measured at clinical follow-up or detected by magnetic resonance imaging (MRI). As well as shortly before surgery, patients also underwent MRI shortly after discharge and at ≥6-month follow-up. It was found that 16.3% of patients in the control group met the primary endpoint, compared with 5% in the left atrial appendage closure group (hazard ratio: 0.3; 95% confidence interval: 0.1–0.8; p=0.0197). Dr Park-Hansen concluded: "Based on the LAACS study, it would be advisable to systematically add surgical closure of the left atrial appendage to planned open heart surgery. Our results need to be replicated in larger cohorts that can also confirm the safety of the procedure."

Blood Pressure Control Essential in Atrial Fibrillation Patients

VARIABILITY in blood pressure can result in a major risk of adverse effects for all types of atrial fibrillation (AF) patients. Reported in a ESC press release dated 28th August 2017, analysis of a trial comparing AF treatment strategies has revealed the importance of controlling systolic blood pressure in order to reduce major bleeding and the chances of stroke in these vulnerable patients.

More specifically, researchers conducted a post-hoc analysis of the AFFIRM trial. By studying recordings of visit-to-visit variability in mean systolic blood pressure, 3,843 patients were categorised into four quartiles depending on their mean standard deviation in systolic blood pressure, which were defined as: <10.09 mmHg, 10.09–13.85 mmHg, 13.86–17.33 mmHg, and ≥17.34 mmHg for quartiles 1–4, respectively.

The team reported 149 strokes and 248 major bleeding incidences after a mean of 3.6 years of follow-up and concluded that a large range of blood pressure variability directly correlated with higher rates of these events. For example, patients in quartiles 1–4 experienced stroke rates of 2.5%, 3.0%, 3.8%, and 6.2%, respectively (p<0.001). In addition, there was a progressive increase in major bleeding rate across the quartiles, from 10.8% to 11.2%, 15.6%, then 20.8%, respectively (p<0.001). The analysis elucidated that patients in the 3rd and 4th quartiles experienced a significant increase in the risk of both stroke (hazard ratio: 1.85 and 2.33; p=0.042 and p=0.004, respectively) and major bleeding (hazard ratio: 1.92 and 2.88; p=0.009 and p<0.001, respectively), equating to higher mortality rates in these patients.

> A better effort in controlling blood pressure in the clinical follow-up is pivotal to obtain a better management of patients with AF and improvement of outcomes.

Commenting on the outcomes of this analysis, Dr Marco Proietti, Institute of Cardiovascular Sciences, University of Birmingham, Birmingham, UK, explained: "A better effort in controlling blood pressure in the clinical follow-up is pivotal to obtain a better management of patients with AF and improvement of outcomes." The study authors concluded that consistency in blood pressure control is essential in all types of AF patients, regardless of factors like age and clotting risk.

NIPPON Follow-Up Results: Shorter Dual Antiplatelet Therapy is Beneficial

A SHORT COURSE dual antiplatelet therapy (DAPT) after drug-eluting stent (DES) insertion was found to be as beneficial as a long course to patients at 3-year follow-up, according to a long-term follow-up of the NIPPON study, presented at this year's ESC congress and reported in a ESC press release dated 28th August 2017.

> "In real-world practice, it is not easy to find the balance between risks and benefits of DAPT duration, and consensus criteria for individualisation therapy have not been established."

The original NIPPON results presented at the 2016 ESC congress showed no significant difference in safety and efficacy endpoints in DES patients who were randomised to either a 6 or 18-month course of DAPT. The 3-year follow-up results focussed on 3,307 patients. There was found to be no significant difference in either efficacy or safety between those treated for 6 months versus 18 months; however, a numerically higher rate of better outcomes in the long-term DAPT group (hazard ratio: 1.53; 95% confidence interval: 0.81–2.87; p=0.17) was observed by researchers, including Prof Masato Nakamura, Division of Cardiovascular Medicine, Toho University Ohashi Medical Center, Tokyo, Japan. These results indicated that there was no benefit to patients in continuing DAPT for >6 months as there was no discernible difference between outcomes for both therapy groups.

To further understand these results, researchers conducted a subgroup analysis to evaluate if any subsets of the study population benefited from longer DAPT. It was found that in patients 70–77 years of age with diabetes or more severe coronary artery disease, the efficacy rate was 0.0% for the long-term therapy as opposed to 18.8% for those on short-term therapy. The patients "represent a high-risk population for ischaemic events who might be good candidates for prolonged DAPT," researchers concluded.

Prof Nakamura commented: "In real-world practice, it is not easy to find the balance between risks and benefits of DAPT duration, and consensus criteria for individualisation therapy have not been established." He continued: "The present findings may provide some assistance, although it is essential to obtain confirmation by further investigation." Although the results are intriguing, as Prof Nakamura stated, further research is much needed to assess whether shortening DAPT would still ensure treatment success, and if not, which subgroups would need alternative treatment lengths.

Pooled Analysis Data on Anti-Aldosterones Revealed

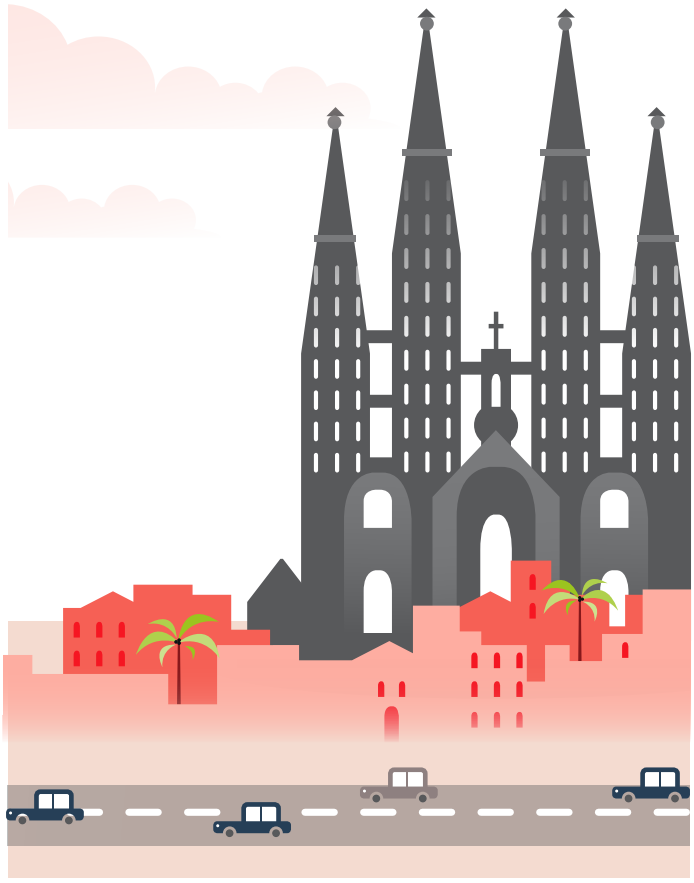
MINERALOCORTICOID receptor antagonists (MRA) could open up a new avenue of treatment for heart patients with ST-segment elevation myocardial infarction (STEMI), according to the results of a pooled data analysis reported in a ESC press release dated 28th August 2017. Investigators used data from the ALBATROSS and REMINDER trials to demonstrate improved outcomes in this patient cohort when MRA are administered alongside traditional treatment methods.

> "These findings highlight the need for more studies that are adequately sized and specifically designed to confirm the potentially major clinical benefit associated with these low-cost treatments."

The trials in question examined the effect of MRA in different cohorts: ALBATROSS considered spironolactone-based MRA in comparison with standard therapy in the treatment of mixed STEMI and non-STEMI patients but did not draw any statistically significant conclusions, while REMINDER exclusively enrolled STEMI patients and demonstrated that administering eplerenone within the first 24 hours of standard therapy reduced a clinico-biological endpoint compared with standard therapy.

Commenting on the motivation for re-examining the results of these previously published trials, Prof Farzin Beygui, Centre Hospitalier Universitaire de Caen, Caen, France, explained: "There was a suggested potential significant mortality reduction in the STEMI subgroup [of the ALBATROSS trial], that was worth investigating further." The analysis included data on a total of 2,241 patients who were randomised to receive either standard therapy with the addition of a MRA (n=1,118) or standard therapy alone (n=1,123). The results were very positive. At a median follow-up of 190 days, there had been significantly fewer deaths in the MRA-treated patient subgroup than those receiving standard therapy alone (0.4% versus 1.6%; stratified odds ratio: 0.22; 95% confidence interval: 0.07–0.65; p=0.006). This demonstrates that STEMI patients who suffer a heart attack are significantly more likely to survive if treated with this regimen than with standard therapy alone.

"The evidence from our analysis is not as strong as from a specifically designed randomised trial; however, the reduction of mortality in STEMI supports the use of MRA in this indication," Prof Beygui commented, adding: "These findings highlight the need for more studies that are adequately sized and specifically designed to confirm the potentially major clinical benefit associated with these low-cost treatments."



A Rethink of Dietary Guidelines?

A RETHINK of dietary guidelines should be undertaken, according to the results of the PURE study, which were reported on in ESC press releases dated 29th August 2017. This study used food frequency questionnaires to assess diet in 135,335 people from 18 low, middle, and high-income countries. All participants were aged 35–70 years.

One aspect of the study focussed on the association between fruit, legume, and vegetable intake with cardiovascular disease risk and death. The researchers noted that current guidelines in the USA and Europe suggest a daily intake of 400–800 g per day of these foods, which can be unaffordable for those with a low income. One of the study investigators, Dr Andrew Mente, Population Health Research Institute, McMaster University, Hamilton, Canada, commented: "Our findings indicate that optimal health benefits can be achieved with a more modest level of consumption, an approach that is likely to be much more affordable." Specific findings included that 375–500 g (equivalent to 3–4 portions) daily of fruits, vegetables, and legumes, was just as beneficial in regard to total mortality as higher servings (hazard ratio [HR]: 0.78; 95% confidence interval [CI]: 0.69–0.88).

The PURE study analysis also considered carbohydrate and fat intake. This analysis was also of great interest, with one of the study investigators, Dr Mahshid Dehghan, Population Health Research Institute, McMaster University, explaining: "Our findings do not support the current recommendation to limit total fat intake to <30% of energy and saturated fat intake to <10% of energy." In the study population, over a median follow-up of 7.4 years, there were 5,796 deaths and 4,784 major cardiovascular events. In this subgroup, it was shown the highest quintile of carbohydrate consumption as compared to the lowest quintile was associated with a 28% increase in the risk of total mortality (HR: 1.28; 95% CI: 1.12–1.46; p≤0.0001) but not cardiovascular disease risk. By comparison, the highest quartile of fat consumption was associated with a 23% reduction of total mortality risk, a 30% decrease in the risk of non-cardiovascular disease mortality, and an 18% reduced risk of stroke. Dr Dehghan suggested that those with a carbohydrate intake of >60% of energy could potentially benefit from reducing their carbohydrate intake and increasing their total fat intake.

The PURE study has offered a wealth of data from a diverse selection of societies, providing an excellent opportunity to discern the impact of diet across heterogenous settings. Further results from the study are awaited with interest.

Praise Given to ESC Guidelines on Hypertrophic Cardiomyopathy

A LARGE cross-continental study has supported following ESC recommendations for the prediction and subsequent prevention of sudden cardiac death (SCD) in hypertrophic cardiomyopathy patients, as described in a ESC press release dated 29th August 2017. Following this study, the 2014 ESC guidelines, which suggest clinicians use the HCM Risk-SCD calculator to estimate patients' 5-year risk of SCD and refer only high-risk patients to receive implantable cardioverter defibrillators (ICD), have demonstrated applicability across the world.

> "We calculated that for every 13 high-risk patients who receive an ICD as recommended by ESC guidelines, 1 patient could potentially be saved from SCD."

Designed using European hypertrophic cardiomyopathy patients only, researchers aimed to validate the application of the HCM Risk-SCD tool across a broader range of healthcare systems and medical expertise, as well as possibly different disease patterns. The HCM-EVIDENCE study evaluated 5-year SCD rates of 3,703 patients from North America, Europe, the Middle East, and Asia in order to test the accuracy of their HCM Risk-SCD scores. Study investigators reported that the scores given by the tool successfully correlated with the actual SCD rates of the patients, and the HCM Risk-SCD calculator was able to accurately differentiate between patients with low and high risks of SCD. More specifically, when the prediction tool classified patients as low-risk by having a SCD

incidence of <4% at 5 years, the actual data showed the incidence in these patients as 1.4%. Similarly, high-risk patients had a 5-year incidence of SCD of 8.9%, agreeing with the prediction of >6% incidence using the HCM Risk-SCD calculator.

Dr Constantinos O'Mahony, St. Bartholomew's Centre for Inherited Cardiovascular Disease, St Bartholomew's Hospital and the Centre for Heart Muscle Disease, Institute of Cardiovascular Science, University College London, London, UK, emphasised: "We calculated that for every 13 high-risk patients who receive an ICD as recommended by ESC guidelines, 1 patient could potentially be saved from SCD." Investigators also concluded that by following ESC guidelines and using the HCM Risk-SCD tool, unnecessary ICD implantation in low-risk patients could be avoided. Although all cases of SCD cannot be predicted, Dr O'Mahony noted: "Quantification of risk enhances the shared decision-making process."

New SPRINT Results: Redefining the Ideal Blood Pressure Target

A POST-HOC analysis of previous SPRINT results suggests that for patients with a systolic blood pressure (SBP) of ≥160 mmHg, reducing the severity of blood pressure control may be more beneficial than trying to reach a universal blood pressure target of 120 mmHg, according to a ESC press release dated 28th August 2017. One of the study's authors, Dr Tzung-Dau Wang, National Taiwan University Hospital, Taopei, Taiwan, commented: "A universal blood pressure target may not be appropriate for all, and that for some [...] the harms of aggressive treatment might outweigh the benefits."

The original SPRINT results led to much debate regarding blood pressure guidelines. A total of 9,361 patients with a SBP of ≥130 mmHg were randomly selected for intensive treatment, targeting a SBP of ≤120 mmHg, or standard treatment, with a target of <140 mmHg. Despite better overall outcomes being found in the intensive group, it was suggested that aggressively lowering blood pressure could cause risks to the patient as well as benefits to them.

Therefore, the new SPRINT post-hoc analysis evaluated the results of the 480 patients who originally had a SBP of ≥160 mmHg. Within the group, after adjustment for age and sex, those who received the aggressive treatment had almost three-times the risk of death from any cause compared to those treated less aggressively (4.9% versus 1.7%; hazard ratio: 3.12; 95% confidence interval: 1.00–9.69; p=0.012). By comparison there was no significant difference in increased risk in the intensively treated patients with a lower initial baseline SBP.

Dr Wang commented that these results may inform the original debate sparked by SPRINT. "It seems there was an intricate interaction between each individual's baseline blood pressure, their inherent cardiovascular risk, and their degree of blood pressure reduction, so we have to consider all three of these elements in managing hypertensive patients," he concluded.

"A universal blood pressure target may not be appropriate for all, and that for some [...] the harms of aggressive treatment might outweigh the benefits."

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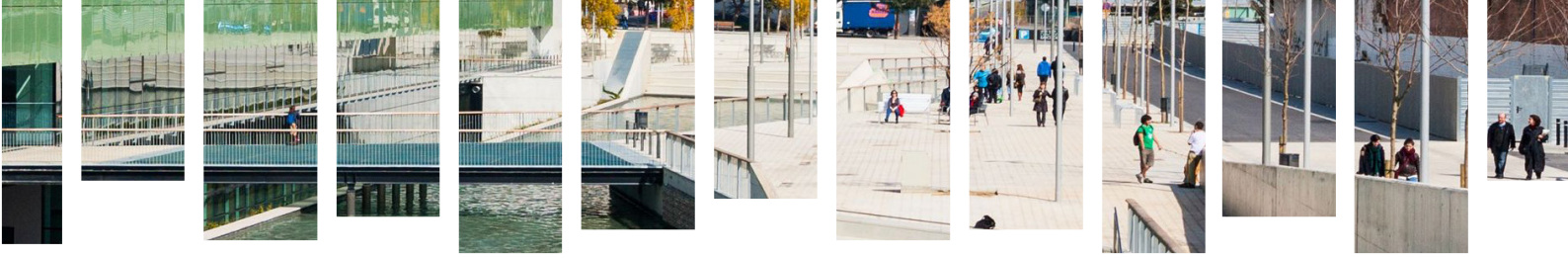


Attila Roka

Clinical Cardiac Electrophysiologist, Cardiovascular Institute of the South, Meridian, Mississippi, USA.

Q: As a specialist in cardiac electrophysiology, can you provide insight into your role within clinical practice?

A: A cardiac electrophysiologist diagnoses and treats diseases affecting the electrical system of the heart. These are most commonly arrhythmias, or irregular heartbeats, although the spectrum of conditions is wide, ranging from occasional skipped beats to heart failure and sudden cardiac arrest. We work closely with other specialists and general practitioners, as arrhythmias are often caused by diseases that originated from various heart issues or even other organs, and may have consequences affecting several other organ systems. We provide medical and interventional treatments for electrical heart problems.

Q: What enticed you to pursue a career studying this therapeutic area?

A: Clinical cardiac electrophysiology is a young and rapidly evolving field in medicine. It is exciting to experience the rapid pace of innovation and clinical utilisation of new results in our practice. The burden of arrhythmias is high in the general population and may affect people young and old, or those without conventional cardiac risk factors. It is very rewarding to be able to work with a diverse group of patients and offer effective treatments for conditions that may severely affect quality of life or lead to premature death.

Q: Upon joining the Internal Medicine Clinic, Meridian, Mississippi, USA, you were the first to perform catheter ablation. Why is this technique so vital in cardiovascular care?

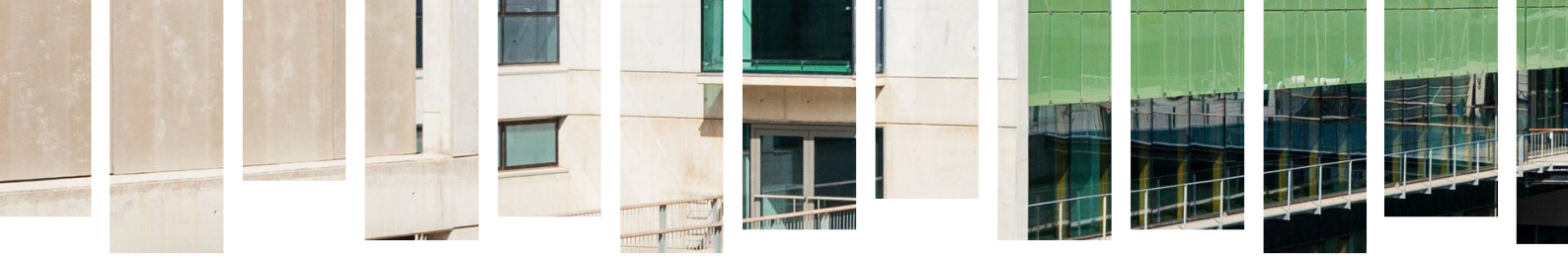
A: Some of the arrhythmias are caused by abnormal electrical tissues or signals in the heart. Catheter ablation offers a curative option for these conditions; after successful ablation, they are cured from this arrhythmia. Without this option, patients must take medications long-term, exposing them to side effects, expense, and the limited efficiency of these medications.

Q: Although the quality and accuracy of care has improved substantially over the past decade, cardiovascular disease is still the leading cause of mortality in the USA. Do you feel that more emphasis needs to be placed on funding?

A: The burden of morbidity and mortality of cardiovascular disease remains very high in the USA, despite advances in diagnosis and treatment. Most conditions are consequences of risk factors that were not addressed in time: smoking, obesity, physical inactivity, high blood pressure, cholesterol, or diabetes. Although significant efforts are being made in primary prevention, the results will not be as quick and dramatic as with some treatments, addressing acute issues. Continuous funding of population-wide screening and education will be required to maintain the trend of decreasing cardiovascular morbidity and mortality.

Q: Do you believe that public awareness regarding the signs and risk factors is lacking? In what ways could governments and the media assist with this?

A: Awareness is lacking in some important areas. Atrial fibrillation, the most common sustained heart rhythm disorder, is generally unknown to the population. It may have no symptoms at all, until some of its complications, such as stroke, occur. No population-wide screening programmes exist to address this issue. The screening methods are not very sensitive, because this arrhythmia is often intermittent and may need longer term heart rhythm monitoring for proper diagnosis, which is sometimes inconvenient for the patient and is a burden for the healthcare providers. A campaign to raise public awareness about symptoms, complications, and risk factors of atrial fibrillation, such as sleep apnoea, heart disease, diabetes,



high blood pressure, and prior stroke, may help to guide these patients to their providers before complications occur.

Q: Can you allude to any areas of research currently being undertaken in the field that you find particularly fascinating?

A: Some of the arrhythmias require interventional techniques for proper diagnosis and treatment. These are being performed with catheters, which are introduced into the heart via veins and occasionally arteries. Arrhythmias are dynamic phenomena and require careful study before treatment can be attempted; most of the time, this needs identification of a very small area of abnormal tissue or electrical pathway within the heart. Traditionally, one of the methods for navigation within the heart is fluoroscopy, which uses X-rays to identify the positions of the catheter. This has several disadvantages, of which harmful radiation and lack of physiologic data are the most severe. Electroanatomical mapping uses magnetic fields and electrical measurements to reconstruct three-dimensional anatomical data and display important electrophysiological data in real time. This allows identification of arrhythmia mechanisms in a beating heart, with millimetre accuracy, with minimally invasive techniques. The research in this field is intense and the technology is rapidly evolving, so we can treat arrhythmias more safely and effectively each year.

Q: This year's European Society of Cardiology (ESC) Congress was held in Barcelona, Spain. Why are events such as these important for the progression of the field?

A: International conferences of major medical organisations provide the opportunity for researchers and physicians to meet in person and exchange ideas. Lectures and poster presentations are excellent opportunities to discuss the results and implications of clinical research with a diverse group of international professionals. Even in the era of a highly interconnected world and widespread use of social media, conferences remain the main venue of scientific exchange.

Q: Are there any other cardiovascular events this year highlighted in your calendar? Why have these interested you so?

A: Major international conferences are also held in the field of cardiac electrophysiology. The USA-based Heart Rhythm Society (HRS) had its annual meeting in Chicago, Illinois, USA this year and the 39th Annual Scientific Sessions will be held in Boston, Massachusetts, USA in May 2018. The European Heart Rhythm Association (EHRA)'s yearly conference, Europace-Cardiostim, is going to be held in Vienna, Austria this year. Both conferences are prestigious events and have a large international audience.

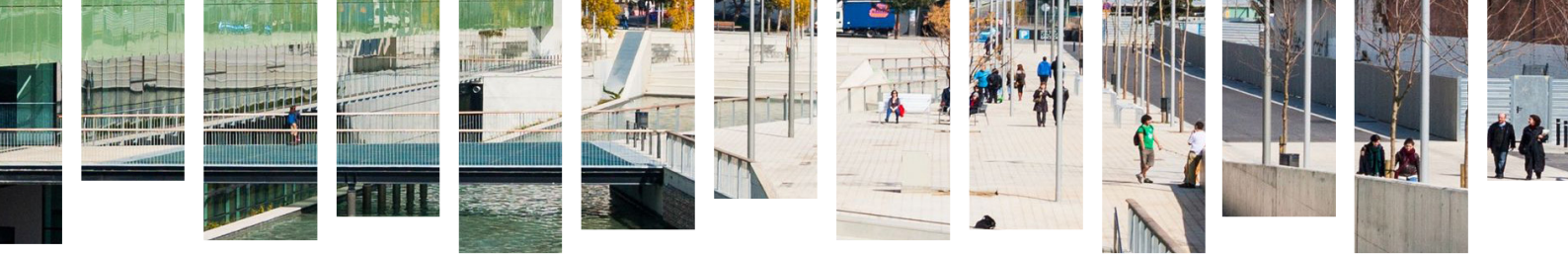
Q: Looking back on your career in retrospect, what achievement(s) are you most proud of and why?

A: Starting a new electrophysiology lab and programme in Meridian was a very rewarding experience. The burden of cardiovascular disease is high in Mississippi, and improving access to effective preventative, diagnostic, and treatment options is our priority. I am thrilled to work with a very competent team every day to accomplish these goals.

Q: Can you deliver any words of wisdom to the future generation of cardiac electrophysiologists?

A: Cardiac electrophysiology is a rapidly evolving field in medicine, addressing complex cardiac pathologies. Keep an open mind and incorporate newer, safer, and more effective technologies into your practice. This sometimes takes serious effort and may push us out of our comfort zone for some time; find a mentor or instructor until you feel confident. The concepts we deal with on a daily basis are hard to understand for non-professionals. It takes time and effort to educate patients, which is often difficult in a busy practice. However, informed patients may make better choices, and this should be a focus in good patient care, even in interventional fields of medicine.

> "I am thrilled to work with a very competent team every day to accomplish these goals."



Khai Pham Gia

Councillor and Past President, Vietnam Heart Association, Vietnam.

Q: What are your main duties and responsibilities as a Councillor of the Vietnam Heart Association? Could you tell us more about the main aims of this society?

A: My main duties and responsibilities as Councillor of the Vietnam Heart Association are:

- To review full texts and their abstracts which have been sent by their authors for Medical Review (in English and French), and participate in Bach Mai Hospital scientific reunions (bi-monthly).
- To attend Vietnam Heart Association council meetings, where people ask for my advice on the content of activities to be carried out, especially in my fields of interest.
- The Vietnam Heart Association is a reference centre for the whole country in terms of cardiovascular diseases, where diagnostic and therapeutic criteria are being communicated nationwide, and recognised international guidelines (mainly European and American) are being made known.

Q: You are renowned for aiding the development of interventional cardiology in Vietnam; what would you say have been the most influential changes in this area of cardiology during your working career?

A: I am really happy that my dedication to cardiovascular diseases in Vietnam since the 1970s has brought about substantial results; our patients nationwide are better cared for, many lives are saved, and most patients enjoy a better quality of life. I realise that Vietnam is a big nation in terms of population, but still small in terms of scientific achievements; my contributions have helped the country participate more actively towards regional and international progress in the field of cardiology.

Q: What area of interventional cardiology are you currently studying, and what do you expect to be gained from this research for furthering the field?

A: Interventional cardiology deals with coronary dilation, stenting, radiofrequency ablation of arrhythmological foci, and occlusion of intracardiac shunts. Each speciality is exciting by itself, but coronary disease is my main sphere of study, partly because I personally have been catheterised and stented; my left main coronary artery has been stented by my young colleagues, I am now feeling comfortable, and medicines are being regularly given to me. Current practices should be upgraded, with stem cells and with novel stents. An important detail should not be overlooked: the upgraded learning curve.

Q: What are some of the biggest challenges currently being faced in cardiology research?

A: Some of the biggest challenges currently being faced in cardiology research are:

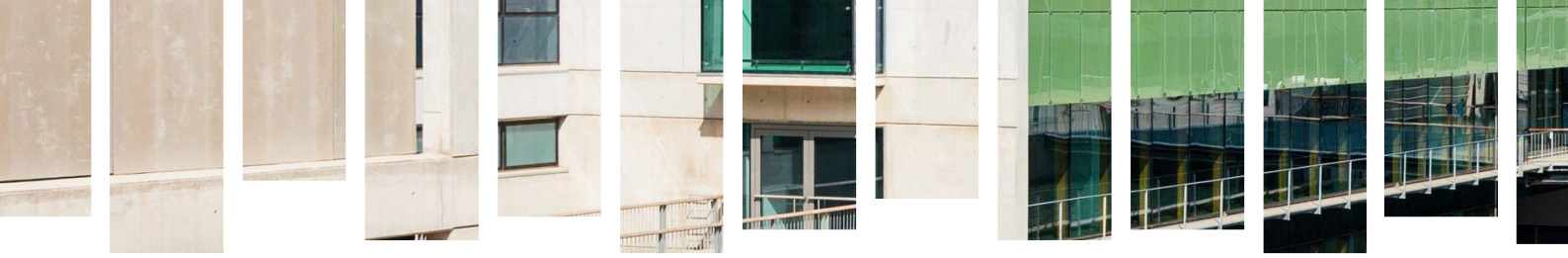
- Consensus on intervention: surgical versus stenting
- The financial problem
- Hybrid/surgery/interventional approaches
- The learning curve

Q: What do you expect to be the up-and-coming, innovative developments in interventional cardiology in the near future?

A: We are used to inviting colleagues from centres where advanced technology is being successfully applied.

Q: What would you accredit with inspiring you to pursue a career in cardiology and your subsequent specialisation in interventional cardiology?

A: Interventional cardiology could not replace all other activities in cardiology. It sits alongside clinical practice and surgery. I consider it as an important contributor to diagnosis and therapy, one leg of the tripod. But since the development of interventional cardiology, exchanges



in cardiovascular diseases at regional and international level have significantly increased and benefited both staffs and patients.

Q: Please tell us about your work in promoting public health? What changes have you seen in this area over the course of your career?

A: Through the long years of my career, I am convinced that we should not forget public health, and at the same time, we should bear responsibility if technology is only reserved for the 'happy few'. A capable network should be at the disposal of the society and teaching is quite necessary, taking full account of the realities: the number of staff, local resource possibilities, and real local health demands. I am delighted that cardiology in Hanoi, my hometown, has become appreciated for its contributions in recent years, and that this has spread throughout other parts of the country.

Q: For someone wanting to pursue a career in interventional cardiology, what main piece of advice would you give them?

A: The career of an interventionalist: they should learn the basics thoroughly before carrying out any intervention. The 'hands on' principle, that consists of having an experienced coach at your side who helps every one of your technical gestures, is essential, but this is possible only if you possess the basics.

Q: What has been the proudest achievement in your career so far?

A: I pioneered external cardiac recordings, echocardiography, and interventional cardiology in Northern Vietnam, which now reaches the whole country through the work of my young colleagues.

Q: How important is an interdisciplinary approach for interventional cardiologists?

A: An interventional cardiologist should be fully aware of that they are just one part of the tripod: clinical cardiology, surgery, and interventional cardiology. The patient should be seen as a whole, and never for the sole purpose of interventional cardiology. Everything should be pondered before the intervention, and patient follow-up is mandatory.

Andy Wai Kwong Chan

Andy Wai Kwong Chan Heart Centre, Hong Kong.

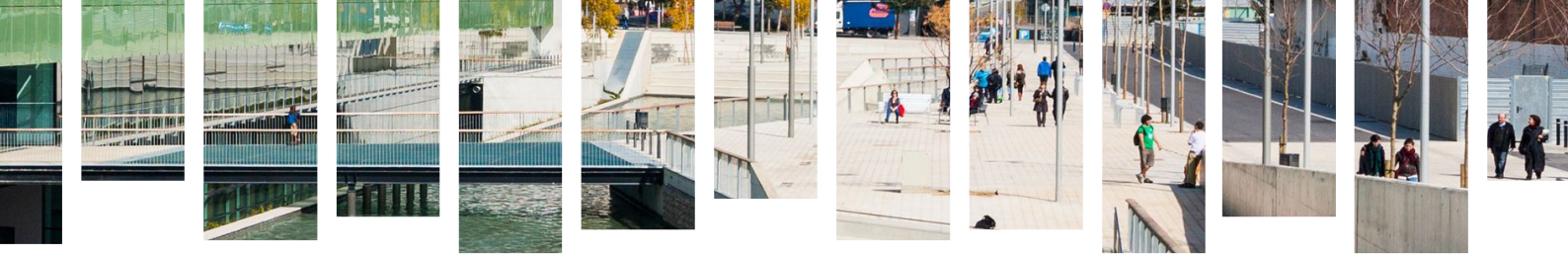
Q: What was your inspiration to set up the Andy Wai Kwong Chan Heart Centre? Tell us about the growth of this centre over time.

A: I worked in government hospitals from 1985–2007. One of the limitations of working there was cost constraints; we were not always able to apply the best evidence-based treatment option to our patients. In setting up our private heart centre, we can provide various options of evidence-based treatment to our patients, regardless of cost, which hopefully benefits the patients the most. We are grateful that we have been able to help more and more patients over the past 10 years in our heart centre.

Q: What areas of cardiology do you specialise in? What is it about these areas that you find most fulfilling?

A: I specialise in interventional cardiology. It is very challenging and advances in this field occur rapidly. The effects of treatment usually appear very quickly; for example, a patient with angina due to significant coronary artery stenosis will improve instantaneously with treatment by coronary artery stenting.

> "Prevention is always better than cure. Better primary care and more emphasis on preventative aspects are very important."



Q: This year's European Society of Cardiology (ESC) congress was held in Barcelona, Spain. Why are events such as these important for the progression of the field, and science in general?

A: They provide a very good platform for cardiologists all over the world to learn and share updated clinical trial results and knowledge. These are important for improving our patient care. They are also a good platform for us to present and share new clinical ideas and data, which, in turn, may stimulate further clinical trials. These are tremendously important for the advancement of medicine.

Q: Has there been a change in the number of patients requiring invasive cardiology techniques in recent years? Why do you think this trend has occurred?

A: Yes, the number is increasing. Improvements in invasive cardiology techniques and software are making the procedures safer and more effective, and increasing awareness of various cardiovascular diseases by patients contributes to this increase.

Q: Although the quality and accuracy of care has improved substantially over the past decade, cardiovascular disease is still the leading cause of mortality in the USA. What more do you believe could be done on a national, and international, level to reduce the burden of heart disease on health services around the world?

A: Prevention is always better than cure. Better primary care and more emphasis on preventative aspects are very important. Better education of physicians, such as adherence to disease management guidelines, is also important. Last but not least, the best evidence-based treatment option should be made available to patients.

Q: Are there any key differences in the approach Hong Kong takes to combat this problem compared with other areas, such as Europe?

A: In Hong Kong, the emphasis on primary care may not have been enough in the past. Our government emphasises that more effort will be put on primary care and prevention aspects in the near future.

Q: Are there any differences in the types or prevalence of heart conditions in the general population in Hong Kong compared to other regions of the world? If so, what are the main reasons for this?

A: Heart disease is the third leading cause of death in Hong Kong, whereas in the USA and most parts of Europe it is the first killer. Different diet, lifestyle, and ethnicities may account for the difference.

Q: In your opinion, what has been the greatest breakthrough in the field of cardiology to date and why?

A: In interventional cardiology, drug-eluting stents have been a great breakthrough in the treatment of coronary artery stenosis, as they greatly reduce the restenosis rate and are also safe. For drugs, statins were widely studied and were shown to improve the cardiovascular morbidity and mortality of patients. They really help and benefit a lot of patients.

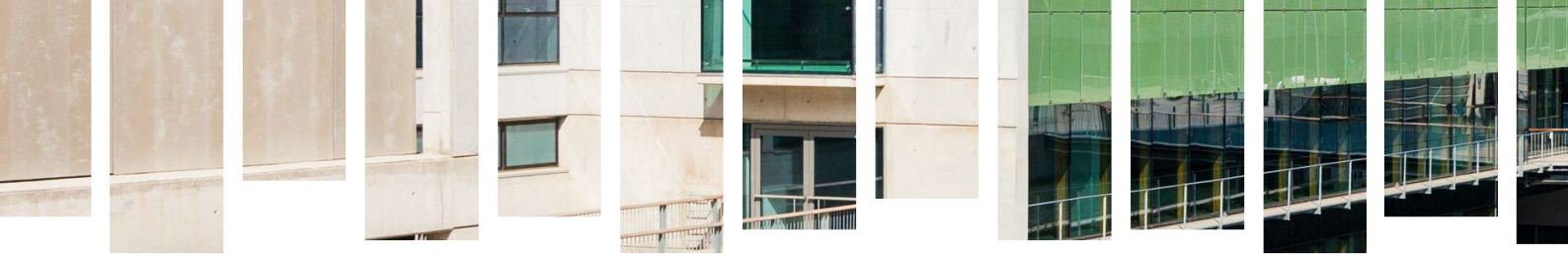
Q: Where do you see the field of cardiology progressing over the next decade? What developments are you most eager to see?

A: Cardiovascular disease, especially coronary artery disease, is still a major cause of morbidity and mortality. Better cardiovascular imaging modality, more effective drugs, as well as safer and more effective (yet simple) invasive cardiology techniques and software, are longed for.

Q: And finally, if money was no object, which cardiac disease or defect would you chose to be cured immediately, and why?

A: I would choose ischaemic heart disease, as it is the number one killer in most places.

“In interventional cardiology, drug-eluting stents have been a great breakthrough in the treatment of coronary artery stenosis, as they greatly reduce the restenosis rate and are also safe.”



Çetin Erol

İbn-i Sina Hospital, Faculty of Medicine, Department of Cardiology, Ankara University, Ankara, Turkey.

Q: As Head of the Department of Internal Medicine at Ankara University, Ankara, Turkey, could you describe your typical working day? What do you enjoy most about this role?

A: I am Head of the Cardiology Department and Head of Medical Sciences at Ankara University. I am at the department from 8 a.m. everyday. I begin with my patients who have appointments. Then, I go to visit the patients on the ward with the research fellows and specialists. Every Monday, we have seminars, and every Wednesday there are case discussions at lunch time. Usually I check the results of my patients' laboratory tests in the evening. We also have administrative meetings two or three times a week.

The aspect I enjoy most is solving the problems we have in the department.

Q: Could you tell us about what piqued your interest to pursue a career in cardiology and, in particular, invasive cardiology? What attracted you specialise in this subject?

A: When I was doing my internship at the Faculty of Medicine, I worked with a cardiologist during the summer. I really enjoyed the objectivity of cardiology, both in terms of diagnosis and treatment, so I decided to become a cardiologist. When I became a cardiologist, I was thought of as an echocardiographer first, but since then I have become an invasive cardiologist. I am very good at opening chronic total occlusions, which gives me a great deal of satisfaction and happiness.

Q: Could you tell us more about the methods and importance of invasive cardiology and how they have progressed since you started working in the field?

A: Invasive cardiology has been improving since the first balloon angioplasty performed by Grüentzig in 1977. The technique, the materials we use, the balloons, and the stents are much, much better now. Also, the implementation of invasive cardiology has expanded to the treatment of structural heart disease and valve disease.

Q: We understand that you are particularly interested in angioplasty and stent implantation. Could you describe these techniques and comment on their role in the management of patients with heart disease?

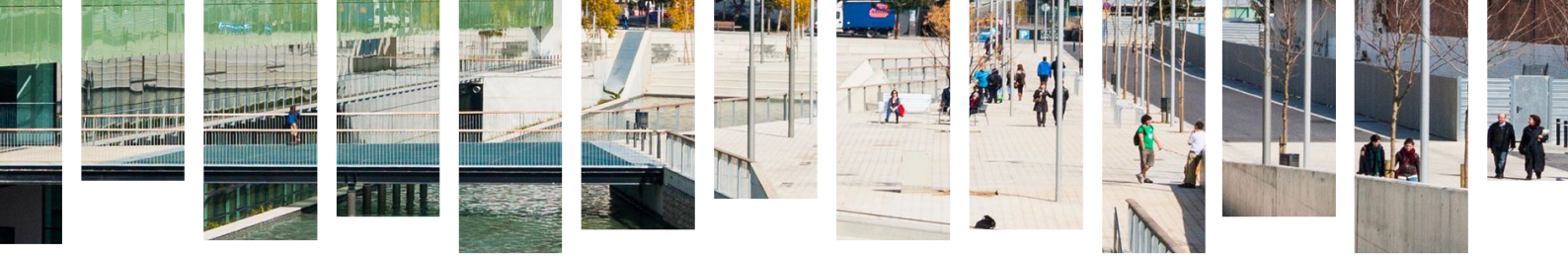
A: Angioplasty is very convenient for the patients compared to coronary bypass or other operations. Patients feel very happy and safe with this technique, because they stay in hospital for just one day, with the same or better results than they could have gotten with an operation; no pain, few complications, and the ability to go to work afterwards.

Q: Has there been a change in the number of patients requiring invasive cardiology techniques in recent years? Why do you think this trend has occurred?

A: Yes, almost all patients want to have non-invasive cardiology techniques first. If there is no chance to be able to do that, then we have to convince them to have operations. I have explained the reasons for this in the previous answer.

Q: Do you think that members of the public are aware of the risk factors of heart disease? How would you suggest that patient education could be improved?

> “Angioplasty is very convenient for the patients compared to coronary bypass or other operations. Patients feel very happy and safe with this technique...”



A: The awareness of the risk factors of heart disease is not great enough yet. It should begin during childhood and in the family, and the government, especially the Ministry of Health, should do as much as possible to increase awareness.

Q: How valuable do you consider congresses such as the European Society of Cardiology (ESC) congress to be in contributing to the progression of cardiology research? Which part of these congresses do you most look forward to?

A: The ESC is the biggest and most important cardiology congress in the world. I am so happy to be a Fellow of the ESC. This congress is a boost to all the participants in many ways. You can meet with the researchers, all well-known cardiologists, and friends during this congress to discuss all the topics you are interested in.

I most look forward to being a contributor to this congress.

> “Ageing, obesity, and increasing prevalence of diabetes mellitus are the challenges in the future. We have to fight to overcome these factors...”

Q: Are there any invasive cardiology technologies in development which particularly excite you? What do you believe the implications of these new techniques will be for the field of cardiology?

A: I think it would have to be valve implementation that particularly excites me. This technique will add much to cardiology if it is going to be available for all valves.

Q: Are there any aspects in the field of cardiology that you believe will present challenges in the future? What will motivate you to overcome these challenges?

A: Ageing, obesity, and increasing prevalence of diabetes mellitus are the challenges in the future. We have to fight to overcome these factors by focussing on preventative cardiology.

Q: In your opinion, what has been the greatest breakthrough in the field of cardiology to date and why?

A: In my opinion, the greatest breakthrough in cardiology is balloon angioplasty and the advancements in invasive cardiology generally. It was a revolution in the treatment of coronary heart disease. It is a great improvement, both scientifically and technically.

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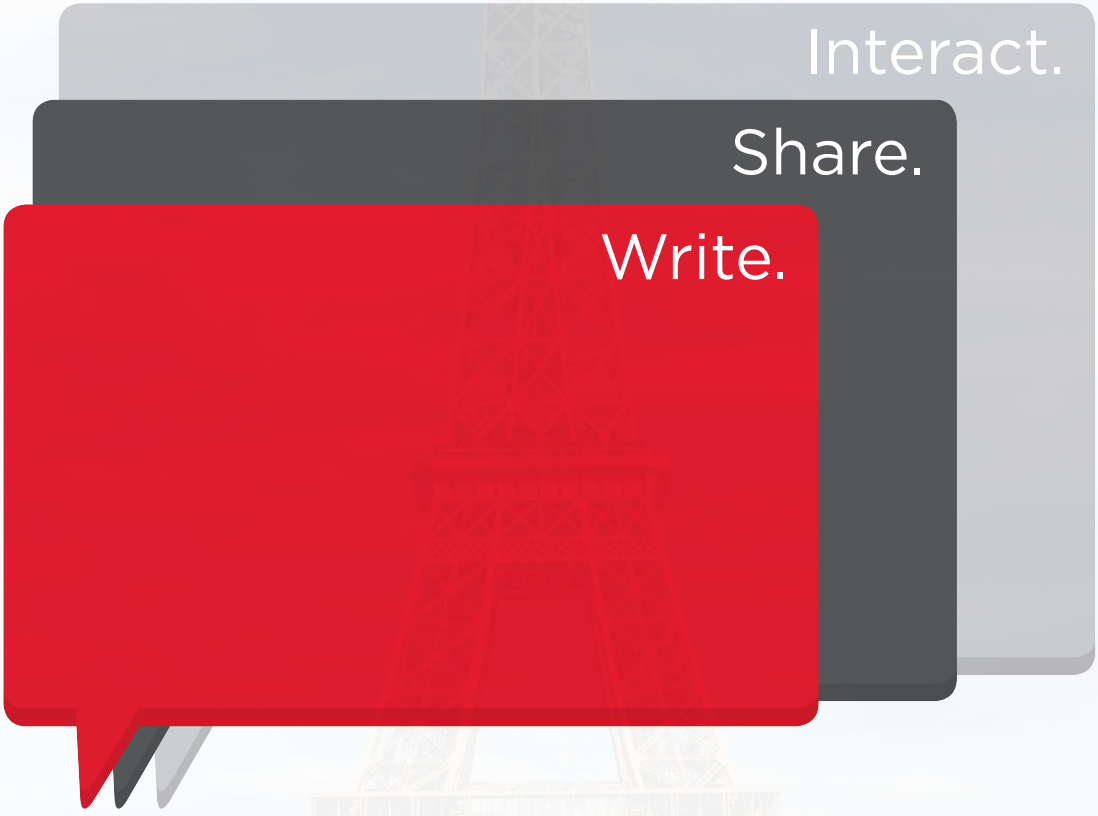

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DIFFERENCES IN THE EXPRESSION OF LECTIN-LIKE OXIDISED LOW-DENSITY LIPOPROTEIN RECEPTOR-1 IN HUMAN EPICARDIAL AND INTRAMYOCARDIAL CORONARY ARTERIES

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Citation: EMJ Cardiol. 2017;5[1]:37-38. Abstract Review No. AR1.

Keywords: Intramyocardial paradox, atherosclerosis, inflammation.

The difference in atherogenic properties of intramyocardial coronary arteries (ICA) and epicardial coronary arteries (ECA), known as the intramyocardial paradox, has been a point of interest for many investigators. Briefly, ICA and ECA covered by myocardial bridges appear to be resistant to atherosclerosis, while ECA that are in close contact to epicardial adipose tissue (EAT) appear to be more vulnerable to atherosclerosis. This effect can be explained partly by the mechanical properties of the arteries and by the close anatomical relation of the EAT and the inflammatory interaction between ECA and EAT.[1-3] The aim of the study was to test the possible involvement of lectin-like oxidised-low-density lipoprotein receptor-1 (LOX-1) on the initiation of the intramyocardial paradox. Previous studies have shown that LOX-1 is involved in the initiation of atherosclerosis, but with no reference on its expression at the ICA and ECA course.[4,5] In patients with coronary artery disease (CAD) that underwent coronary artery bypass grafting, we investigated whether there was a difference in LOX-1 expression between the intramyocardial and the epicardial parts of the coronary arteries.

METHODS

We studied 13 consecutive male patients who underwent coronary artery bypass graft surgery due to three vessel occlusive CAD at the Department of Cardiac Surgery, Euroclinic of Athens, Athens, Greece. All patients underwent total arterial myocardial revascularisation using both pedicled mammary arteries and a radial artery, with a mean of 3.6 grafts per patient. During the dissection and the grafting process, we obtained a rhomboid-shaped total wall ECA and ICA sample, with a long axis of 7–9 mm and a short axis of ~1 mm, of the vessels from each patient. We further used reverse transcription-polymerase chain reaction for *LOX-1* messenger ribonucleic acid (mRNA) and the total mRNA was directly extracted from ECA and ICA samples by the acid guanidinium-phenol-chloroform method using RNeasy kit (Qiagen, Düsseldorf, Germany). Each *LOX-1* mRNA was normalised with a band of the relative internal reference *GAPDH* mRNA. The relative intensities of the bands of interest were analysed using Gel Doc 2000 (Bio-Rad Labs, Hercules, California, USA) and expressed as a ratio to the *GAPDH* mRNA band. Statistical analysis was performed with the commercially available software (SPSS Inc., Chicago, Illinois, USA). Quantitative data were presented as rates or mean value ± standard deviation. Probability values were two-sided from the Student's t test for continuous variables. Non-continuous values were compared by a chi-square test. One-way analysis of variance was used to compare mean *LOX-1/GAPDH* between the two groups. A value of $p<0.05$ was considered significant.

RESULTS

Regarding the revascularisation process, we recorded absolute safety with zero early mortality for all patients and a mean hospital duration stay of 6.2 days. We used a mean number of 3.6 arterial grafts in each patient. *LOX-1* mRNA was expressed in all samples from both ECA and ICA, and interestingly there was a significant difference between the expression of *LOX-1* in ECA and ICA samples, as mean *LOX-1/GAPDH* ratio was 0.48±0.07 for the ECA samples compared to 0.35±0.03 for the ICA samples, p<0001. This higher expression of *LOX-1* in the extramyocardial segments of the coronary arteries in patients with CAD can contribute to the explanation of the intramyocardial paradox, although further studies are needed to clarify the extent of the effects induced by many other factors, including coronary microcirculation, shear stress, and EAT.

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MORE THAN 1,500 PROCEDURES EXPERIENCE IN NO X-RAY CATHETER ABLATION OF SUPRAVENTRICULAR ARRHYTHMIAS

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Citation: EMJ Cardiol. 2017;5[1]:38-39. Abstract Review No. AR2.

Keywords: Catheter ablation (CA), supraventricular arrhinias.

Catheter ablation (CA) with the use of fluoroscopy became a gold standard of treatment for recurring regular supraventricular tachycardias (SVT) and substrates, including atrioventricular nodal re-entrant tachycardia, accessory pathways, atrial flutter, and atrial tachycardia. The development of three-dimensional electro-anatomic mapping systems and invasive electrophysiology enabled physicians to perform CA in various SVT types with the complete elimination of fluoroscopy; this is called the no X-ray (NXR) method. This method of catheter navigation and mapping has been evaluated in various non-randomised and small randomised trials with a limited number of patients; however, there are still limited data on performing NXR CA in SVT.

Beginning in 2012, the prospective ELEKTRO registry recorded >1,500 consecutive patients (including paediatric cases) referred for NXR CA of SVT as a standard approach. They were compared to >700 patients who underwent classical mapping and navigation with the use of fluoroscopy. Procedures were performed by experts and fellows in CA. In all cases, the simplified 2-catheter protocol from femoral access was used (the left-

sided accessory pathways retrograde approach was preferred if no patent foramen ovale was found) with a 15-minute observation period after successful application. The only contraindications for the NXR approach were in cases of cardiac electronic implanted devices and planned pulmonary vein isolation for atrial fibrillation.

There was a significant decrease of procedural time in the NXR group compared to the X-ray approach. In the NXR group, <9% of procedures required conversion to the X-ray approach, with a significant reduction in fluoroscopy time compared to the X-ray approach; the mean fluoroscopy in NXR group was <1 minute. There were no major differences in acute success or complication rates in the NXR group compared to the traditional X-ray approach. Moreover, after incorporating the NXR approach in fellow training there was a minimal, but significant, increase in procedural time between the last quartile and the first quartile in the NXR group but with significant reduction of fluoroscopy time. No major complications were reported.

These data show that in a wide range of patients with SVT, NXR is safe and effective. NXR may become the gold standard for CA treatment and training for a new generation of CA experts in the near future, which may significantly reduce radiation exposure for patients as well as for physicians and allied professionals.

PREVIOUS CATHETER ABLATION: THE STRONGEST PREDICTOR OF CONVERSION IN ACUTE ATRIAL FIBRILLATION

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Disclosure: The authors have declared no conflicts of interest.
Acknowledgements: This study was supported by the German Center of Cardiovascular Research (DZHK e.V.) and the Cardiovascular Research Center Hamburg.
Citation: EMJ Cardiol. 2017;5[1]:39-41. Abstract Review No. AR3.

Keywords: Atrial fibrillation (AF), catheter ablation, recurrence, intervention, ablation therapy.

The prevalence of atrial fibrillation (AF) increases every year; some scientists project that between 2010 and 2060 the number of AF patients in the European Union (EU) aged ≥55 "will more than double."[1] In the context of population ageing, expert members of AF-SCREEN, an "international collaboration [...] formed in September 2015 to promote discussion and research" about AF prevention, recommend AF-screening for patients ≥65 years old.[2] Other studies, for instance REVEAL AF,[3] show that undetected AF is extremely frequent, especially in patients with increased risk factors. This demonstrates the importance of this topic and confronts us with the question of therapeutic control mechanisms.

Within the observational HAMBURG-AF study, we aimed to evaluate the determinants of conversion into sinus rhythm during initial stay at the emergency department of a large tertiary care centre. A total of 1,384 subjects were recruited between October 2014 and April 2017. We included patients with AF as a primary diagnosis and excluded patients with permanent AF. For those with repeated visits we used only the first visit (Figure 1). A total of 663 (71%) were classified as paroxysmal AF. Of these, 68.4% converted into sinus rhythm during the hospital stay, 29.6% due to medication (potassium/magnesium and/or beta-blocker), and 31.6% due to electric cardioversion. The remaining 7.2% converted spontaneously into sinus rhythm. The mean patient age was 75.0 (65.0–81.0) years. Of the patients, 45.7% were male, 69.0% presented with hypertension, 21.1% with coronary artery disease, and 30% with secondary

AF, such as bacterial infection. In multivariate age and sex-adjusted logistic regression analysis, previous interventional ablation therapy was strongly associated with conversion in sinus rhythm during the hospital stay (Table 1). Less surprisingly, our large, real-world study documented a strong negative predictive effect of secondary AF, as well as impaired left-ventricular ejection fraction on conversion rates.

Catheter ablation has now emerged as a key interventional therapy and is recommended for drug-refractory AF. Over recent decades, catheter ablation has established itself as a frequently applied treatment strategy for patients with AF.

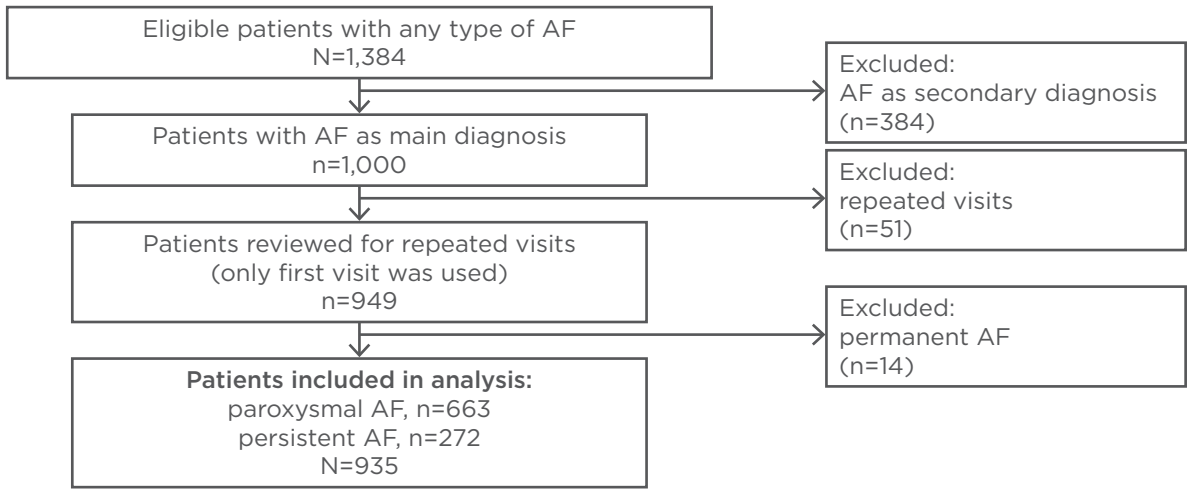

Figure 1: Criteria for inclusion in study.
AF: atrial fibrillation.

Table 1: Analysis of study results.

	OR (95% CI)	p-value	Number of events
Secondary AF	0.37 (0.26–0.51)	**<0.001**	609
Previous ablation	3.87 (2.40–6.54)	**<0.001**	609
Antiarrhythmic medication	0.89 (0.65–1.20)	0.44	609
First diagnosis of AF	0.87 (0.65–1.17)	0.36	609
Hypertension	1.11 (0.80–1.52)	0.53	609
Dyslipidaemia	1.12 (0.75–1.67)	0.59	571
Diabetes	0.69 (0.46–1.04)	0.075	610
Family history of CAD	2.57 (1.30–5.70)	**0.011**	604
CAD	0.87 (0.63–1.24)	0.43	608
Previous electric cardioversion	2.54 (1.77–3.70)	**<0.001**	608
LVEF: 46–55%	0.89 (0.50–1.63)	0.69	376
LVEF: 36–45%	0.46 (0.27–0.79)	**0.0047**	
LVEF: 1–35%	0.30 (0.16–0.54)	**<0.001**	

AF: atrial fibrillation; CAD: coronary artery disease; CI: confidence interval; LVEF: left ventricular ejection fraction; OR: odds ratio.

After successful ablation therapy, patients benefit from fewer symptoms, better heart function, a reduced risk of stroke events, and a reduced all-cause mortality. Nevertheless, multiple studies suggest high recurrence rates and guidelines nowadays recommend further ablation therapies in those with symptomatic relapses.

This first prospective real-world report on the determinants of facilitated conversion in sinus rhythm in those with recent-onset AF strongly documents the long-standing benefits of interventional catheter ablation therapy.

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EVALUATION OF SPECIFIC BIOMARKERS OF MYOCARDIAL INFLAMMATION AND REMODELLING PROCESSES AS PREDICTORS OF OUTCOME AND MORTALITY IN HIGH-RISK PATIENTS UNDERGOING PERCUTANEOUS MITRAL VALVE REPAIR (MITRACLIP®)

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Citation: EMJ Cardiol. 2017;5[1]:41-42. Abstract Review No. AR4.

Keywords: Heart failure, MitraClip®, mitral regurgitation (MR), inflammation, remodelling.

The detrimental effect of severe mitral regurgitation (MR) on morbidity and mortality is well established.[1] In patients with MR, myocardial inflammation, extracellular matrix (ECM) turnover, and collagen deposition play key roles in the development and progression of myocardial remodelling processes and fibrosis, which contribute to the progression of heart failure.[1] Percutaneous mitral valve repair (PMVR) is an interventional treatment option for patients with severe MR, whose risk from open-heart surgery is high.[2] In this approach, both mitral valve leaflets are attached with ≥1 clip (MitraClip®, Abbott, Santa Clara, California, USA), resulting in a so-called 'double-orifice' mitral valve, which provides an improvement in MR.[2] To date, there is no evidence of the beneficial effects of PMVR on myocardial remodelling and recovery processes in patients with severe MR and congestive heart failure, although these processes are of prognostic interest.

This study is the first analysis of the effect MitraClip-based PMVR procedures have on biomarkers for myocardial inflammation, ECM turnover, and myocardial remodelling processes. A 6-month follow-up after PMVR demonstrated that there were no alterations in the matrix metalloproteinase (MMP) levels, indicating an absence of recovery processes in heart failure patients after PMVR. Likewise, the analysis of specific biomarkers reflecting the myocardial inflammatory processes that are pathophysiologically related to ECM turnover, deposition in MR, and heart failure did not provide any evidence of beneficial effects of PMVR on myocardial inflammation in heart failure patients. Furthermore, subgroup analysis of patients according to age, as well as several heart failure-associated comorbidities, such as chronic kidney disease, diabetes, and atrial fibrillation, did not show any evidence of recovery processes at the 6-month follow-up.

Although the MitraClip procedure is safe and feasible in patients who have a high risk for open-heart surgery, valid clinical predictors of overall survival and heart failure, as well as rehospitalisation, have not yet been identified.[3] Established clinical risk models for short and mid-term procedural outcomes are generally based on cohorts of patients undergoing cardiac surgery and poorly predict outcomes in patients undergoing interventional procedures, such as aortic valve replacement or mitral valve repair.[1,3] In the present study, biomarkers of cardiac inflammation (high-sensitivity C-reactive protein, interleukin-6) and remodelling (MMP-2, MMP-9) as predictors of mortality in patients undergoing PMVR were identified. The predictive value of these biomarkers was even more pronounced in high-risk patients with congestive heart failure and severe reduced left ventricular function. Thus, assessment of biomarkers reflecting inflammatory processes and myocardial recovery may provide helpful information for risk stratification and prognosis in high-risk patients undergoing PMVR.

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APOLIPOPROTEIN CIII AND TRIGLYCERIDES IN THE NECROTIC CORE CONTRIBUTE TO PLAQUE VULNERABILITY IN PATIENTS WITH STABLE CORONARY DISEASE

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Disclosure: The authors have declared no conflicts of interest.
Citation: EMJ Cardiol. 2017;5[1]:42-43. Abstract Review No. AR5.

Keywords: Atherosclerosis, stable coronary disease, plaque vulnerability, coronary plaque progression, apolipoprotein CIII (Apo CIII), triglyceride (TG).

Apolipoprotein CIII (Apo CIII) not only regulates triglyceride (TG) metabolism[1] but also contributes to atherosclerotic formation and cardiovascular disease.[2,3] However, it is unclear whether Apo CIII and TG affect vascular composition in humans and whether they are associated with plaque vulnerability. This study aimed to elucidate the relationship between plaque composition, determined using virtual histology-intravascular ultrasound (VH-IVUS), and Apo CIII and TG levels in 115 consecutive patients with stable coronary disease. We categorised patients, according to median Apo CIII level (8.5 mg/dL), into low Apo CIII (LAC group [≤8.5 mg/dL; n=59]), and high Apo CIII (HAC group [≥8.5 mg/dL; n=56]) groups and compared VH-IVUS findings between the two groups. Plaque vulnerability was estimated by measuring high-sensitivity C-reactive protein (hsCRP) levels in all patients, and the independent factor associated with plaque vulnerability was identified using lipids, including TG, low-density lipoprotein cholesterol, high density lipoprotein cholesterol, Apo CIII, apolipoprotein B, and apolipoprotein A-I.

Lesion length, plaque volume, and percentage necrotic core volume (assessed by VH-IVUS) were significantly greater in the HAC group than the LAC group. The hsCRP level was also significantly higher in the HAC group than the LAC group (1,861.464±420.424 ng/mL and

1,468.140±512.799 ng/mL, respectively; p=0.0104). Interestingly, the percentage necrotic core volume correlated with levels of Apo CIII (r=0.246; p=0.0079) and TG (r=0.289; p=0.0019). Moreover, Apo CIII levels strongly correlated with TG levels (r=0.731; p<0.0001).

We defined patients with hsCRP levels above the 3rd quartile level (1,245 ng/mL) as being susceptible to a coronary event (postsurgical cardiac event). Multiple logistic regression analyses revealed that TG was the only independent risk factor for a postsurgical cardiac event (odds ratio: 1.008; 95% confidence interval: 1.0010–1.0151; p=0.025). Our results suggest that Apo CIII and TG expand the necrotic core, contributing to the progression of plaque vulnerability in humans. Furthermore, compared with other lipids, TG, including the Apo CIII-TG system, are the most influential independent factors for latent vulnerability of a stable plaque.

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LEFT ATRIAL PARAMETER TO DIFFERENTIATE BETWEEN PHYSIOLOGICAL OR PATHOLOGICAL PROCESS OF THE LEFT VENTRICLE

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Keywords: Left atrial function, global longitudinal left atrial strain (GLS), physiological left atrial remodelling, pathological left atrial remodelling.

Athletes with pathological hearts are at risk of sudden death through cardiac events. Athletes undergo physiological changes to the heart, which mimic pathological changes seen in conditions such as hypertrophic cardiomyopathy. Little is known regarding the parameters that differentiate between these two distinct processes. Assessing parameters of the left atrium (LA) may be a novel method to differentiate between physiological and pathological changes.

We performed a descriptive single-centre, cross-sectional study looking at the left atrial parameters of three distinct groups, which comprised i) professional footballers, ii) healthy controls, and iii) patients with cardiomyopathy. Using two-dimensional echocardiography, we obtained values representing LA reservoir and conduit and pump function, which were expressed as LA total emptying, passive emptying fraction, and active emptying fraction, respectively. Global longitudinal LA strain (GLS) was also calculated using conventional software.

There were 23 professional athletes, 20 recreational athletes, and 27 subjects with cardiomyopathy included in this cohort. Their mean ages were 23±1.9 years, 26±2.1 years, and 35±2.4 years, respectively. Professional athletes and cardiomyopathy subjects had a significantly larger LA volume index compared to recreational athletes (38.1±11.1 mL/m^2, 25.6±7.7 mL/m^2, and 28.89±12.9 mL/m^2, respectively). Cardiomyopathy subjects had a significantly lower LA reservoir

capacity (mean LA total emptying fraction: 0.38±0.1, 0.57±0.1, and 0.59±0.8, respectively; p<0.01) lower conduit function (mean LA passive emptying fraction: 0.2±0.1, 0.5±0.3, and 0.4±0.2, respectively; p=0.001), lower pump function (mean LA active emptying fraction: 0.2±0.1, 0.30±0.1, and 0.32±0.2, respectively; p=0.02), and lower LA GLS (mean: 9.8±6.7, 23.9±12.1, and 27.8±14.6, respectively; p<0.001).

When comparing professional to recreational athletes, no significant differences were seen between LA function value and GLS. Of these parameters, GLS was the best discriminatory factor between physiological and pathological LA remodelling (GLS sensitivity: 86%, specificity: 97%, area under the curve: 0.8; p<0.001). LA remodelling occurs differently in response to exercise and diseases. GLS LA outperforms current conventional parameters as a discriminatory factor for physiological versus pathological LA remodelling. To improve on this study, greater sample numbers are required for each category and less heterogeneity of the cardiomyopathy cohort, in order to concentrate on specific cardiomyopathies, such as hypertrophic cardiomyopathy.

P-WAVE DISPERSION AND ITS ASSOCIATION WITH HYPERTENSION

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Keywords: Hypertension, P-wave dispersion (PwD), surface electrocardiogram (ECG).

BACKGROUND

Hypertension and obesity in adults have been associated with increased P-wave dispersion (PwD). This is postulated due to the correlation of hypertension with diastolic dysfunction and atrial enlargement. In hypertension, left ventricular hypertrophy and diastolic dysfunction can cause an increase in atrial strain, fibrosis, and dilation. These changes result in inhomogeneous atrial conduction. Heterogeneity in atrial conduction can be seen as variation in P-wave duration between differently oriented surface electrocardiogram (ECG) leads. Interlead variation in P-wave duration is called PwD.

OBJECTIVE

The aim of the study was to measure PwD and its association with hypertension in the REDISCOVER Malaysia population.

METHODS

The REDISCOVER study is a longitudinal, community-based study that tracks lifestyle changes, risk factors, and chronic disease in urban and rural areas of Malaysia. This study was conducted between 2007 and 2014, and included consenting adults of >30 years of age. Participants

were required to complete questionnaires on cardiovascular risk factors and medical history, and undergo physical examinations, blood tests, ECG, and echocardiography examinations. Demographic variables including weight, height, blood pressure, serum glucose, and serum lipid were recorded. Exclusion criteria included previous myocardial infarction, thyroid dysfunction, diabetes, valvular heart disease, cardiomyopathy, electrolyte imbalance, alcoholism, and medications that affect atrial conduction. Maximum and minimum P-wave durations were calculated from standard 12 lead ECG in sinus rhythm. A minimum of 9 out of 12 leads of P-wave duration were measured. PwD was then calculated by subtracting the minimum P-wave duration from the maximum P-wave duration in any of the 12 leads. PwD were calculated manually with hand-held callipers on paper by two cardiologists, independently. A total of 125 participants with hypertension were randomly selected and their PwD were compared to 125 randomly selected, age-matched healthy control subjects.

RESULTS

A total of 10,805 subjects participated in the REDISCOVER study. Mean age for the cohort was 52.6 (±11.6) years, and 56% were female. Of these subjects, 4.4% had a diagnosis of ischaemic heart disease, 1.3% had experienced a previous stroke, 16.7% had diabetes, and 45.6% had hypertension. The baseline characteristics of the hypertensive and normotensive groups are summarised in Table 1.

The mean age for the hypertensive cohort was 55.8 years (±10.1) while the control group was 51.3 (±13.6). Mean blood pressure for the hypertensive cohort was 154/87 mmHg, compared to the control group with 134/79 mmHg. In the hypertensive cohort, maximum P-wave duration was significantly increased at 116.8±17.7 ms, compared to 103.2±22.0 ms in the control group ($p<0.001$). There was also a significant increase in minimum P-wave duration in hypertensive subjects at 53.7±11.8 ms, compared to control group with 48.6±15.7 ms ($p=0.004$). There was a significant increase in the PwD in the hypertensive group at 63.0±18.2 ms, compared to controls with 54.6±21.9 ms ($p=0.001$).

CONCLUSION

Both maximum P wave duration and PwD were significantly increased in our hypertensive cohort. Surface ECG markers could be a simple, non-invasive method of screening and predicting risk of hypertensive cardiomyopathy in prehypertensive and hypertensive patients.

Table 1: Mean baseline characteristics of hypertension.

	Normotensive	Hypertension
Number of subjects	125	125
Age, years	51.3 (±13.6)	55.8 (±10.1)
Heart rate, bpm	79.1 (±13.4)	79.0 (±14.2)
BMI, kg/m^2	26.3 (±5.0)	27.1 (±4.4)
Systolic blood pressure, mmHg	133.9 (±19.6)	154.1 (±22.4)
Diastolic blood pressure, mmHg	78.7 (±11.7)	87.1 (±12.1)
Total cholesterol, mmol/L	5.6 (±0.9)	5.8 (±1.5)

bpm: beats per minute.

EDITOR'S PICK

Our Editor's pick for this issue is a thought-provoking paper from Ronald J. Krone, discussing the role cardio-oncology has in protecting the heart in cancer patients. Collaboration between oncologists and cardio-oncologists is imperative in developing cardiologists with expertise in understanding the impact that various cancer regimens have on the heart and to develop programmes to manage or prevent heart damage, ultimately ensuring better quality of life in the cancer patient.

Samantha Warne

PROTECTING THE HEART IN CANCER PATIENTS: THE ROLE OF CARDIO-ONCOLOGY

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ABSTRACT

Cardiac disease often impacts cancer therapy, from direct toxicity of cancer therapeutic agents to the coronary endothelium, the myocardium, heart valves, and other structures. This has spawned the development of cardio-oncology programmes, emphasising collaboration between oncologists and cardio-oncologists in order to develop cardiologists with expertise in understanding the impact of various cancer regimens on the heart and developing programmes to manage or prevent heart damage. Cardiac disease and cancer both become more common as people age, as such cardiac disease, including coronary disease, should be screened for and risk factors treated when possible. Cancer-caused cardiac damage is much more responsive to therapy if treated early, so protocols for monitoring heart function to identify early injury need to be established and followed. Newer measures of ventricular function can identify heart injury before a reduction in ejection fraction to permit early initiation of therapy, and protocols to utilise these measures need to be incorporated into routine surveillance. Research is underway to evaluate regimens for cardiac protection prior to the cancer therapy, but at present, the data do not permit broad recommendations.

Keywords: Cardiology, medical oncology, cancer therapy, cardio-oncology, cardiotoxicity, chemotherapy, myocardial dysfunction, surveillance, antineoplastic agents, cardiovascular agents, cardiovascular diseases, humans.

INTRODUCTION

The growing awareness of the potential for serious cardiotoxicity of cancer treatment and the specific problems of managing cardiac disease before, during, and after cancer therapy[1,2] has led to the emergence of cardio-oncologists (or the oncocardiologists[3]): cardiologists with special interest and expertise in partnering with oncologists to develop systems to permit maximum treatment of cancer while minimising the potential severe cardiac toxicities that have been seen in the past. There has been considerable research aimed at understanding the mechanisms of toxicity of treatments[4] and developing strategies of management.[5-7] A key principle has been close co-ordination between cardiologists and oncologists with the common goal being to minimise or prevent

heart problems from interfering with the best management of the cancer.[8-10] This has spawned the development of cardio-oncology societies around the world.[11,12] Multiple symposia are held annually to bring together cardiologists, oncologists, and the latest advances in this field.[13] The goal of the cardiologist is not just to protect the heart, which would be achieved by simply stopping chemotherapy. The goals have to be to keep the heart protected so that the cancer therapy is not compromised and to work out surveillance for the survivors, so late deterioration can be identified and managed to maintain the hard-won quality of life.

SCREENING FOR CORONARY DISEASE IN CANCER PATIENTS: RATIONALE AND PRACTICE

Cardiac disease and cancer incidences both increase as people age.[14] The likelihood of a cardiac event can be reduced with risk reduction.[15,16] Evaluation of coronary risk primarily means screening for elevated cholesterol, diabetes, hypertension, and cigarette smoking,[17] as well as family history of premature coronary disease, peripheral vascular disease, and coronary calcification.[18] Calcification of coronary arteries can be approximated on chest computed tomography (CT) scans, and peripheral vascular disease by a careful history and evaluation of the carotid and femoral arteries for bruits. Reducing cardiac risk in addition to interdiction of cigarette smoking and control of diabetes means aggressive control of blood pressure and lowering of low-density lipoprotein cholesterol, if elevated, with statins.[15] Statins have been shown to reduce the risk of coronary events, both in terms of secondary prevention (i.e. patients with existent disease)[19] and for primary prevention.[18,20] An electrocardiogram should be obtained prior to initiating therapy, as it may disclose unsuspected cardiac disease and can be used as reference later in therapy. Patients about to undergo potentially toxic chemotherapy need a baseline evaluation of left ventricular function, and protocols for follow-up have been described.[21,22]

PROTECTING THE HEART DURING CHEMOTHERAPY

Strategies to protect the heart during chemotherapy have recently been discussed in detail.[7,11,22-24] Cardinale et al.[25] showed that the initiation of heart failure therapy in patients with cardiac dysfunction secondary to doxorubicin therapy is much more effective if started within 3 months of the development of heart failure, since none of the patients responded ≥6 months after its development. They showed that the cumulative cardiac event-free rate was >90% over 2 years in responders and ≤35% for partial or no responders.

MONITORING CARDIAC FUNCTION

Waiting for symptoms alone is unreliable as a strategy to identify patients early, because physicians pick up only a fraction of the symptoms experienced by patients.[26] The gold standard for monitoring is measurement of the left ventricular ejection fraction, although it is a late representative of myocardial damage.[21,22,24] While multigated acquisition scans were originally used for this purpose, newer imaging modalities give more information and also provide information earlier than the reduced ejection fraction, which occurs relatively late and with more severe injury. Cardiac magnetic resonance imaging (CMR) is considered the gold standard for cardiac measurements and, of the modalities available to make these measurements, is the least susceptible to acquisition errors.[27] In addition, with the infusion of gadolinium, CMR can evaluate the myocardium for fibrosis, inflammation, and oedema, as well as segmental wall motion abnormalities and myocardial strain. It is an excellent measure of ventricular volume; however, it is expensive, has limited availability, and cannot be used in some patients, such as those who are extremely obese or claustrophobic. Two-dimensional echocardiography is widely available, but quality of the results can be a problem.[27] The need for precision in the measurement of left ventricle (LV) function is critical in the oncology field, especially because important treatment decisions are based on these results. The quality of the echoes varies considerably in different laboratories and if the oncologist uses echo values as guides, they need to be sure that the quality is high and that the echo laboratory is focussed on careful results, with echo contrast used in all but unusually clear cases. The echocardiogram also provides information about pulmonary systolic pressure and fluid state by examining the inferior vena cava. Newer machines can acquire ventricular strain data, as well as providing an automated three-dimensional (3D) measure of ejection fraction. 3D echo has been shown to be more reproducible and correlates better with magnetic resonance imaging (MRI).[27] Changes in global

longitudinal strain and tissue Doppler imaging precede changes in ejection fraction, allowing an earlier recognition of LV dysfunction[28] and introduction of therapy.

Serum biomarkers monitored during treatment have been shown to identify patients at risk for deterioration. Cardinale et al.[29] proposed the use of troponin I (TnI) levels to monitor LV injury during doxorubicin administration. The early presence and persistence of a positive TnI identified patients destined to develop cardiomyopathy. Brain natriuretic peptides have been advocated as a biomarker for early LV injury,[30] but their sensitivity to establish early LV injury is not clear,[31] and at present they are not recommended.[22] The study from Fallah-Rad et al.,[28] however, indicates that these biomarkers are not a substitute for direct cardiac imaging in patients treated with trastuzumab, which may cause less myocardial death then dysfunction. The specificity of an elevated TnI may be adequate to justify the institution of cardioprotective measures.

TREATMENT FOR CARDIAC DYSFUNCTION DEVELOPING DURING CHEMOTHERAPY

Current treatment for heart failure includes beta-blockers (carvedilol, metoprolol succinate, bisoprolol, and nebivolol), angiotensin converting enzyme inhibitors, or angiotensin receptor blockers and aldosterone blockers, and is designed to protect the heart from the body's deleterious hormonal response to heart failure.[32-36] This approach can improve or reverse the LV depression in a high percentage of cases.[37] Perhaps decreasing hormonal stress on the heart allows the damaged heart to heal, as detailed by Topkara et al.[38] The combination of an angiotensin receptor blocker (valsartan) with a neprolysin inhibitor has been shown to be more effective than enalapril alone in improving heart failure,[34,39] and ivabradine, an inhibitor of the I_f current in the sinus node, selectively slows heart rate and reduces the composite endpoint of death and rehospitalisation in patients with increased heart rate and reduced ejection fraction.[35,40] The effect of these agents in heart failure caused by chemotherapeutic toxicity has not been studied. Ivabradine is particularly intriguing, because sinus tachycardia is common in cancer patients, but studies in this group have not been done.[41] Of course, the development of LV dysfunction has serious implications for cancer treatment, since in most cases treatment has to be interrupted or altered.

PRETREATMENT WITH CARDIOPROTECTIVE MEASURES

Due to the importance of preventing cardiac depression and the implications for the continuation of cancer therapy, as well as avoiding the serious long-term consequences of serious cardiac damage, there is great interest in preventative therapy with cardioprotective agents. The current state of the art practices have been reviewed by Curigliano et al.[6] and Hamo et al.[7]

Beta-blockers

Beta-blockers differ in their mechanism of actions and their effectiveness in this role of protecting against LV depression from chemotherapy varies. Carvedilol, a non-selective beta-blocker with antioxidant activity,[42] and nebivolol, a cardio-selective agent with antioxidant activity and a nitric oxide donor,[43] have been shown to reduce the depression caused by cardiotoxic anticancer drugs, but metoprolol did not protect in several studies.[44,45] The effects of carvedilol against doxorubicin cardiotoxicity have been shown to have a protective effect against mitochondrial dysfunction induced by doxorubicin, as well as carvedilol's antioxidant properties. These effects were not shared with propranolol,[46] but have also been shown to be a feature of nebivalol.[47] This suggests that many of the protective effects of carvedilol, and perhaps nebivolol, are not the result of their beta-blocking activity and may explain why carvedilol appears more effective than other beta-blockers. A randomised study, evaluating bisoprolol and perindopril in patients with breast cancer treated with trastuzumab, showed that both drugs attenuated the decrease in ejection fraction but did not attenuate the dilatation of the LV,[48] so these drugs cannot be assumed to be protective in the prophylactic setting.

Angiotensin-Converting-Enzyme Inhibitors

Several studies with angiotensin-converting-enzyme inhibitors have been published, primarily utilising enalapril with positive results, although one large study with 125 patients showed no effect.[45] The combination of enalapril and carvedilol prevented LV deterioration with doxorubicin. Valsartan,[49] telmisartan,[50] and candesartan[44] have all shown protective efficacy.

Spironolactone

Spironolactone has been shown to protect myocardial function when given simultaneously with doxorubicin.[51] However, the potential relative increase in oestrogens due to the antiandrogen effects of spironolactone are a theoretical concern.

Eplerenone

Eplerenone may be an alternative, but there are no data as yet on this subject.

Statins

Statins have been explored as a possible cardio-protection agent.[52,53] Lovastatin administered to mice attenuated doxorubicin proliferation of mitochondria, reduced increased marker for stress, and reduced the decreased LV function.[54] Several studies give some credence to this relationship. In a propensity match analysis, 67 women taking statins were compared to a control group of 134 women not taking statins and the authors found fewer heart failure hospitalisations within the statin-taking group.[55] In a second comparison with 51 patients, using cardiac MRI as the endpoint, the 14 patients taking statins showed no decline compared to the patients not taking statins.[56] A randomised clinical trial using atorvastatin 40 mg compared to placebo showed no difference to the primary endpoint of ejection fraction <50% after 6 months; however, there were some late study effects (less increase in LV systolic and diastolic diameter and a sudden decline in LV ejection fraction).[53] One should note that the lipophilic atorvastatin and simvastatin are metabolised by the CYP3A4 pathway and may interact with other chemotherapeutic agents to modify the metabolism of both. The hydrophilic statins, pravastatin, rosuvastatin, and pitavastatin do not have this problem.

Dexrazoxane

Dexrazoxane, a drug developed to chelate iron and prevent the formation of free radicals that disrupt many aspects of the cellular architecture, has been found to interfere with topoisomerase (TOP)2α in tumour cells and TOP2β in cardiac cells. By blocking the effects of doxorubicin on TOP2β, dexrazoxane is cardioprotective, but there remain concerns that it may also block the tumouricidal effects on TOP2α.[4] At present, in adults the administration of dexrazoxane is given after 300 mg/m^2 of doxorubicin because of concerns of loss of efficacy. Additional studies are sorely needed to clarify this concern.[57,58]

The approach to pretreatment prophylaxis is described in the recent 2016 European Society for Cardiology (ESC) Position Paper.[22] They restrict prophylactic treatment to patients at high risk of developing cardiac toxicity; i.e. those with pre-existing cardiac disease or at high risk of coronary disease or previous potentially cardiotoxic therapy. Administration of cardioprotective therapy, an alternative anthracycline, with modified delivery such as liposomal doxorubicin or continuous infusion is recommended for those at high risk. New analogues of doxorubicin targeting only TOP2α are being developed and are in the early phases of testing. The execution of prophylactic treatment using these agents is limited by the frequent development of side effects, namely hypotension and orthostatic hypotension, and as such there is no consensus about protocols for identifying early toxicity. The sensitivity and specificity of the biomarkers has not been established and echocardiography is expensive. The ejection fraction is recognised to be a late expression of toxicity, so there is considerable support for using earlier markers of decreased function, namely global longitudinal strain and possibly diastolic dysfunction, as a trigger for prophylactic therapy to better justify the side effects and effort needed to monitor the pressure.[21,59]

MONITORING TYROSINE KINASE INHIBITORS

Tyrosine kinase inhibitors targeting vascular endothelial growth factor (VEGF) signalling pathways (sorafanib, sunitinib, bevacizumab, and cediranib) are associated with severe hypertension in up to 42% of treated patients, often developing within a few days of treatment. Aggressive pressure control often permits continued chemotherapy with these effective agents, but if untreated the hypertension can lead to heart failure. This effect is similar to that described by Topkara et al.[38] in mice. They developed a transgenic mouse that developed heart failure when exposed to inflammation, which activated a proinflammatory pro-gene. When inflammation was suppressed by doxycycline, a decrease in cardiac function did not occur, although some fibrosis was noted on electron microscopy. However, when this heart was exposed to severe hypertension (by an aortic constriction) exaggerated hypertrophy and increased mortality developed compared to normal mouse littermates. The heart in VEGF treatment has some injury, which is expressed as LV dysfunction when

stressed by the extreme hypertension; therefore, early monitoring and treatment is essential.

CONCLUSION

Cardiac toxicity with chemotherapeutic agents is common and early treatment of the cardiac dysfunction is likely to be effective, whereas delay, even as little as 6 months, will limit results. To minimise this serious problem, the cardio-oncologist should first calculate the risk of underlying coronary disease and treat any extant risk factors. Then, based on cancer treatment, identify persons at high risk of developing cardiotoxicity and consider prophylactic therapy with the agents described. In the patients judged to be at low risk, careful surveillance with biomarkers and newer echocardiographic indicators of dysfunction strain and tissue velocity. High-quality echocardiograms, ideally utilising 3D images for calculation of ejection fraction and myocardial strain, need to be developed and quality controlled.

Treatment with heart protective therapy, if deferred, can then be initiated at the earliest sign of LV depression, before the damage progresses to the point that the cancer therapy has to be interrupted. Patients taking tyrosine kinase inhibitors targeting VEGF should be very closely monitored by the development of hypertension, and treated aggressively and promptly. Close co-operation between cardiologists and oncologists can make it possible to administer cancer therapy minimising the collateral damage to the heart. This can pay big dividends in the quality of life in the cancer survivor. Needless to say, more data are needed of this unique population to better develop therapy to meet these goals.

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BIORESORBABLE CORONARY SCAFFOLDS: CURRENT STATE OF EVIDENCE

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ABSTRACT

Second-generation drug-eluting stents are currently considered the standard of care in patients undergoing treatment for coronary artery disease with percutaneous coronary intervention. Despite significant improvements in stenting technology and stent material over the past three decades, the concern that a permanent metallic prosthesis within the coronary vasculature can serve as a trigger for stent-related adverse events, mainly stent thrombosis and in-stent restenosis, still persists. In order to overcome the disadvantages of drug-eluting stents there has been a robust development in the field of bioresorbable coronary scaffolds (BRS). These devices aim to provide temporary scaffolding to restore vessel patency and, after serving its purpose, fully degrade and thus allow restoration of vasomotion along with luminal enlargement. The initial experience with bioresorbable scaffolds in low-risk patients presenting with simple lesions was satisfying and generated optimism among interventional cardiologists by promising better patient outcomes. However, the unrestricted use of these devices in patients presenting with a higher baseline risk and more complex lesions came at the cost of alarmingly high rates of adverse cardiac events, especially the late device thrombosis. Although its non-inferiority compared to metallic everolimus-eluting stents was formally met in the clinical trials, there was a clear trend towards an increased occurrence of myocardial infarction and device thrombosis during the first year after device implantation, which persisted even at long-term follow-up raising concern on the future of BRS. This review article discusses the development, design, clinical data, and future directions in the field of BRS.

Keywords: Bioresorbable coronary scaffold (BRS), coronary artery disease, percutaneous coronary intervention (PCI), coronary stenting, in-stent restenosis, stent thrombosis.

INTRODUCTION

Techniques for coronary artery revascularisation using percutaneous coronary intervention (PCI) have undergone significant advancements over the past few decades. The first major advancement in the field of PCI involved the use of balloon angioplasty; however, it was associated with a restenosis rate of about 40% and an unfavourable coronary anatomy precluded balloon angioplasty in 50% of cases.[1] Coronary stents were created with the advent of bare-metal stents (BMS) to overcome these shortcomings and marked the second phase of revolution in PCI. BMS resolved the issue of acute vessel closure by sealing the dissection flap and preventing elastic recoil, as was shown in the landmark BENESTENT trial, with the rate of subacute occlusion reduced to 1.5% and restenosis rates reduced from 32% to 22% at 7-month follow-up.[2] However, the use of BMS was associated with increased incidence of neointimal hyperplasia and in-stent restenosis, which led to

repeat revascularisations and hence limited its widespread adoption.[3] In order to overcome the limitations of BMS, drug-eluting stents (DES) were developed, incorporating controlled local release of anti-proliferative agents with the aim of preventing neointimal hyperplasia and reducing the risk of restenosis. The introduction of DES heralded the third phase of revolution in the field of PCI and demonstrated a dramatic reduction in rate of restenosis compared to BMS.[4] The frequency of stent thrombosis with second-generation DES are now reported to be at an all-time low at <1%.[5] Despite these improvements, newer-generation DES have not managed to address all the limitations of permanent coronary stents, such as the persistent risks of target lesion revascularisation and neoatherosclerosis, hindrance of late lumen enlargement, and the lack of reactive vasomotion in the stented vessel. Furthermore, implanting DES can hinder surgical revascularisation, jail side branches, require long-term antiplatelet therapy, create blooming artefact on imaging, and predispose the vessel to late stent thrombosis.[6]

Everolimus-eluting bioresorbable coronary scaffolds (BRS) were presented as the 'magic bullet' for overcoming the limitations and adverse effects associated with permanent indwelling drug-eluting metallic stents. However, mid-term and long-term data on the leading BRS (Absorb, Abbott Vascular, Santa Clara, California, USA) contradicted the expected advantages of the BRS and showed a higher rate of late scaffold thrombosis.[7-9] This article will briefly review the key concepts in and current clinical evidence for BRS.

Table 1: Summary of currently approved and under investigation bioresorbable scaffolds with their technical specifications.

Device (manufacturer)	Alloy	Strut thickness (mm)	Resorption time (months)	First-in-human clinical trial	Regulatory status
Igaki-Tamai Stent (Kyoto Medical Planning Co., Kyoto, Japan)	PLLA	170	24–36	Igaki-Tamai[50]	CE marked for peripheral use
DESolve (Elixir Medical Corporation, Sunnyvale, California, USA)	PLLA	150	12–24	DESolve Nx[24]	CE marked
ReZolve (REVA Medical Inc., San Diego, California, USA)	Polytyrosine-derived polycarbonate	115–230	4–6	RESTORE[51]	Investigational
ReZolve 2 (REVA Medical Inc., San Diego, California, USA)	Polytyrosine-derived polycarbonate	115–230	4–6	RESTORE-2[52]	Investigational
Fantom (REVA Medical Inc., San Diego, California, USA)	Polytyrosine-derived polycarbonate	125	36	FANTOM II[20]	CE marked
Absorb BVS 1.1 (Abbott Vascular, Santa Clara, California, USA)	PLLA	156	24–28	ABSORB Cohort B[53]	CE marked, FDA approved
FORTITUDE (Amaranth Medical, Inc., Mountain View, California, USA)	PLLA	150–200	3–6	MEND-II[54]	Investigational
DREAMS 1G (Biotronik SE & Co. KG, Berlin, Germany)	Mg Alloy	125	9	BIOSOLVE-I[14]	Investigational
DREAMS 2G (Biotronik SE & Co. KG, Berlin, Germany)	Mg Alloy	150	9	BIOSOLVE-II[15]	Investigational
Ideal BioStent (Xenogenics Corporation, Lincoln, Rhode Island, USA)	PLLA	200	6–9	WHISPER[55]	Investigational
ART PBS (Arterial Remodeling Technologies, Paris, France)	PLLA	170	3–6	ARTDIVA[56]	Investigational

CE: Conformité Européene; FDA: U.S. Food and Drug Administration; PLLA: polylactic acid.

CURRENTLY AVAILABLE BIORESORBABLE CORONARY SCAFFOLD TYPES AND THE CLINICAL EVIDENCE

A summary of currently approved and under investigation bioresorbable scaffolds with their technical specifications is presented in Table 1.

Metal Alloy Scaffolds

So far, only two metal alloy-based BRS have been developed, which are composed of either iron or magnesium.[10] The absorbable metal stent (AMS)-1 (Biotronik, Berlin, Germany) (Figure 1) was the first metallic scaffold created and was composed of a non-drug-coated magnesium alloy with a strut thickness of 165 µm and resorption time of 4 months. The AMS-1 was evaluated in a prospective, multicentre, non-randomised clinical trial (PROGRESS AMS) for neointimal formation and vascular remodelling. No safety concerns, such as myocardial infarction, stent thrombosis, or death, were observed; however, the restenosis rate was unacceptably high (47.5% at 4 months and 45% at 1 year), requiring repeat revascularisation.[11] Patients enrolled in the trial had intravascular ultrasound (IVUS) at 4 months, which revealed late lumen loss due to early recoil resulting from the scaffold dissolving at a much faster rate than expected.[12] This prompted the development of second-generation AMS-2 and AMS-3 (Figure 1) with the purpose of extending the duration of time needed for complete degradation.[13] AMS-3 DREAMS was tested in a prospective, non-randomised, multicentre trial study BIOSOLVE-I. At 12 months, target lesion failure was observed in 3 (7%) of the 43 patients.[14] DREAM has since been modified to the DREAMS-2 or Magmaris scaffold, which incorporates radiopaque markers at both ends of the device to improve placement and elutes sirolimus instead of paclitaxel. The safety and performance of this device were examined in a prospective, multicentre, non-randomised trial study BIOSOLVE-II and demonstrated a significantly improved in-segment late lumen loss (0.27 mm) and in-scaffold late lumen loss (0.44 mm) at 6 months.[15]

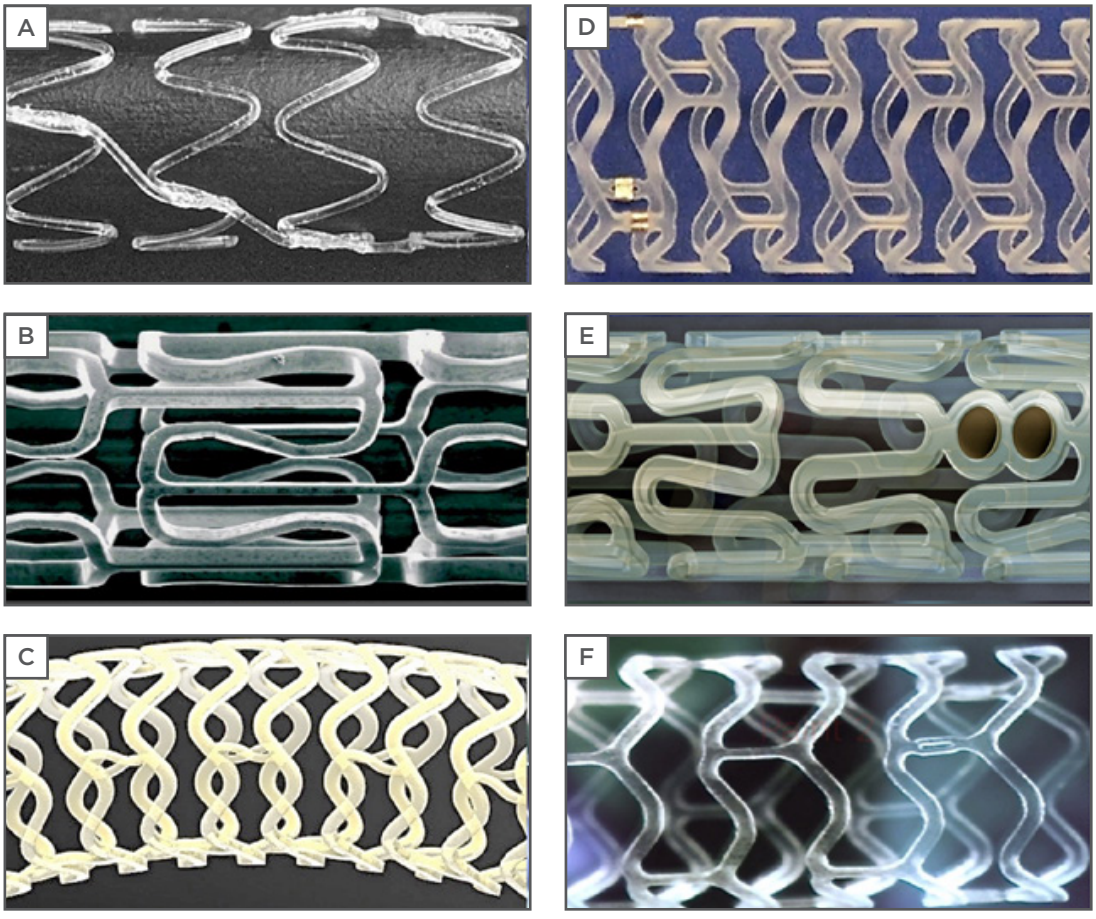

Figure 1: Design of various bioresorbable coronary scaffolds.
A) Igaki-Tamai; B) absorbable metal stent; C) Fantom; D) DESolve; E) Absorb GT1; F) Fortitude.

ReZolve Scaffold

The ReZolve scaffold (REVA Medical Inc., San Diego, California, USA) (Figure 1) consists of an absorbable tyrosine-derived polycarbonate polymer coated with sirolimus, strut thickness of 122 µm, and a resorption period ranging from 4–6 months.[16] The first-generation scaffold was tested in the RESORB trial. This was a prospective, non-randomised, single-arm study enrolling 27 patients showing a higher rate of target lesion revascularisation (66.7%) at 6 months.[17] After redesigning the device using a proprietary desaminotyrosine polycarbonate polymer coated with a sirolimus antiproliferative agent, the newer generation scaffold named Fantom (REVA Medical Inc.) was created. It had a strut thickness of 125 µm and a resorption time of 36 months.[18,19] The safety and performance of the Fantom device are being evaluated in the FANTOM II trial. The trial is currently being expanded to determine the safety and effectiveness in more complex cases, including two lesions in one or more arteries and lesions >20 mm in length.[20]

DESolve Scaffold

The DESolve BRS (Elixir Medical, Sunnyvale, California, USA) (Figure 1) is composed of a poly lactic acid backbone coated with myolimus. It has a strut thickness of 150 µm and a resorption time ranging from 12 to 24 months.[21] Uniquely, it also contains a self-correction feature of increasing the scaffold dimensions to minimise mal-positioning if underdeployed.[22] The latest generation device DESolve-150 has a novolimus drug coating and is estimated to be completely reabsorbed within 2 years.[23] The efficacy of DESolve-150 was assessed in the DESolve Nx trial, which showed late lumen loss at 6 months to be 0.20±0.32 mm and a major adverse cardiovascular events rate at 24 months of 7.4% with no definite scaffold thromboses.[24]

Absorb Scaffold

The Abbott Vascular everolimus bioresorbable vascular scaffold (BVS) is the most widely used and investigated BRS. The Absorb GT1 BVS (Abbott Vascular) (Figure 1) obtained a Conformité Européene mark in 2010 and was approved by the U.S. Food and Drug Administration (FDA) in July 2016 for use in the USA.[25] Seven randomised clinical trials comparing Absorb BVS with everolimus-eluting metallic stents have been conducted.[9,26-32] Six of these trials (ABSORB II, ABSORB III, ABSORB China, ABSORB Japan, EVERBIOII, and AIDA Trial) included patients presenting with stable ischaemic heart disease, whereas one study (TROFI II)[29] included patients with ST-segment-elevation myocardial infarction. At 1-year follow-up, the results of these studies suggested that there were no differences in the rates of the composite patient orientated and device-orientated adverse events between the two devices. However, long-term data from the aforementioned trials and a recently published meta-analysis have raised safety concerns, with the Absorb BVS showing a significant increase in the risk of target lesion failure (driven by a significant increase in target vessel myocardial infarction and ischaemia-driven target lesion revascularisation) and scaffold thrombosis compared with everolimus-eluting stents.[8] The possible proposed mechanisms for the excessive thrombotic event in the BVS group include strut malapposition (either persistent or late acquired); late device discontinuity, which is a programmed phenomenon in the bioresorption process of the polymeric device; delayed vessel healing; and neoatherosclerosis.[33-36]

ABSORB III trial was a pivotal study that paved the way for the BVS device approval in the USA.[27] In this multicentre, single-blinded, active-treatment, randomised trial, 2,008 patients with stable or unstable angina due to noncomplex obstructive coronary artery disease were randomly assigned in a 2:1 ratio to receive either the Absorb BVS (n=1,322) or Xience stent (Abbott Vascular) (n=686).[27] Target-lesion failure at 1 year was observed in 7.8% (99 of 1245 patients) receiving an Absorb BVS versus 6.1% (44 of 726 patients) receiving Xience.[27] No significant difference was noted between BVS versus metallic stent in rates of cardiac death (0.6% and 0.1%, respectively; p=0.29), target-vessel myocardial infarction (6.0% and 4.6%, respectively; p=0.18), or ischaemia-driven target-lesion revascularisation (3.0% and 2.5%, respectively; p=0.50).[27] Device thrombosis was noted in 1.5% of patients receiving the Absorb BVS versus 0.7% of patients receiving Xience within 1 year (p=0.13).[27] Recently, 2-year data from ABSORB III was reported with the rate of target lesion failure being 11.0% in the Absorb group and 7.9% in the Xience group (p=0.03) along with a higher rate of device thrombosis (1.9% versus 0.8%) with BVS.[37] This prompted the FDA to issue a safety notice limiting the use of Absorb BVS to centres participating in clinical registries. The 3-year outcomes from the ABSORB II trial were also reported recently and revealed a two-fold increased risk of target vessel myocardial infarction

and late scaffold thrombosis when compared to the Xience device along with six reported cases of definite very late scaffold thrombosis (>365 days).[9] In addition, the co-primary endpoint of superior vasomotor in Absorb BVS was not met, an unexpected finding given the rate of resorption. This was due to the fact that the metallic stents exhibited an unexpected change in diameter not previously reported in the literature.[38] However, the overall vasodilation of the scaffold observed in ABSORB II study (0.047 mm [standard deviation (SD): 0.11]) was very similar to the vasodilation observed in the first-in-human study at 3 years (0.054 mm [SD: 0.12])[25] and in the ABSORB Japan randomised trial at 2 years (0.06 mm [SD: 0.14]).[26] Future trials might consider alternative imaging, different vasodilator responses, or later follow-up to confirm whether there is a true vasomotor advantage for the bioresorbable scaffold or whether this proposed benefit is not realised in practice when compared with contemporary metallic DES.

The most recent clinical data for Absorb BVS comes from the Amsterdam Investigator-Initiated Absorb Strategy All-Comers Trial (AIDA). It was a single-blinded, multicentre, investigator-initiated, noninferiority, randomised clinical trial that included 1,845 patients selected to receive either a BVS (n=924) or a metallic stent (n=921).[31] At 24 months, target vessel failure occurred in 11.7% of patients receiving the Absorb BVS and 10.7% of patients receiving the Xience device, which was statistically nonsignificant.[31] Also, there was no difference in the risk of target vessel revascularisation events or cardiac related deaths. However, a significantly elevated risk of target vessel myocardial infarction in the BVS versus metallic stent group (5.5% versus 3.2%, respectively; p=0.04) prompted an early report of the data due to safety concerns.[31] Ongoing trials, such as the ABSORB IV trial, continue to determine the long-term safety and efficacy of Absorb BVS by examining rates of target lesion failure within 5 years of device placement.

PATIENT AND LESION SELECTION FOR BIORESORBABLE VASCULAR SCAFFOLD

Lessons learned from the clinical trials conducted with first-generation Absorb BVS have sounded a note of caution to the operators using BVS. We discuss a few of the important considerations that should be taken into account prior to implanting a BRS.

Large vessels with a luminal diameter >4.0 mm should be excluded from BVS implantation, since the largest available BVS diameter is 3.5 mm with a corresponding maximum post-implantation balloon diameter of 4 mm. Overexpansion of BVS could lead to fracture, whereas leaving the BVS malapposed can cause scaffold thrombosis.[39,40] In contrast, BVS should not be deployed in very small vessels, especially those with a diameter <2.5 mm. This is based on the fact that BVS strut thickness is 156 µm and if implanted in a small vessel, the final lumen area after BVS implantation would become excessively narrow, thereby increasing the risk of scaffold thrombosis.

The operator should have a low threshold for intravascular imaging use to confirm lumen/vessel diameter when it is difficult to define diameter before deciding to use BVS, especially in small/large vessels and/or diffuse lesions.[41] Operators should also be careful in making a decision to implant BVS in lesions with large differences between proximal and distal reference diameters (>0.5 mm). This is because, if undersized proximally, malapposition may occur, which could be difficult to correct without risking fracture after deployment. In contrast, if oversized distally, vessel injury around the distal edge may occur if expanded fully, or there could be increased device vessel wall coverage and strut volume in the vessel lumen.[42]

It has been postulated that the current BVS with bulky struts may require more potent and prolonged antiplatelet therapy secondary to a higher incidence of scaffold thrombosis.[43] Therefore, it would be better to avoid using current BVS in patients at high risk of bleeding, planned surgery, and/or who are unlikely to adhere to taking medication. To date, there are little data available regarding BVS for left main trunk lesions, which can be challenging lesion subsets even with DES.[44] Therefore, when considering using BVS for left main disease, the operator must carefully evaluate the lesion to treat due to issues of lumen/vessel diameter and the presence of ostial lesions.

IMPLANTING TECHNIQUES

Studies have revealed various success rates with BVS implantations.[34] This can be partly attributed to varying operator techniques. In a pooled study containing 2,973 patients treated with the Absorb BVS, only 82.3% of patients were noted to have optimally sized vessels (vessel diameter ≥2.25 mm to ≤3.75 mm). Additionally, only 60.1% underwent

pre-dilatation and only 12.4% underwent adequate high-pressure post-dilatation.[45] A three-phase preparation, sizing, and post-dilatation (PSP) implantation technique is currently advised in order to achieve maximal effectiveness.[46]

Phase 1: Preparing the Lesion

The vessel is initially dilated using a noncompliant balloon. The goal is to achieve a pre-dilatation lumen diameter matching the reference diameter (1:1 balloon-to-artery ratio) of the BVS chosen for implantation.

Phase 2: Sizing the Vessel

Prior studies have shown appropriate sizing is of paramount importance in achieving the maximal effectiveness of BVS.[34,44] Currently, the Absorb BVS is indicated for coronary artery lesions that are ≤24 mm long and with a reference vessel diameter of ≥2.5 mm and ≤3.75 mm. Due to thick scaffold struts, scaffold overlapping should be minimal, which could predispose the overlapped area to stent thrombosis. Also, BVS have a reduced range of expansion when compared to DES, which should be taken into consideration when sizing the lumen. The use of optical coherence tomography, IVUS, or quantitative coronary analysis is encouraged for optimal placement.

Phase 3: Post Dilatation of the Bioresorbable Vascular Scaffold

The last phase involves high-pressure post-dilation, up to ≤0.5 mm above the nominal scaffold diameter, to ensure the scaffold struts are embedded into the vessel wall. After completing this phase, the goal amount of residual stenosis should be <10%.

The Italian Diffuse/Multivessel Disease ABSORB Prospective Registry (IT-DISAPPEARS) was developed to investigate the procedural and clinical performance of the Absorb BVS in patients with long (>24 mm) single vessel disease and/or multivessel disease.[47] In the registry, a pre-specified technique for scaffold implantation was mandated. Indeed, quantitative coronary analysis, optical coherence tomography, or IVUS to assess reference vessel diameter and lesion length, as well as to guide optimal scaffold implantation were recommended. Moreover, high-pressure post-dilatation with non-compliant balloons was also recommended to achieve a residual stenosis ≤10%.[47] A total of 2,040 BVS were implanted in 956 patients during the study period. At 1-year follow-up, the rates of all-cause death, non-fatal myocardial infarction, and revascularisation were found to be 1.2%, 5.4%, and 10.9%, respectively. This registry prospective demonstrated that, when a careful technique is used, Absorb BVS implantation can be associated with an excellent safety and efficacy profile, even in patients with high lesion complexity.[47] The Absorb IV trial is currently being conducted, which will evaluate the PSP technique prospectively.

COMPARISON OF BIORESORBABLE CORONARY SCAFFOLDS VERSUS DRUG-ELUTING METALLIC STENTS

Table 2 compares the advantages and disadvantages of BRS over drug-eluting metallic stents.

Table 2: Bioresorbable coronary scaffolds: Advantages versus disadvantages over drug-eluting metallic stents.

Advantages	Disadvantages
Restoration of vasomotion	High cost
Vessel remodelling with late luminal enlargement	Pre-dilation necessary with directing stenting unavailable
Reduction in late stent thrombosis	Limited scaffold size availabilities
Reduction in duration of dual antiplatelet therapy	Difficult placement in complex coronary lesions: ostial disease, chronic total occlusions, bifurcations, dissections, small vessels, heavily calcified areas
The use of noninvasive imaging for detecting stenosis	Rheological alterations caused by thick struts
Ability to reintervene, including the placement of bypass grafts	Accurate placement requiring OCT, IVUS, or QCA
Alleviating patient concerns regarding placement of a permanent foreign object	Thick scaffolds preventing ideal expansion

IVUS: intravascular ultrasound; OCT: optical coherence tomography; QCA: quantitative coronary angiography.

Future Directions

Many new developments are being carried out to improve the shortcomings of older generation BRS. The design of newer generation devices is aimed at producing thinner struts and a smaller crossing profile as compared with the currently available BRS. The new scaffolds under development include the DEsolve, MeRes100 (Meril Life Science, Vapi, India), and Biolute, which have a strut thickness of 100, 100, and 108 µm, respectively.[48] This improvement, if successful, will allow proper radial strength to be obtained with a simultaneous decrease in the crossing profile. Additionally, thinner struts might minimise coronary blood flow perturbations and strut protrusion into the vessel lumen resulting in decreased thrombogenicity. Analogous technical improvement can be observed with the Mirage BRS, a microfibre scaffold with streamlined strut geometry and round struts that are supposed to decrease blood flow separation and ensure high shear stress, subsequently reducing platelet activation.[49] Another important issue with the BRS is its limited ability to post-dilate (preferably over expand), specifically the Absorb BVS, without fracturing the device. In this regard, the Fantom (a desaminotyrosine-derived polycarbonate scaffold), the DEsolve, and the Fortitude (Amaranth Medical, Mountain View, California, USA) (both PLLA-based polymer scaffolds) have shown greater resistance to overexpansion. In addition to reduced strut thickness, the future iterations for BRS that are currently being worked on include an effective delivery system, complete bioresorption, vessel geometry preservation, vulnerable plaque passivation, vascular physiology, and vasomotor function restoration.

CONCLUSION

In order to overcome the shortcomings of DES, specifically in-stent restenosis and late stent thrombosis, there has been a robust development of BRS. Initial data using BRS demonstrated vasomotor restoration, regression of underlying plaque, and vessel remodelling leading to an increased lumen size. However, the first-generation BRS have demonstrated poor acute performance and increased safety concern, limiting their use in real-world clinical settings. The safety risks associated with Absorb BVS have already resulted in a recent FDA warning to USA physicians, and severe use limitations in Europe, Japan, Australia, and other countries. Newer generation BRS are being developed to overcome the challenges of the first-generation BRS. However, we should not repeat history with BRS, as we did with first-generation DES, without understanding the greater stent thrombosis risk they posed. Research on BVS should be more intense with any new BVS required to undergo proper long-term evaluation in randomised trials versus the best second-generation DES before its widespread clinical adoption.

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PATHOPHYSIOLOGY OF ISCHAEMIC MITRAL VALVE PROLAPSE: A REVIEW OF THE EVIDENCE AND IMPLICATIONS FOR SURGICAL TREATMENT

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ABSTRACT

Ischaemic mitral prolapse (IMP) is a pathologic entity encountered in about one-third of patients undergoing surgery for ischaemic mitral regurgitation. IMP is generally the result of a papillary muscle injury consequent to myocardial infarction, but the recent literature is progressively unveiling a more complex pathogenesis. The mechanisms underlying its development are the impairment of one or more components of the mitral apparatus, which comprises the annulus, chordae tendineae, papillary muscle, and left ventricular wall. IMP is not only a disorder of valvular function but also entails coexistent aspects of a geometric disturbance of the mitral valve configuration and of the left ventricular function and dimension. A correct understanding of all these aspects is crucial to guide and tailor the correct therapeutic strategy to be adopted. Localisation of prolapse and anatomic features of the prolapsed leaflets and the subvalvular apparatus should be carefully evaluated as also constituting the major determinants defining patient outcomes. This review will summarise our current understanding of the pathophysiology of and clinical evidence on IMP, with a particular focus on surgical treatment.

Keywords: Mitral valve, prolapse, ischaemic mitral regurgitation (IMR), functional mitral regurgitation, surgery.

STATE OF THE ART

Ischaemic mitral prolapse (IMP) is a common and easily overlooked valvular dysfunction, secondary to papillary muscle (PM) injury after myocardial infarction (MI).[1-6] The prevalence is estimated to be in more than one-third of patients with ischaemic mitral regurgitation (IMR), and there is a male predominance of approximately 3:1.[4] The complication of prolapse is due to a regional ventricular injury or wall motion abnormality, rather than a global left ventricular (LV) dysfunction,[7,8] and the clinical significance is more daunting than any other ischaemic cardiac lesion.[9,10] Despite its importance, our understanding of IMP disease is incomplete and questions remain unanswered about the morphological and functional impairment of the annulus and subvalvular apparatus.[11-15] Although much of the original focus is centred on the abnormal restriction of the valve leaflets, the disease is significantly more complex.[16,17] IMP is not only a disorder of valvular function but also entails coexistent aspects of a geometric disturbance of the mitral valve configuration and of the LV function and dimension.[13,18,19] This review will summarise our current understanding of the pathophysiology, clinical use, and clinical evidence of IMP disease with a focus on surgical treatment.

PATHOPHYSIOLOGY

The mitral valve and subvalvular apparatus encompasses the annulus, valve leaflets, chordae tendineae, PM, and LV wall (Figure 1).

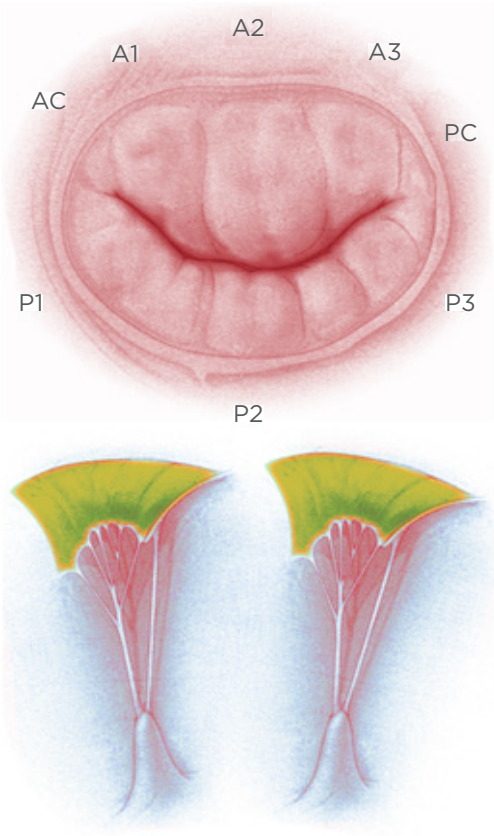

Figure 1: Anatomy of the mitral valve apparatus.
Top: Mitral valve and anatomical description of anterior, posterior leaflet, and relative scallops. Bottom: Representation of papillary muscle and chordae tendineae with attachment on the mitral leaflets.

The valve has anterior and posterior leaflets, and each leaflet typically consists of three distinct segments or scallops; namely, P1, P2, and P3 in the posterior mitral-valve leaflet, and A1, A2, and A3 in the anterior leaflet. The valve leaflets receive chordae tendineae from the anterolateral (AL) and posteromedial PM. Competence of the mitral valve relies on the co-ordinated interaction of the valve and subvalvular apparatus.

Papillary Muscle Morphology

Pioneering work in mitral anatomy showed a range of morphological diversity of PM anatomy and led to an anatomical classification with important implications for IMP surgery.[20] Intraoperative inspection of the mitral valve allowed a classification to be compiled, which includes five segmentation and morphological types of the PM:[3,4] Type I, single uniform unit; Type II, groove with two apexes; Type III, fenestrations with muscular bridges; Type IV, complete separation in two adjacent heads; and Type V, complete separation with two distant heads. Division can occur according to two directions corresponding to a sagittal plane or to a coronal plane. One leads to a separate posterior leaflet head, whereas the second leads to a separate commissural head. On the basis of this classification, the mechanisms of ischaemic mitral valve prolapse result in: a) necrosis of a separate commissural head inserted close to the annulus, with rupture of the anchorage of the commissural chord; b) necrosis of a single head PM subdivided in multiple heads with partial rupture; or c) necrosis of a fenestrated PM, with detachment of its main insertion favouring an 'incomplete' rupture. With time, incomplete rupture mimics PM elongation. In anterior MI, the most common mechanisms of IMP are represented by single PM with complete and total rupture (d) (Figure 2).

From these classifications, it is possible to extrapolate other potential classifications of IMP, including a 'true prolapse' (i.e. rupture of PM) and 'pseudo prolapse', as in conditions of functional mitral regurgitation (MR) associated to excessive symmetric or asymmetric tethering, but in the absence of clear evidence of PM rupture (myocardial ischaemia with LV remodelling and/or PM dyssynchrony). Also, from the clinical point of view, an 'acute' presentation (i.e. acute PM rupture) might be differentiated from a 'chronic' presentation in cases of chordal elongation or chronic partial PM rupture. This clinical classification is important for guidance in surgical timing and strategy, because the majority of reparative techniques, such as subvalvular apparatus surgery, are indicated in more chronic circumstances.

Distribution of Coronary Blood Flow in Papillary Muscles

The uneven coronary distribution and the differences in PM anatomy account for a heterogeneous morphological variability of papillary damage. Asymmetric distribution of blood supply accounts for the rare involvement of the anterior PM, which is perfused by both the left anterior descending coronary artery and diagonal branch. In addition, the tension exerted by the chordae on this PM is relatively low due to its superficial location with regard to the annulus. Conversely, the posterior PM is more sensitive to ischaemia (91% of the cases in our series),[3,21] because its blood supply relies on distal branches exclusively furnished by either the right coronary or the circumflex artery; furthermore, its location

deep in the LV subjects this muscle to a higher shear force. PM microcirculation relies on both an independent blood supply, provided by a well-identified arterial trunk perforating the PM from base to apex (Kugel's artery), and a segmental distribution.[20] However, features of microcirculation imbricate with anatomical characteristics of PM, and the relative importance of one of the two circulatory systems depends on the morphology and position of the PM within the ventricle and on the presence of muscular bridging, which favours collateralisation. Clearly, the importance of the truncal system increases as the PM is more individualised from the ventricular wall, as in Type IV–V, with the apex becoming more prone to rupture due to the fragility of its truncal blood supply and to the degree of physical stress. Partial PM rupture or elongation limited to a single head are therefore more likely to occur than in cases of multiple muscular bridges that guarantee an adequate collateral compensation.

The morphology of the posterior PM, which is the usual site of ischaemic injury, is more complex than the anterior PM, and its subdivision into several heads is very frequent. IMP is frequently caused by a partial PM rupture or elongation limited to a single head. Alternatively, prolapse can be favoured by an incomplete detachment of a head due to a rupture of its main insertion with the body while remaining fixed to the ventricle via muscular bridges ('incomplete' PM rupture). The incidence of IMP is typically unequal for topographic distribution in the leaflet. In the majority of patients, the disease is manifested by a prolapse of the posteromedial commissure, extended often in A2-A3 scallops.[2-4,22] The PM commissure and the neighbouring scallops are susceptible to repair, such as that which occurs with mitral valvuloplasty.[23] The morphologic patterns of the restrictive leaflet valve are normally included in functional Type II Carpentier classification.[23] This anatomic abnormality results in the mitral orifice not closing completely during systole, causing regurgitation.[24] The IMP involves an imbalance between tethering forces and closing forces in the valvular and subvalvular apparatus.[2,22,25-30] Accumulating evidence suggests that the presence of primary lesion or dysfunction of PM leads to prolapse in 86.4% of IMR patients.[21,31] In our series, ALPM was involved in 18.2% and posteromedial PM in 63.8%. In 13.6%, the prolapse was determined by necrosis of a restricted area of the myocardium adjacent to the PM, which was responsible for its abnormal traction and its dyssynchrony.[4]

CLINICAL EVIDENCE

Although the clinical presentation of patients with IMP can vary from severe to moderate valve regurgitation, evidence from observational series strongly suggests that surgical intervention is beneficial.[1,32-35] We evaluated the effect of early surgery on long-term outcomes in 75 patients with mitral regurgitation for IMP. Patients with total rupture of PM and cardiogenic shock showed a higher rate of death in comparison to patients in which the culprit morphological injury was chordae lesion or incomplete rupture.[3,4,36] The clinical manifestations were related to the residual function of the mitral valve (severe or moderate incompetence), extension of MI, residual myocardial ischaemia, and acquired complications, such as LV dysfunction and rhythm disturbance.[1,36]

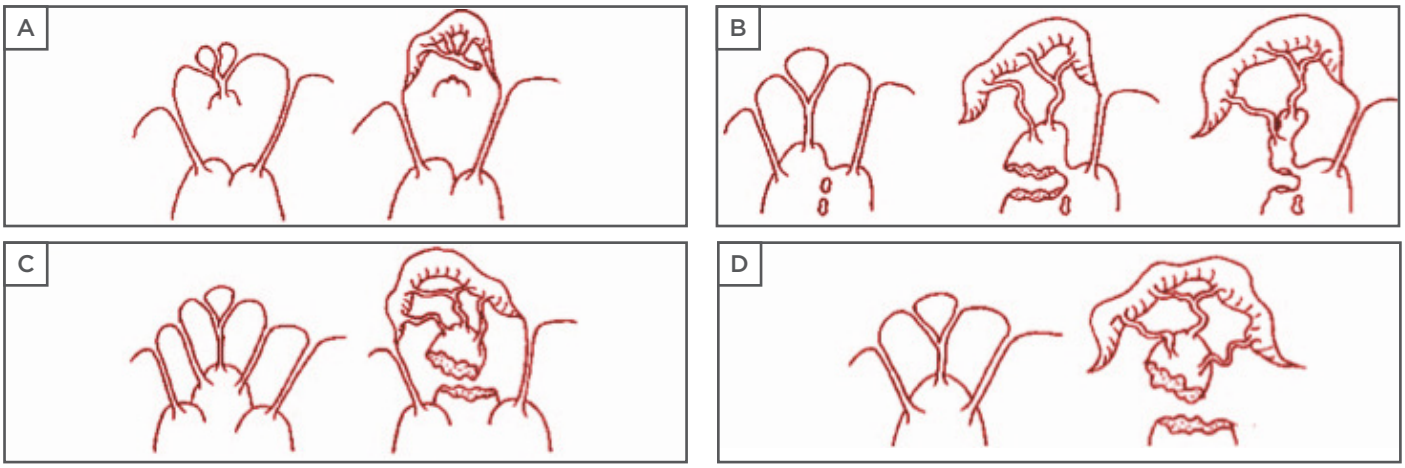

Figure 2: Mechanisms of ischaemic valve prolapse.

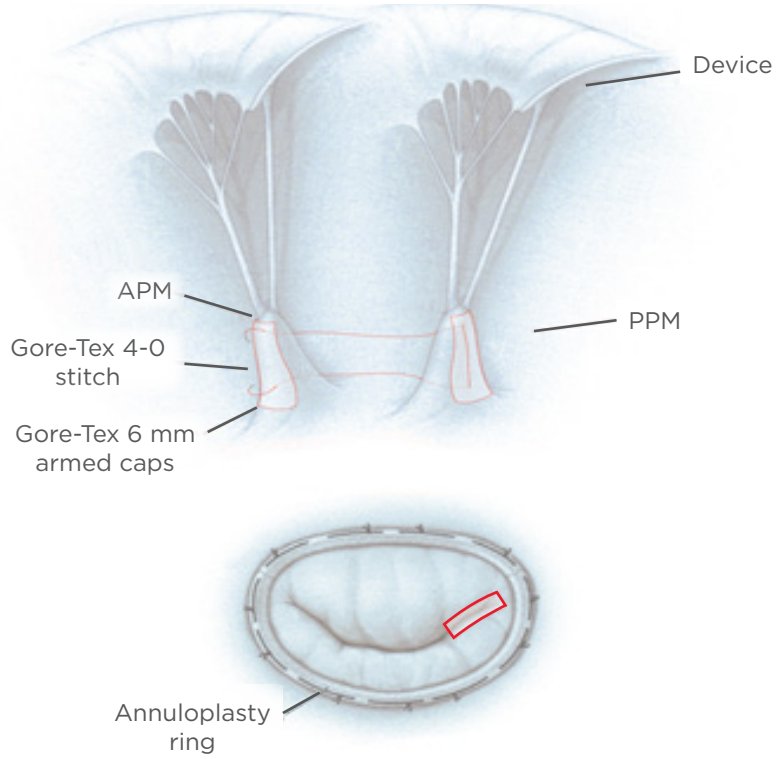

Figure 3: Surgical reparative strategies.
Top: PMA. A Gore-Tex® cap is used to reinforce the heads of the papillary muscle and a Gore-Tex 4-0 suture is used to approximate the two papillary muscles and therefore increase leaflets coaptation. Bottom: mitral annuloplasty performed in association with PMA (red rectangle).
APM: anterior papillary muscle; PMA: papillary muscle approximation; PPM: posterior papillary muscle.

Also, there is evidence that suggests that the presence of a mitral leaflet prolapse in IMR should represent an indication for surgery of the mitral valve in combination with coronary artery bypass grafting.[35] Earlier studies on non-corrected mitral regurgitation in the context of IMP date back to the era of cardiac catheterisation.[37-39] The late outcomes of patients with coronary disease and moderate mitral valve dysfunction with leaflet prolapse who have not undergone mitral repair have been studied.[39,40] Although results are not univocal, estimates of the prevalence of complications and outcomes have varied depending on the era of the study, the cohort selected, and the method used to diagnose IMP (clinical exam versus cardiac catheterisation versus echocardiography). To our knowledge, two large recent series have helped to better define the clinical course of unoperated IMP in the modern era.[37,41-43]

CLINICAL USE

Patients with IMP should have a careful assessment of symptoms after MI and should undergo electrocardiography, primarily to evaluate localisation and extension of the necrosis and secondly to evaluate cardiac rhythm. Transthoracic echocardiography should always be performed to assess the mechanism and severity of IMP, as well as LV size and function. A semi-quantitative scale is often used to grade mitral regurgitation: 1+ (trace), 2+ (mild), 3+ (moderate), and 4+ (severe).[44] Patients with a total rupture of ALPM who have severe mitral regurgitation with cardiogenic shock symptoms, pulmonary oedema, severe LV dysfunction (ejection fraction, <40%), or dilatation (LV end-systolic dimension, >40 mm) should be presented quickly to a surgeon.[45] Likewise, symptomatic patients with moderate LV dysfunction or dilatation, with or without atrial fibrillation or pulmonary hypertension, should be considered for surgery after 60 days.[3,4] In not extended inferior MI, patients with chordae lesion injury, mild-to-moderate mitral regurgitation, and no evidence of LV dysfunction or dilatation should be observed until the development of either symptoms or severe mitral regurgitation. Frequently, these patients have a percutaneous coronary intervention-stenting procedure.[3,4]

Before the advent of mitral valve repair, valve replacement was the preferred procedure for severe IMR alone or with leaflet prolapse.[22] Valve replacement may still be preferred in certain situations, such as in patients with advanced age, total PM rupture, and severe LV dysfunction, in which a combined or complex surgical procedure is needed.[45] In the case of extensive prolapse of A2-A3 scallops, mitral valve sparing operations should be the preferred option.[32] In such cases, chordae sparing valve replacement for MR may be a suitable alternative to repair the leaflet prolapse. Individual and institutional experience is crucial in determining the likelihood of a repair procedure's success. Many centres worldwide report the lowest mortality rates with the highest proportion of patients undergoing mitral valve repair rather than replacement.[46] Current debate on IMR is animated by several studies introducing parameters or variables predicting the prognosis or outcome of mitral repair. Kron et al.[47] reported a set of clinical and echocardiographic variables able to predict recurrence of MR after surgical repair.[1,2,28,48] On account of these results, the surgeon should precisely evaluate the likelihood of successful repair, in light of his or her own experience, when counselling the patient and may recommend a second opinion. Failure of the repair can lead to conversion in mitral replacement; the decision between a mechanical valve and a bioprosthesis should be discussed with the patient before the operation. After IMP surgery, a functional Type II residual MR with a structurally normal mitral valve may occur. In addition, cases of systolic restricted leaflet motion on the remaining leaflets (Type III-b) and some degree of annular dilatation (functional Type I) may also be present, highlighting the aforementioned imbalance between tethering forces and closing forces in IMP.[23,24]

In our group, we have treated 214 patients with surgery for IMR and 75 of those had IMP. Mitral valve repair was performed in 90.7% of cases and valve replacement was required in 9.3% of cases.[3,4] Intraoperative observation revealed leaflet prolapse with structurally normal mitral valve (functional Type II) in all patients. The mechanism of prolapse was PM injury in 88% of cases and chordal injury in 12% of patients. Anatomical classification of PM injury demonstrated an ALPM lesion in 20% of the patients, posteromedial PM lesion in 66.7% of cases, and posteromedial PM elongation in 13.3% of the population considered. Patients with isolated total PM rupture, or a partial rupture with an extensive prolapse of A3-PC-P3 scallops, had a mitral valve replacement. The posteromedial commissure prolapse, which was encountered in the majority of the patients, was repaired with isolated stitch. Various techniques may be used to repair the anterior leaflet, including artificial chordal replacement with Gore-Tex® (expanded polytetrafluoroethylene sutures), chordal transposition, and limited triangular resection. The prolapse of the posterior middle scallop (P2), which is encountered in a minority of patients with IMR, is usually repaired with limited resection of this scallop. Finally, in all cases, a downsized annuloplasty was performed to stabilise the annulus, which was normally found to be distorted, dilated, or both.[49]

Another important point thoroughly discussed in the literature are the real benefits of PM treatment in reducing LV dysfunction in IMR surgery. Different types of procedure are codified in this context: PM approximation, PM sling, and PM relocation.[50,51] Several procedures have been compared, with PM approximation being an effective alternative among the available options[52] (Figure 3), but there are no large randomised trials in which the real benefit of those procedures in the long-term follow-up is demonstrated. In this context, a recent propensity-matched study demonstrated that the combination of ring annuloplasty and PM sling produced a significant improvement in mitral valve apparatus geometry and resulted in reduction of MR recurrence in the early postoperative period.[53] Similarly, a randomised control trial and its further sub-analysis demonstrated the superiority of combined restrictive annuloplasty and PM approximation over the simple annuloplasty, in terms of LV remodelling and cardiac outcomes.[54,55] A recent meta-analysis summarised the current evidence on this argument and demonstrated that combined subvalvular procedures plus mitral annuloplasty are associated with greater LV reverse remodelling and systolic function, less recurrence of moderate or greater MR, and an improved geometry of the MV apparatus at short and mid-term follow-up.[56]

In our series, concomitant coronary artery bypass grafting was accomplished in all patients using an internal thoracic artery with left anterior descending artery lesion. We routinely advise intraoperative transoesophageal echocardiography during IMP surgery to evaluate the effectiveness of the repair. Transoesophageal echocardiography provides precise anatomic and functional data that are

helpful in understanding the mechanism and severity of mitral regurgitation, including the extent of leaflet prolapse, the condition of the subvalvular apparatus, the diameter of the mitral annulus, and ventricular function, and are therefore fundamental in planning the best operative strategy.[44] We recommend a postoperative echocardiographic follow-up after mitral valve repair 6–8 weeks after discharge. Usually, patients are then transferred to the care of their cardiologist and family physician, and we advise the echocardiography be performed annually thereafter.

COMPLICATIONS AND PITFALLS

Mitral valve repair or replacement in IMR alone or with leaflet prolapse is associated with an operative mortality of ≤6%. In our experience, the most frequent primary causes of death were found to be multisystem organ failure (37.5%), heart failure (12.5%), and renal failure (10%). Predictors of death include advanced age and poorer New York Heart Association (NYHA) class. This condition is frequently encountered in patients who underwent hospitalisation for PM rupture and cardiogenic shock associated with extended anterior MI.[41] Other determinants are represented by lower preoperative ejection fraction, high preoperative LV end-systolic dimension, and other coexisting conditions, including diabetes, renal disease, chronic lung disease, and obesity. In an analysis from the Society of Thoracic Surgeons (STS) National Adult Cardiac Surgery Database, the major postoperative complications before discharge included prolonged (>24 hours) ventilatory support (10.4% of patients), renal failure (4.8%), and stroke (2.4%). Thromboembolism after mitral valve repair occurred in approximately 2.8% of patients within the first 12 months after surgery. Intraoperative conversion to mitral valve replacement occurred in 2–10% of cases.[36,45] The most important complication of mitral valve repair is recurrent MR, which may occur in as many as 5–30% of patients requiring reoperation.[47,57]

Considering our series estimates of IMP, the rate of late cardiac events (medical and surgical complications) were approximately 34.7%, with a mean survival of 114.2 months, including patients with in-hospital mortality. After 5 and 10 years, survival from cardiac-related events was 75% and 50%, respectively. Cardiac event rates were higher if one or more risk factors were present: age >70 years, total rupture of ALPM in anterior MI, severe mitral incompetence, cardiogenic shock, and surgery before 30 days. In our cohort, 76.5% of patients with IMP had no significant MR after surgery within 10 years of follow-up, while 24% of the patients required reoperation. Of note, the majority of patients developed rhythm disturbances before operation, namely atrioventricular blocks and QRS prolongation, suggesting that the appearance of these abnormalities should prompt decision towards some form of intervention. However, further investigations are warranted to confirm this finding.

CONCLUSION

IMP is a daunting condition in IMR, which deserves full consideration in terms of both diagnosis and treatment. The presence of IMP is regarded as an indication to perform surgery, as it underlies more than a simple annular dilation, which can be mainly addressed by myocardial revascularisation and interrupting the ventricular remodelling process. Conversely, the appearance of IMP indicates an alteration of more than one of the components of the mitral apparatus and valve configuration (annulus, PM, chordae, LV geometry) and therefore requires more careful attention in the operative work-up. In this scenario, PM surgery is still a debated argument and there is no final answer on the correct surgical approach to use. A randomised trial to elucidate this point is needed in this context.

FUTURE DIRECTIONS

IMP is a challenging disease and a comprehensive understanding is necessary in order to correctly address its repair. Thanks to improvement in imaging techniques, more and more sophisticated analyses are achievable, with the possibility to combine them with advanced mathematical modelling of the mitral valve. Approaches such as finite element analysis (FEA) enable us to precisely dissect the pathogenic events occurring in IMP to evaluate the changes induced by the application of different operative techniques.[58-60] In the future, application of these and other *in silico* studies at the preoperative stage may be extremely helpful to plan the optimal strategy to be adopted for each patient. However, to produce a clinically usable patient-specific algorithm, more data and subgroup analyses are still required.

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MOLECULAR IMAGING OF CARDIAC METABOLISM, INNERVATION, AND CONDUCTION

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ABSTRACT

Cardiac diseases have complex molecular origins. However, current clinical diagnostic tools are often inadequate to uncover specific molecular components of cardiac pathologies. Thus, we are still lacking a detailed understanding of disease progression, and both patient diagnosis and treatment are often inaccurate. Molecular imaging could play a leading role in translating basic research to both preclinical and clinical cardiac research, ultimately improving our understanding and management of human disease. In this review, we highlight the diversity of current molecular imaging tools that have been used in clinical research or have reached the stage of clinical translation. Facilitated by the steadily increasing infrastructure of clinical positron emission tomography and positron emission tomography-magnetic resonance imaging cameras and advancing gating analysis, these tools allow the implementation of clinical cardiac molecular imaging trials to deepen our knowledge of human disease and improve patient care.

Keywords: Positron emission tomography (PET), cardiac imaging, single photon emission computed tomography (SPECT), heart disease.

INTRODUCTION

Cardiovascular disease remains the leading cause of death in Europe and worldwide.[1] Almost all major pharmaceutical companies run large programmes on cardiovascular and cardiac drug development. Molecular imaging may play an important role in improving not only diagnosis but also treatment of cardiac diseases. The current understanding of molecular heart function is sufficient to implement more molecular imaging tools in the clinics for interrogating major aspects of cardiac function, including metabolism, innervation, and conduction. The infrastructure for clinical positron emission tomography (PET) and PET-magnetic resonance imaging is steadily growing, allowing for routine application of cardiac scans, including motion correction for heartbeat and breathing. The purpose of this review is to provide an overview of established and upcoming molecular imaging probes for cardiac function, which could aid our understanding of the human heart in health, disease, and as a function of treatment.

METABOLISM

In contrast to skeletal muscle, cardiomyocytes sustain an everlasting cycle of contraction and relaxation in order to feed our body with blood and maintain the homeostasis of nutrients and metabolic gases.[2] This highly specialised task is facilitated by a specific molecular architecture. With their steady and sustained workload, cardiomyocytes are specialised for aerobic metabolism of fatty acids (FA) and are packed with mitochondria performing oxidative phosphorylation and β-oxidation. This unique molecular architecture offers numerous opportunities to use cardiac FA metabolism as a platform for molecular imaging (Figure 1). Although cardiac metabolism has a wide adaptive capacity and plasticity when facing challenging heart energy production conditions, most forms of cardiac diseases are associated with acute or chronic changes in energy metabolism.

The heart rapidly extracts FA via either passive diffusion or a protein carrier-mediated pathway.[2,3] Oleate and palmitate are the most abundant FA in the blood pool. Once inside the cytosolic

compartment of the cardiomyocyte, FA are esterified to long-chain acyl-coenzyme A (CoA) esters by FA-CoA synthase. The activated FA can then be esterified to triacylglycerols, or transferred to carnitine via carnitine palmitoyltransferase 1 (CPT1). The acylcarnitine is then shuttled into the mitochondria by carnitine-acylcarnitine translocase, where the majority is converted back to FA-CoA by carnitine palmitoyltransferase 2 and enters mitochondrial FA β-oxidation.

Ventricular hypertrophy and dilated cardiomyopathy (DCM) are characterised by decreased myocardial capacity of FA oxidation and a shift to glucose metabolism, as a result of a decreased expression and activity of proteins involved in FA metabolism.[4,5] By contrast, diabetic cardiomyopathy results in an increase of FA oxidation due to increased circulation levels and consequential accumulation of intramyocardial lipid metabolites.[2] Ischaemic heart disease involves reduced oxidative metabolism due to reduced oxygen supply and increased anaerobic glycolysis, even though FA oxidation recovers quickly during reperfusion following ischaemia.[2] Given this molecular pathology, current PET imaging of myocardial metabolism utilises ^{11}C-labelled natural FA and ^{18}F-labelled FA analogues, as well as the canonical [^{18}F]fludeoxyglucose.[6] For the purpose of this review, we will focus on FA metabolism, which is an independent predictor of left ventricular mass in hypertension and left ventricular dysfunction.[7]

[^{11}C]palmitate has been used to assess various steps of myocardial FA metabolism in the human heart, including storage as a triglyceride and β-oxidation (Figure 1B). Given the small storage capacities of cardiomyocytes for triglycerides and the vast number of mitochondria, the signal is dominated by the oxidation pathway and can thus be used for evaluating the enzymatic activity of CPT1, the enzyme that catalyses the acyl transfer from FA-CoA to carnitine.[8] Using this imaging probe, it has been demonstrated that obesity and diabetes mellitus (DM) are associated with an increase in myocardial FA metabolism and reduced glucose utilisation.[9,10]

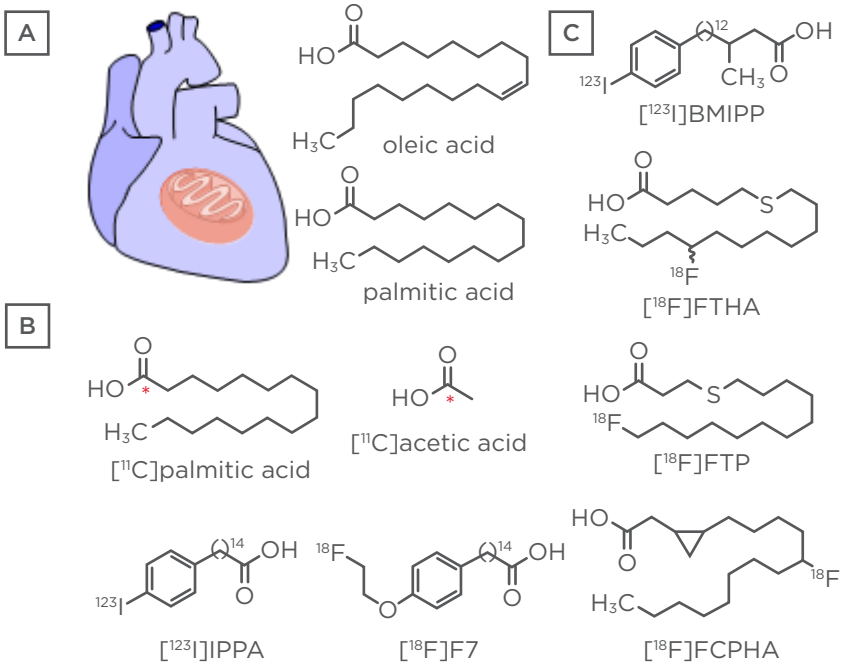

Figure 1: Cardiac fatty acid metabolism.

A) Chemical structures of native unsaturated and saturated FA, oleic acid, and palmitic acid. B) PET and SPECT radiotracers that are isotopes of native FA ([^{11}C]palmitic acid and [^{11}C]acetic acid), or mimic their metabolism ([^{123}I]IPPA and [^{18}F]F7). C) FA analogues as SPECT ([^{123}I]BMIPP) and PET ligands ([^{18}F]FTHA, [^{18}F]FTP, and [^{18}F]FCPHA) that facilitate mitochondrial trapping.

BMIPP: β-methyl-para-[^{123}I]-iodophenyl-pentadecanoic acid; F7: fluoroethoxy phenyl pentadecanoic acid; FA: fatty acid; FCPHA: fluoro-3,4-methyleneheptadecanoic acid; FTHA: fluoro-6-thia-heptadecanoic acid; FTP: fluoro-4-thia-palmitate; IPPA: pentadecanoic acid; PET: positron emission tomography; SPECT: single photon emission computed tomography.

By contrast, patients with idiopathic DCM exhibited alterations in myocardial metabolism characterised by decreased FA oxidation and increased glucose metabolism.[11] Thus far, the routine clinical use of [^{11}C]palmitate has been limited by its relatively complicated synthesis and a need for an on-site cyclotron. Recent efforts to improve synthesis and a growing infrastructure of hospital cyclotrons may facilitate future clinical use of this radiotracer.[12]

Analogously to FA, acetate is rapidly extracted by cardiomyocytes and oxidised in mitochondria via the tricarboxylic acid (TCA) cycle to CO_2 and H_2O.[13] [^{11}C]acetate has been used to measure myocardial blood flow in patients with hypertrophic cardiomyopathy[14] and enabled simultaneous quantification of myocardial perfusion, oxidative metabolism, cardiac efficiency, and pump function at rest as well as during exercise in athletes.[15]

15-(p-[^{123}I]iodophenyl)-pentadecanoic acid ([^{123}I]IPPA) was the first single photon emission computed tomography (SPECT) ligand to image myocardial FA metabolism *in vivo*, showing rapid accumulation in the heart and similar clearance kinetics as palmitate, which are directly correlated with β-oxidation in animal disease models and in humans.[16,17] Currently, [^{123}I]IPPA is commercially available in Europe and Canada, and its usefulness as a cardiac imaging agent has been explored in clinical trials.

Tu et al.[18] designed an ^{18}F-labelled radiotracer, 15-(4-(2-[^{18}F]fluoroethoxy)phenyl)pentadecanoic acid ([^{18}F]F7), based on [^{123}I]IPPA. [^{18}F]F7 is capable of mimicking [^{11}C]palmitate with regard to its ability to capture all key aspects of FA metabolism, including uptake, β-oxidation, and storage as a triglyceride. In addition, it is more feasible for clinical use due to the longer half-life of ^{18}F, and it allows quantitative PET imaging with improved temporal resolution compared to SPECT. Small animal PET studies in Sprague-Dawley rats displayed high uptake in the heart, good imaging contrast over blood and other tissues, and similar biphasic washout kinetics as [^{11}C]palmitate.

In addition to isotopes of native FA, FA analogues acting as false substrates or inhibitors of FA metabolism have been explored as PET and SPECT ligands, whose signal emphasises myocardial β-oxidation (Figure 1C). These analogues are recognised by the cytoplasmic acyl-CoA synthase and CPT1 in the mitochondrial membrane but are trapped inside the mitochondria due to incomplete β-oxidation.

For example, β-methyl-p-[^{123}I]-iodophenyl-pentadecanoic acid ([^{123}I]BMIPP) has been developed as a derivative of the aforementioned [^{123}I]IPPA with the intention of preventing β-oxidation by blocking the β-position with a methyl functional group, thus enforcing accumulation in mitochondria. [^{123}I]BMIPP imaging has been used for identifying patients with recent exercise-induced myocardial ischaemia[19] and non-invasive diagnosis of coronary artery disease in patients with heart failure.[20]

Pandey et al.[21] investigated long-chain [^{18}F] fluorothia FA for their use as myocardial β-oxidation probes. CoA thioesters of 4-thia FA analogues are potent inhibitors of β-oxidation through inhibition of acyl-CoA dehydrogenase, thus leading to an accumulation of radiotracers in the mitochondria after incomplete β-oxidation.[22-24]

14(R,S)-[^{18}F]Fluoro-6-thia-heptadecanoic acid ([^{18}F]FTHA) uptake was reduced by 81% in mice after pharmacological inhibition of CPT1 using 2-[5-(4-chlorophenyl)pentyl]-2-oxiranecarboxylate.[25] Likewise, β-oxidation inhibition by lactate infusion in pigs reduced the myocardial [^{18}F]FTHA signal by 89%, demonstrating that nearly all of the PET ligand taken up by the heart enters the mitochondria.[26,27] Both studies confirmed that the unidirectional uptake rate of [^{18}F]FTHA reflects β-oxidation and allows the measurement of cardiac FA-metabolism *in vivo*, which has been exploited in numerous clinical studies. For example, accumulation of [^{18}F]FTHA in the myocardium was increased by aerobic exercise in human volunteers due to increased energy demand.[28] In patients with coronary artery disease, [^{18}F]FTHA imaging displayed a reduced signal in accordance with reduced oxidative metabolism.[29] In addition, the [^{18}F]FTHA signal was reduced in healthy volunteers with glucose/insulin clamp, demonstrating the ability to detect a change in energy substrate preference from FA to glucose.[30] Furthermore, [^{18}F]FTHA has recently been used to investigate the role of metabolic alterations in the development of a maladaptive right ventricular response in pulmonary arterial hypertension.[31]

Following the same chemical strategy of inhibiting β-oxidation, 16-[^{18}F]fluoro-4-thia-palmitate ([^{18}F] FTP) was developed to improve sensitivity to changes in FA oxidation caused by hypoxia,

and was found to have prolonged myocardial retention.[32] [18F]FTP showed reduced FA oxidation in hypoxic rat hearts, showing comparable imaging qualities as [18F]FTHA in swine, but was not influenced by altered plasma substrate levels.[33] Elevated uptake of [18F]FTP was found in patients with Type 2 DM.[34] This is in line with the aforementioned increase in myocardial FA oxidation found in this patient group using [11C]palmitate.

Shoup et al.[35] introduced trans-9-[18F]fluoro-3,4-methyleneheptadecanoic acid ([18F]FCPHA), which features a cyclopropyl group to block β-oxidation, as a new radiolabelled FA analogue. [18F]FCPHA revealed fast blood clearance, high myocardial uptake, and good retention in rats and rhesus monkeys. [18F]FCPHA is currently undergoing a Phase II clinical trial to assess myocardial FA perfusion and uptake in coronary artery disease patients.[36]

INNERVATION

Heart function is controlled by the autonomous nervous system (Figure 2). While cholinergic neurons dominate innervation to the sinoatrial node, setting a constant rhythm of contractions,[37] adrenergic fibres predominantly innervate the ventricles.[38] Adrenergic activity induces several cardiovascular effects, including an increase in cardiac contractility (inotropy), frequency (chronotropy), rate of relaxation (lusitropy), and acceleration of impulse conduction through the atrioventricular node (dromotropy).[39] These effects are triggered by the catecholamine neurotransmitters noradrenaline and adrenaline acting on β_1-adrenergic receptors.[38]

The importance of the sympathetic nervous system in cardiac disorders, including ischaemic heart disease and heart failure, is well established.[40] Aberrant adrenergic function, including increased neurotransmitter release and reduced reuptake, occurs early in the development of heart failure as a compensatory mechanism for sustaining the cardiac output despite, for instance, a physical insult to the myocardium or increased peripheral resistance. However, if increased activity persists over time, the heart will progress into a state of chronic decompensated heart failure, and the hyperactive adrenergic activity will continue to stimulate the heart to work at a level much higher than the cardiac muscle can handle.[38]

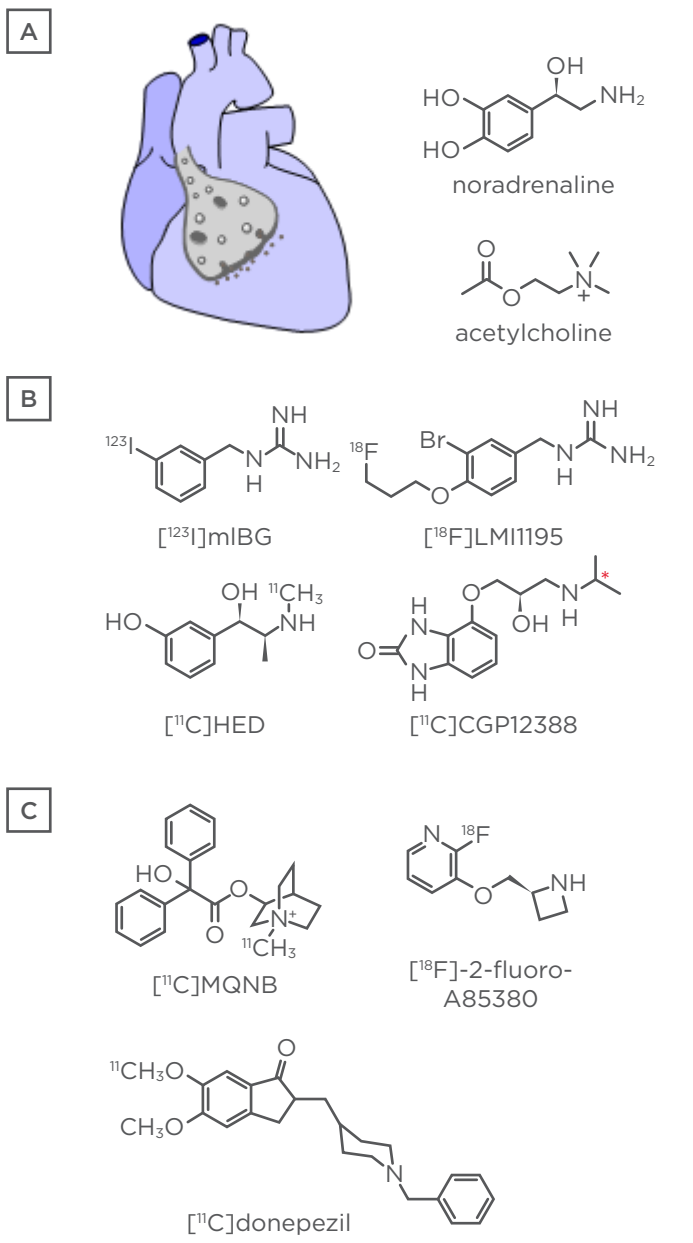

Figure 2: Cardiac innervation.
A) The heart is innervated by sympathetic and parasympathetic neurons, which signal through the neurotransmitters noradrenaline and acetylcholine, respectively. B) SPECT and PET radiotracers for assessing adrenergic innervation by measuring the presynaptic NAT ([123I]mIBG, [11C]HED, and [18F] LMI1195) and β_1-receptors ([11C]CGP12388). C) PET radiotracers for assessing parasympathetic innervation of the heart by measuring muscarinic receptors ([11C]MQNB), nicotinic $\alpha_4\beta_2$ receptors ([18F]-2-fluoro-A85380), and AChE ([11C]donepezil). AChE: acetylcholinesterase; mIBG: meta-[123I]iodobenzylguanidine; MQNB: N-[11C]methyl-quinuclidin-3-yl benzilate; NAT: noradrenaline transporter; PET: positron emission tomography; SPECT: single photon emission computed tomography.

This pathological adrenergic innervation can be measured using molecular imaging, for example SPECT and PET. Even though the cardiac specific isoforms of proteins involved in adrenergic signalling would allow, in theory, the development of dedicated and cardiac-specific imaging tools, the current toolbox is centred on general mimetics of the native neurotransmitters (Figure 2B).

Meta-[^{123}I]iodobenzylguanidine ([^{123}I]mIBG), an iodinated adrenergic neurotransmitter analogue, is commonly used for SPECT imaging of the presynaptic noradrenaline transporter (NAT).[41] NAT is a transmembrane protein that functions as a rapid noradrenaline reuptake system located at or near presynaptic terminals, and terminates noradrenergic signaling.[42] The cardiac signal of [^{123}I]mIBG is lower in individuals with heart failure due to a higher NAT occupancy, allowing the use of [^{123}I]mIBG as an independent predictor of heart failure progression and cardiac mortality. [^{123}I]mIBG has been used clinically in different continents for almost three decades.[43-45]

In order to make adrenergic innervation imaging available for quantitative and non-invasive PET imaging, ^{11}C and ^{18}F-labelled ligands have been developed (Figure 2B). For example, [^{11}C]meta-hydroxyephedrine ([^{11}C]HED) was developed based on metaraminol,[46] a synthetic false transmitter analogue of noradrenaline, which is transported by NAT. It is, however, resistant to catechol-O-methyl transferase and monoamine oxidase metabolism and is thus retained in nerve terminals due to continuous cyclical release and reuptake.[47] [^{11}C]HED displayed a lower myocardial signal in patients with congestive heart failure,[48] which correlated to patient prognosis.[49] The ^{18}F-labelled N-[3-bromo-4-(3-[^{18}F]-fluoro-propoxy)-benzyl-guanidine ([^{18}F]LMI1195) is structurally related to [^{123}I]mIBG and showed a reduced signal in rodent models of heart failure.[50] Additionally, first-in-human clinical trials showed its potential for assessing myocardial sympathetic activity *in vivo*.[51] The sensitive and quantitative PET imaging using [^{11}C]HED and [^{18}F]LMI1195 allowed evaluation of regional denervation and heterogeneity of innervation in the heart, and could be used for predicting sudden cardiac death.[48,51]

Following the chemical design of [^{123}I]mIBG, ^{18}F-labelled benzylguanidines (meta-[^{18}F]fluorobenzylguanidine ([^{18}F]mFBG)[52] and para-[^{18}F]fluorobenzylguanidine ([^{18}F]pFBG)) have been developed as alternative probes for imaging NAT using PET.[53,54] Both candidates have been successfully tested in neuroendocrine tumour mouse models but not yet for sympathetic nervous system dysfunction in cardiovascular diseases.

As a consequence of sustained enhanced sympathetic stimulation, postsynaptic β-adrenoceptors are downregulated in heart failure.[55,56] The recently disclosed ^{11}C-labelled beta-blocker S-4-(3-([^{11}C]-isopropylamino)-2-hydroxypropoxy)-2H-benzimidazol-2-one ([^{11}C]CGP12388) (Figure 2B) allowed measurements of postsynaptic β_1-receptor density and occupancy in patients with idiopathic DCM.[57] Thus, the current molecular imaging toolbox for sympathetic innervation enables measurements of all major pre and postsynaptic components of cardiac adrenergic signalling in humans. Given the widespread use of beta-blockers, it will be interesting to interrogate receptor dynamics as a function of (long-term) treatment.

Abnormal function of the parasympathetic system, in particular parasympathetic withdrawal, has been recognised as a key component of the molecular pathology underlying heart disease.[58,59] The highly specific muscarinic acetylcholinergic antagonist N-[^{11}C]methyl-quinuclidin-3-yl benzilate ([^{11}C]MQNB) has been used to measure myocardial muscarinic acetylcholine receptor (mAChR) density *in vivo* (Figure 2C).[60] [^{11}C]MQNB measurements in idiopathic DCM patients revealed an upregulation of myocardial mAChR, presumably as an adaptive mechanism to β-adrenergic stimulation.[61] Likewise, patients with myocardial infarction showed increased [^{11}C]MQNB signal in non-damaged left ventricular regions.[62] Since there is a decreased vagal tone in these pathologies, the role of upregulated expression of mAChR has still to be elucidated, and molecular imaging could play an integral role in understanding the dynamics between sympathetic and parasympathetic signalling in humans.

Acetylcholinesterase (AChE) inhibitors, such as pyridostigmine, have been used as parasympathomimetica, for instance in chronic heart failure patients.[63] Gjerløff et al.[64] tested [^{11}C]donepezil for measurements of AChE density in human peripheral organs and found a homogenous and displaceable signal of the tracer in the left ventricle of the heart, which might help in understanding the role of neurotransmitter metabolism in human disease (Figure 2C).

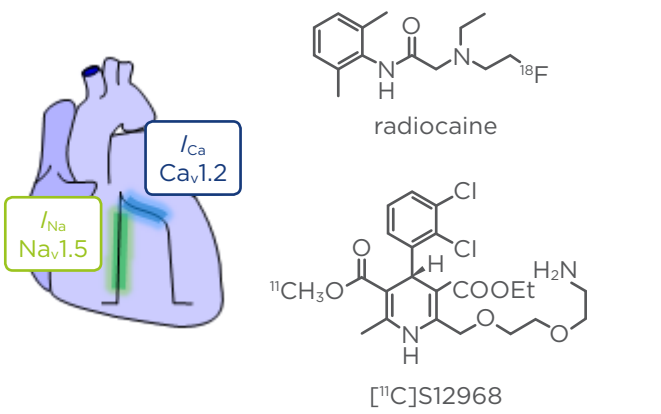

Figure 3: Cardiac conduction.
Electrical signalling through the myocardium couples excitation to contraction by the action of voltage-gated ion channels. Radiocaine imaging allows quantifying cardiac voltage-gated sodium channels *in vivo* using PET. The dihydropyridine derivative [^{11}C]S12968 enables measurements of L-type calcium channels in the heart.
PET: positron emission tomography.

Imaging of nicotinic AChR could help in better understanding their pathophysiological role in atherosclerotic disease progression and could thus be used as a diagnostic tool to risk-stratify patients for myocardial infarction and stroke.[65,66] [^{18}F]-2-fluoro-A85380 was the first PET radiotracer developed for imaging of the cardiac $\alpha_4\beta_2$-nicotinic AChR in healthy subjects and has already been tested in patients with Parkinson's disease and patients with multiple system atrophy (Figure 2C).[67]

Given the currently available imaging technology for muscarinic and nicotinic receptors, as well as AChE, understanding the dynamics of different components of the cholinergic innervation system in humans is within reach and would provide major scientific and clinical impact at relatively low risk of failure.

MYOCARDIAL CONDUCTION

The neuronal input from sympathetic and parasympathetic transmission is translated into cardiac action through a series of ion channels that respond to changes in membrane potential and ultimately couple excitation to contraction (EC-coupling).[68]

Fast activating voltage-gated sodium channels (Na_Vs), mainly $Na_V1.5$ (SCN5A), initiate action potentials and strongly depolarise cardiomyocytes (Figure 3).[69] Subsequent activation of high-voltage activated Ca^{2+} channels (L-type, mainly $Ca_V1.2$) leads to Ca^{2+} influx and further Ca^{2+} release from the sarcoplasmic reticulum, which increases the cytosolic Ca^{2+} concentration from nanomolar to micromolar concentrations.[70] This increase elicits conformational changes of the filament complex to facilitate the actin-myosin interaction and attains myocardial contraction.[68]

Numerous cardiac diseases are rooted in abnormal electrical signalling of the myocardium due to mutated ion channels or pathological expression levels.[71] Heterozygous mutations in *SCN5A* have been implicated in rare genetic arrhythmia, such as Brugada syndrome, long-QT syndrome, and progressive cardiac conduction defect. Abnormal expression levels of SCN5A have also been found in structural heart disease, including heart failure and ischaemic cardiomyopathy.[72] Furthermore, an increase in dihydropyridine (DHP) receptor expression, an L-type calcium channel, has been found in hypertrophied hearts.[73]

Recently, the first PET radiotracer for *in vivo* molecular imaging of cardiac SCN5A has been developed (Figure 3).[74] Radiocaine, an analogue of the classical Class-1b antiarrhythmic lidocaine, allows *in vivo* measurements of density and drug occupancy of cardiac SCN5A, which, to date, could only be determined invasively or through *in vitro* methods. Specific binding to SCN5A has been demonstrated in living rats and baboons; furthermore, autoradiography studies using myocardial tissue from human failing heart explants revealed reduced target density.

In order to assess changes in L-type calcium channel density *in vivo*, several DHP-based drugs have been radiolabelled with ^{11}C for PET imaging (Figure 3).[75] The amlodipine analogue [^{11}C]S12968 showed ≤80% specific binding in the myocardium and was used for *in vivo* measurement of myocardial DHP binding site density in beagles, with low doses of Ca^{2+} channel antagonists.

The ability to measure both Na_Vs and Ca_Vs as determining components of the EC-coupling opens the door for future clinical studies, which will precisely identify the molecular dynamics of myocardial ion channel signalling in human disease.

Table 1: Summary of molecular imaging tools and their (bio)medical application(s).

Radioligand	Imaging of	Application
Metabolism		
[^{18}F]FDG	Glucose uptake and retention	Myocardial viability[6]
[^{11}C]palmitate	FA uptake, β-oxidation, and storage	Diabetes mellitus,[9,10] idiopathic DCM[11]
[^{11}C]acetate	TCA cycle flux	Hypertrophic cardiomyopathy[14]
[^{123}I]IPPA	FA uptake, β-oxidation, and storage	Coronary artery disease, ischaemia[17]
[^{18}F]F7*	FA uptake, β-oxidation, and storage	*Coronary artery disease*,[18] *ischaemia*
[^{123}I]BMIPP	FA storage	Exercise-induced ischaemia,[19] coronary artery disease[20]
[^{18}F]FTHA	FA uptake and β-oxidation	Coronary artery disease,[29] pulmonary arterial hypertension[31]
[^{18}F]FTP	FA uptake and β-oxidation	Type 2 diabetes mellitus[34]
[^{18}F]FCPHA	FA uptake and β-oxidation	Coronary artery disease[36]
Innervation		
[^{123}I]mIBG	Presynaptic NAT, sympathetic innervation	Congestive heart failure[43-45]
[^{11}C]HED	Presynaptic NAT, sympathetic innervation	Congestive heart failure[48,49]
[^{18}F]LMI1195**	Presynaptic NAT, sympathetic innervation	*Congestive heart failure*[51]
[^{18}F]mFBG, [^{18}F]pFBG*	Presynaptic NAT, sympathetic innervation	*Congestive heart failure*[53,54]
[^{11}C]CGP12388	β_1-receptors, sympathetic innervation	Idiopathic DCM[57]
[^{11}C]MQNB	Muscarinic receptors, parasympathetic innervation	Idiopathic DCM,[61] myocardial infarction[62]
[^{11}C]donepezil**	AChE, acetylcholine metabolism	*Congestive heart failure*[64]
[^{18}F]-2-fluoro-A85380**	Nicotinic $\alpha_2\beta_4$ receptors, parasympathetic innervation	*Atherosclerosis*[67]
Myocardial conduction		
Radiocaine*	$Na_v1.5$ (SCN5A)	*Brugada syndrome*,[74] *LQT syndrome, progressive cardiac conduction defect*
[^{11}C]S12968*	LTCC	*Hypertrophic cardiomyopathy*[75]

*Only tested in animal models; **only tested in first-in-human clinical trials; potential future applications in italics.
AChE: acetylcholinesterase; DCM: dilated cardiomyopathy; FA: fatty acid; LTCC: L-type calcium channel; Na_v: voltage-gated sodium channels; NAT: noradrenaline transporter; TCA: tricarboxylic acid; LQT: long-QT.

PERSPECTIVE

Taken together, there is a wealth of well-understood tools for *in vivo* molecular imaging of cardiac function and health, including oxidative metabolism, adrenergic and cholinergic innervation, and myocardial electrical conduction (Table 1). The majority of these tools have already been validated in humans, displaying minor radiation exposure, or have reached the stage of clinical translation, allowing widespread clinical studies in the future. Further evaluation in clinical trials will provide data on the impact of molecular imaging on changing diagnosis, treatment, and prognosis. We are convinced that the growing infrastructure of clinical PET magnetic resonance cameras will play an integral role in expanding the use of molecular imaging in cardiology, in particular with recent advances in cardiac gating reconstruction.[76] The combined information of structural integrity and changes in the cardiac molecular machinery will not only yield impactful insights in basic research but will also improve individualised patient care.

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NEUTROPHILS IN ACUTE CORONARY SYNDROME

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ABSTRACT

Acute coronary syndrome (ACS) encompasses a spectrum of clinical disorders of myocardial ischaemia or infarction, with atherosclerosis leading to coronary plaque formation the predominant disease process. Alterations of endothelial cell integrity involving atherosclerotic plaque surfaces, such as plaque rupture or erosion, can lead to atherothrombosis with subsequent interruption to myocardial blood supply. Over the past two decades, it has become increasingly apparent that inflammation plays a pivotal role in the initiation and progression of atherosclerosis. Inflammatory cytokines have been shown to correlate with the risk and burden of coronary artery disease and there is a growing body of evidence demonstrating the presence of various immune cells in atherosclerotic plaques and coronary thrombus specimens. Due to improved cellular detection methods compared to earlier studies, neutrophils are being increasingly recognised as a key player in the process of athero-inflammation. The aim of this review is to: i) outline the role of neutrophils in ACS and atherothrombosis, ii) describe the process of inflammasome-mediated release of inflammatory cytokines from neutrophils, and iii) discuss multiple parameters of neutrophil activity in ACS, including peripheral neutrophil/lymphocyte ratio; neutrophil microparticle release; expression of neutrophilic granular proteins, including myeloperoxidase, neutrophil elastase, and metalloproteinases; neutrophil extracellular traps release; tissue factor; and neutrophil-macrophage interactions.

Keywords: Neutrophils, acute coronary syndrome (ACS), atherosclerosis, inflammation.

INTRODUCTION

Acute coronary syndrome (ACS) encompasses a spectrum of clinical disorders of myocardial ischaemia or infarction, presenting as unstable angina, non-ST segment elevation myocardial infarction (NSTEMI) or ST-segment elevation myocardial infarction (STEMI). There are various aetiologies underpinning ACS, but the predominant disease mechanism is atherosclerosis, with the potential for subsequent plaque disruption leading to thrombosis and cessation of myocardial blood flow.

Atherosclerosis is a progressive disease of plaque deposition, which consists of lipids, smooth muscle cells, and calcium within the layers of the blood vessel. It is thought to be triggered by the deposition of cholesterol-containing plasma lipoproteins in the subendothelium at points of altered flow haemodynamics, leading to inflammatory changes in endothelial cells.[1] Over time, there is gradual narrowing of the lumen of the coronary artery, leading to myocardial ischaemia as well as disruption of laminar blood flow, further disrupting the integrity of endothelial cells. Disruption of coronary plaque and resultant exposure of its contents (lipids, necrotic core containing inflammatory and apoptotic cells) causes platelet aggregation and thrombosis. If complete occlusion of the coronary blood supply occurs, this results in a STEMI, whereas a NSTEMI results from a transient or incomplete obstruction of flow.[2] These mechanisms have been extensively researched in clinicopathological studies and a spectrum of plaque surface alterations have been identified, including fissuring, erosion, ulceration, and rupture.[3] The mechanism of disruption of atherosclerotic plaques with the highest risk of atherothrombosis have broadly been classified into plaque rupture and plaque erosion. Plaque rupture

is defined as a structural defect in the fibrous cap that separates the lipid-rich necrotic core of a plaque from the lumen of the artery with destruction of the media layer, whereas plaque erosion is when the endothelium is missing but the media layer remains intact. These two processes of plaque remodelling differ phenotypically in terms of cellular content, inflammatory activity, and extracellular matrix composition, as evidenced by autopsy findings of patients with ACS.[4] Ruptured plaques are associated with larger necrotic cores, higher macrophage content, but decreased smooth muscle cells and extracellular matrix (hyaluronic acid, proteoglycans) compared to eroded plaques. Intravascular imaging techniques, such as optical coherence tomography, are now able to identify thin cap fibroatheromas and assess necrotic core thickness, both of which are associated with plaque rupture.[5]

There is convincing evidence from animal studies, that in addition to plaque characteristics, the immune system and inflammation have a significant role in atherosclerosis and the pathogenesis of ACS. Modified lipoproteins trapped within the subendothelium attract circulating inflammatory cells, which then infiltrate into atherosclerotic plaque. Various immune cells, including lymphocyte subsets, dendritic cells, platelets, and monocytes/macrophages, have been implicated in atherosclerosis-associated inflammation. However, there is now growing evidence that neutrophils play a key role in linking the immune system and atherosclerosis. Neutrophils are the most abundant white blood cell in humans and are an important component of the innate immune system, which is the non-specific first line of defence against pathogens. Neutrophils contain a variety of granular proteins, including antimicrobial peptides, proteases, and reactive oxygen species (ROS), which are released to destroy offending pathogens.[6] Neutrophil production is primarily regulated by granulocyte colony stimulating factor (G-CSF) and interleukin (IL)-23 whilst retention of neutrophils in the bone marrow is regulated by chemokine receptors CXCR2 and CXCR4. Hyperlipidaemia can lead to dysregulation of neutrophil homeostasis and promotes mobilisation of neutrophils from the bone marrow as well as stimulation of granulopoiesis in the bone marrow and spleen.[7] Neutrophils are primed by either external stimuli (foreign pathogens) or internal stimuli (cytokines and chemokines), which guide the primed neutrophils to the site of infection or inflammation. This then leads to the mobilisation of intracellular granules that contain preformed receptors to the plasma membranes and results in the expression of receptors (intra and extracellular) and cytokines, which further enhance neutrophil function. Neutrophil granules, which contain lysosomal proteins such as myeloperoxidase (MPO), neutrophil elastase, cathepsin G, protease-3, and matrix metalloproteinases (MMP) are mobilised upon priming of the cell.

In atherosclerosis, failed attempts to clear lipoproteins from the subendothelium of blood vessels and the death of immune cells (mainly macrophages) and smooth muscle cells lead to the formation of a proinflammatory necrotic core. In response to this, local inflammatory cells within the coronary vasculature, such as endothelial cells, leukocytes, and platelets, generate and release cytokines, small proteins involved in cell signalling. These cytokines have the potential to activate humoral and cellular factors causing disruption of the balance of anticoagulants and procoagulants, leading to downstream activation of the complement and coagulation pathways, which leads to inflammation and thrombotic processes. This is reflected in multiple clinical studies demonstrating a strong association between multiple inflammatory biomarkers (hsCRP, IL-6) and the risk of incident coronary artery disease.[8,9] The inflammasome is a multiprotein immunomodulatory complex and consists of many different subtypes. Of these, the NLRP3 inflammasome has been extensively studied and plays a significant role in athero-inflammation.[10] The activation of the NLRP3 inflammasome in neutrophils activates caspase-1, which is responsible for the generation of inflammatory cytokines, including IL-1β and IL-18, both of which have been implicated in coronary artery disease and atherothrombosis.[11,12] Preliminary data from the CANTOS trial, which investigated the efficacy of canakinumab, an IL-1β antagonist, in patients with a history of myocardial infarction and a persistently elevated CRP level despite contemporary secondary prevention strategies, has shown a decrease in the recurrence of major adverse cardiovascular events.[13] Trans-coronary (difference between systemic and coronary sinus) IL-1β and IL-18 levels have also been shown to strongly correlate with disease activity in patients with ACS.[14] Moreover, a reduction in inflammatory cytokines with statin treatment has been shown to reduce atherosclerosis progression on intracoronary imaging, as well as cardiovascular events, including death and myocardial infarction

in patients with ACS, independent of atherogenic lipid levels.[15]

The role of neutrophils in atherosclerosis was largely unappreciated in initial studies due to their limited life span, high turnover with rapid clearance by macrophages, marked phenotypic variation of neutrophil surface markers, and a lack of adequately sensitive and specific detection methods.[7,16] More recently however, their identification in atherosclerotic plaques has increased due to better cellular detection methods. Neutrophils are now able to be identified in tissue specimens thanks to improved live imaging fluorescent intravital microscopy[17] techniques, such as multi-photon excitation imaging.[18] This is used in conjunction with immunohistochemistry, enzyme-linked immunosorbent assay (ELISA), and flow cytometry methods using antibodies against lymphocyte antigen 6 complex locus G6D, Ly6G (expressed on mouse neutrophils), and human neutrophil cell surface markers CD-66b, CD-177, and CD-11b, as well as neutrophilic proteins such as myeloperoxidase (MPO) and elastase. Neutrophils, identified on intravital and confocal microscopy using flow cytometry with staining against Ly6G and leukocyte common antigen CD45, along with enhanced green fluorescence protein detection, have been demonstrated in the shoulder regions of atherosclerotic plaques from enzymatically digested mouse aortas.[19] Another mouse model showed that specific neutrophil depletion led to a reduction in atherosclerotic plaque sizes in mice who were given a high fat diet.[20] In addition to animal studies, CD66b-positive neutrophils have also been identified in human autopsy atherectomy specimens, coronary thrombi, and peripheral blood samples from patients with ACS.[21-23]

NEUTROPHIL EFFECTS ON MONOCYTE/MACROPHAGE FUNCTION

Neutrophils are important facilitators of monocyte/macrophage function. Monocytes migrate into the subendothelial space, ingest unchanged and oxidised lipoproteins, and then transform into cholesterol-laden foam cells. These foam cells contribute to a proinflammatory state within advanced atherosclerotic plaques and also form necrotic cores that can cause plaque destabilisation and rupture.[24] Neutrophils within atherosclerotic plaques play a role in monocyte recruitment and adhesion in early atherosclerosis via monocyte chemoattractant protein-1 (MCP-1), azurocidin, as well as granule proteins cathepsin G and LL-37/cathelicidin.[25] In addition to recruitment, circulating neutrophils also play a role in the activation of monocytes via toll-like receptor (TLR)-4 and the generation of soluble IL-6 receptors.[26] Neutrophils have been shown to effect efferocytosis, the process of removing dying cells and components of the necrotic core within plaques, by releasing high mobility group box 1, which binds to integrins on macrophages and inhibits MFG-E8, a bridging molecule between apoptotic cells and macrophages during efferocytosis.[7] Defective efferocytosis leads to an accumulation of necrotic cells, resulting in persistent plaque inflammation as well as increasing the size of the necrotic core, both of which are associated with plaque rupture.[27]

NEUTROPHILS IN PLAQUE REMODELLING

As mentioned earlier, alterations and remodelling of atherosclerotic plaque surfaces can lead to superimposed thrombosis and clinical events. Neutrophils play a significant role in the process of atherosclerotic plaque erosion, which has been estimated to underlie ~40% of coronary atherothrombotic events.[28] TLR are pattern recognition proteins that are key components of the innate immune system. TLR are found on many cells, including coronary endothelial cells, and their agonism leads to multiple important cellular mechanisms, including the generation of endoplasmic reticulum stress-ROS, endothelial cell apoptosis, and impairment of endothelial cell repair. This causes detachment of plaque endothelial cells, leading to superficial erosion and thrombotic complications. Circulating and intra-plaque neutrophils potentiate and amplify effects of TLR2 agonism, causing the propagation of superficial plaque erosion.[29] A murine model of plaque erosion demonstrated substantial neutrophil accumulation at sites of early erosion as a result of endogenous TLR2 activation of endothelial cells.[30] This is clinically relevant, with autopsy studies showing an increased proportion of ACS cases to be caused by plaque erosion compared to overt plaque rupture.[4]

PARAMETERS OF NEUTROPHIL ACTIVATION AND FUNCTION IN ACUTE CORONARY SYNDROME

Multiple parameters of neutrophil activity in ACS patients have been studied, including peripheral

neutrophil/lymphocyte ratio, neutrophil-specific microparticles, neutrophilic granular protein (neutrophil elastase, MPO, and MMP) release, neutrophil extracellular traps (NET) release, and interactions with tissue factor (Figure 1 and Table 1).

Peripheral white blood cell counts have been shown to be an independent prognostic factor in patients with ACS and positively correlate with the burden of coronary artery disease.[31] The neutrophil to lymphocyte ratio is able to predict short and long-term mortality in patients with ACS and has correlated well with GRACE and SYNTAX scores, which are common clinical scoring systems that predict outcomes in ACS. Systemic polymorphonuclear counts have also been shown to be among the most robust predictors of acute coronary events and to directly impact short and long-term clinical outcomes.[32] The low cost of measuring peripheral blood white blood cell counts is an additional advantage, facilitating its inclusion as an additional biomarker to predict outcomes in these patients.

Microparticles are small vesicles that arise from the plasma membrane of cells, and are commonly released after activation or early apoptosis.

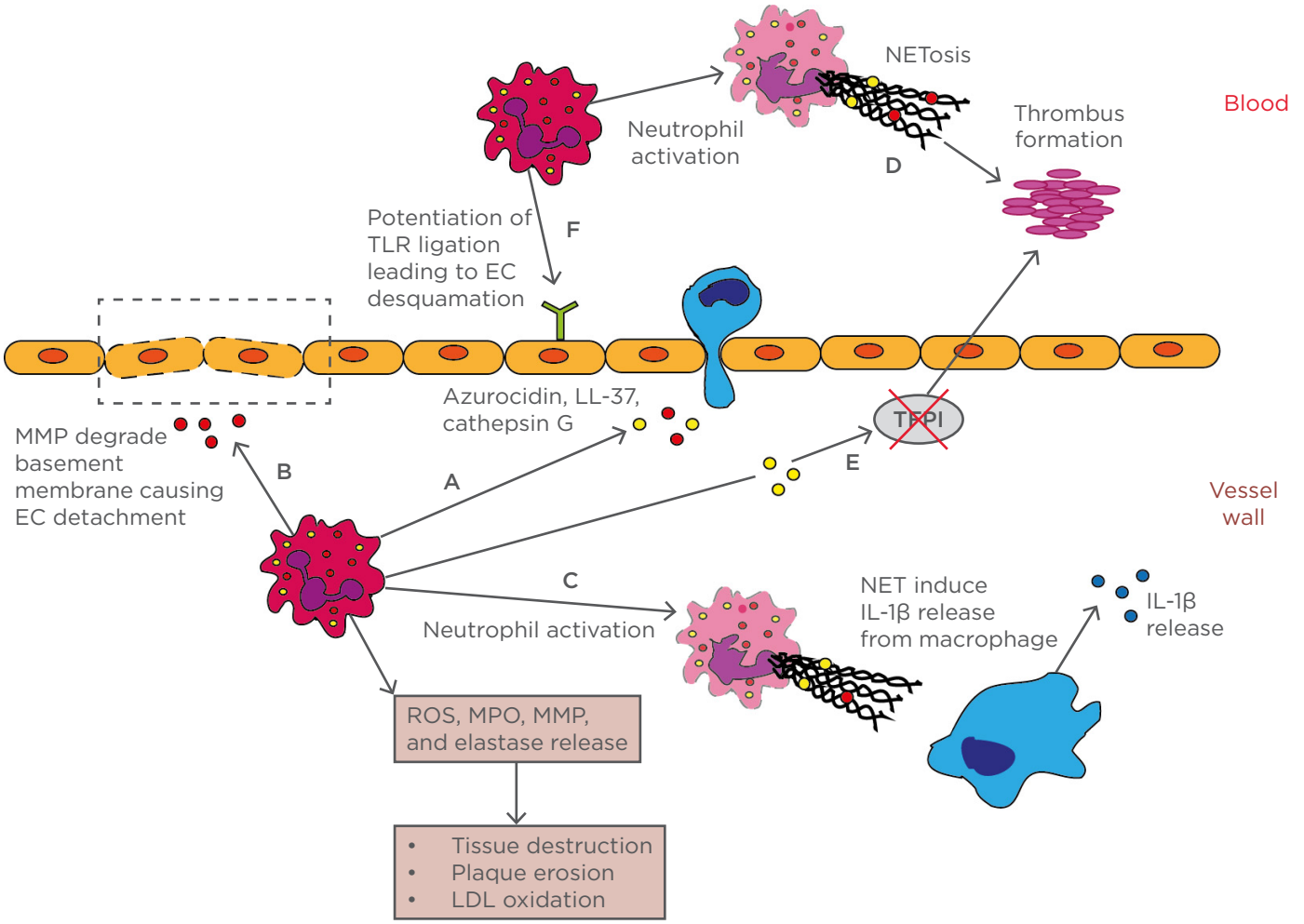

Figure 1: Neutrophils in atherosclerosis.

A) Neutrophils release azurocidin, LL-37, cathepsin G, MPO, and MCP-1, which are monocyte chemoattractants; B) Neutrophilic MMP degrade basement membrane causing endothelial cell detachment; C) NET complexes stimulate proinflammatory cytokine, IL-1β, release from macrophages; D) Activated neutrophils release NET complexes that facilitate thrombus formation; E) Neutrophil elastase and cathepsin G inhibit tissue factor plasminogen inhibitor, leading to thrombus formation; F) Neutrophils potentiate TLR ligation leading to endothelial cell detachment and plaque erosion.

EC: endothelial cells; IL-1β: interleukin-1β; LDL: low-density lipoprotein; MCP-1: monocyte chemotactic protein-1; MMP: matrix metalloproteinases; MPO: myeloperoxidase; NET: neutrophil extracellular traps; ROS: reactive oxygen species; TFPI: tissue factor plasminogen inhibitor; TLR: toll-like receptor.

Table 1: Parameters of neutrophil function in acute coronary syndrome.

Neutrophil effector function/component	Effect
Facilitators of monocyte/ macrophage function	• Monocyte recruitment and adhesion • Monocyte activation of monocytes
Potentiation of toll-like receptor agonism on endothelial cells	• Generation of endoplasmic reticulum stress-reactive oxygen species • Endothelial cell apoptosis • Impairment of endothelial cell repair • Detachment of endothelial cells leading to atherosclerotic plaque erosion
Neutrophil elastase	• Degradation of elastin, collagen, fibronectin, and proteoglycans in the extracellular matrix • Local tissue destruction and mechanical weakening of the fibrous cap on atherosclerotic plaques • Activation of MMP • CD163 cleavage and intraplaque haemoglobin clearance
MMP	• Degradation and turnover of the extracellular matrix leading to destabilisation of fibrotic caps of atherosclerotic lesions • Monocyte recruitment
MPO	• Generation of numerous reactive oxygen species. The reduction of molecular oxygen produces superoxide and is the precursor of most other reactive oxygen species • Increases activity of MMP-8 and MMP-9 • Dissolution of the fibrous cap of plaque, which can lead to plaque rupture
Neutrophil microparticles	• Active role in atherogenesis, inflammation, and thrombosis • Proinflammatory and prothrombotic properties, including activation of tissue factor and the complement cascade • Activation of endothelial cells • Release of MPO, elastase, and MMP
NET	• Potent proinflammatory, cytotoxic, and prothrombotic effects • Primary scaffold for platelets, fibrin, and erythrocytes to adhere to • Component of coronary thrombus • Delivery of active tissue factor
Inflammasome-mediated generation of proinflammatory cytokine IL-1β	• Atherogenesis and atherothrombosis
Surface tissue factor expression and inactivation of tissue factor pathway inhibitor	• Platelet and coagulation cascade activation • Generation of thrombin and subsequent clot formation on ruptured/eroded plaque • Interaction with functional tissue factor bearing NET complexes
Neutrophil-platelet aggregate formation	• Increased adhesiveness of neutrophils to platelets facilitating aggregate formation which contribute to microvascular obstruction

IL-1β: interleukin-1β; MMP: matrix metalloproteinases; MPO: myeloperoxidase; NET: neutrophil extracellular traps.

The microparticles play an active role in atherogenesis, inflammation, and thrombosis with circulating leukocyte-derived microparticles having been shown to be predictive of atherosclerosis.[33] Activated circulating neutrophils shed CD66b+ microparticles, which have proinflammatory and prothrombotic properties, including activation of tissue factor and the complement cascade.[34] Neutrophil specific CD66b+ microparticles also activate endothelial cells and promote the release of proteolytic enzymes, such as MPO, elastase, and MMP-9, all of which can lead to local tissue destruction and mechanical weakening of the fibrous cap on atherosclerotic plaques. Sampling of the coronary sinus directly after percutaneous coronary intervention (PCI) has shown an increased release of neutrophil-derived CD66b+ microparticles and MPO in patients with ACS compared to stable angina.[35] These findings suggest that neutrophils are activated in vulnerable atherosclerotic plaques, with CD66b+ microparticles either being embedded within the

coronary plaque/thrombus complex and released by mechanical disruption from PCI, or *de novo* activation of neutrophils as a result of PCI exposing neutrophils to cholesterol crystals (which are more abundant in vulnerable plaques compared to stable plaques), leading to cell death and the release of NET.[36]

Neutrophil elastase is a serine protease that causes degradation of elastin, collagen, fibronectin, and proteoglycans in the extracellular matrix. Neutrophil elastase has been detected in the shoulder region of atherosclerotic plaques, suggesting that it might play a role in the remodelling of atherosclerotic plaques from its direct effects on extracellular matrix degradation, as well as activation of MMP.[37] Neutrophil elastase also cleaves CD163, a monocyte/macrophage cell surface receptor for haemoglobin-haptoglobin complexes, which clears cell free haemoglobin generated from haemolysis of extravasated red blood cells. The clearance of haemoglobin (which can deposit within atherosclerotic plaques as a result of intraplaque haemorrhage) is significantly impaired by neutrophil elastase induced CD163 cleavage.[23] The resultant accumulation of plaque haemoglobin promotes inflammation and oxidative stress, and can then lead to plaque instability and vulnerability. ACS patients have been shown to have higher neutrophil elastase levels compared to stable angina and control patients, independent of traditional cardiovascular risk factors.[38]

Another important group of neutrophilic enzymes are the MMP. MMP-1, 8, 9, and 13 are responsible for the degradation and turnover of the extracellular matrix and can lead to destabilisation of fibrotic caps of atherosclerotic lesions, causing plaque rupture. These MMP have been shown to accelerate atherogenesis and extracellular matrix degradation in both animal and human studies.[39] Clinical studies of ACS patients have also shown that MMP levels correlate with optical coherence tomography-proven plaque rupture and are predictive of future cardiovascular events.[40,41]

Activated neutrophils also produce MPO, a member of the haem peroxidase superfamily, which is stored in the azurophilic granules of the neutrophil and is responsible for the generation of numerous ROS. The reduction of molecular oxygen (O_2) produces superoxide ($O_2^{\bullet-}$) which is the precursor of most other ROS.[42]

Investigation of MPO in animal models of atherosclerosis have produced variable and contrasting results.[43] In contrast to animal studies, the presence of MPO in human atherosclerosis has been consistently found. ROS have been associated with multiple cardiovascular adverse events, including atherosclerosis, heart failure, and hypertension.[44] MPO typically uses hydrogen peroxide to generate hypochlorous acid, which has microbicidal properties but also disrupts normal vascular haemostasis. MPO-generated ROS increase the activity of MMP-8 and MMP-9.[45] Serum MPO levels have been shown to correlate with severity of angiographic coronary artery disease,[46] as well as being predictive of subsequent cardiac events (nonfatal myocardial infarction, death, and need for coronary revascularisation) in patients presenting with either chest pain or ACS.[47] Elevated levels of MPO have also been described at sites of plaque erosions in patients with ACS,[48] postulating that activated neutrophils adhere to atherosclerotic plaques with impaired endothelial integrity due to erosive events. In addition to this, MPO has been shown to also cause dissolution of the fibrous cap of a plaques, which leads to plaque rupture and superimposed thrombus formation.[49]

Another neutrophil function that has been gathering interest is their ability to release NET. The release process of these chromatin complexes from the nucleus of neutrophils is referred to as NETosis, which is a cell death programme different to apoptosis or necrosis and helps neutrophils to more efficiently eliminate pathogens by forming a mechanical barrier to 'trap' pathogens.[50] NET are made up of neutrophilic granular and cytosolic proteins, proteases, and chromatin, which are wound in sequence around histone protein cores.[51] Citrullination of histones via peptidylarginine deiminases (PAD) is essential in NETosis.[50] Recent evidence has emerged suggesting that in addition to infectious disease, NET also play a role in non-infectious disease processes, including atherosclerosis and thrombosis,[52] and this has resulted in a plethora of studies looking at the specific effects of NET in modulating components of the immune system causing atherogenesis. The release of NET causes potent proinflammatory, cytotoxic, and prothrombotic effects[53,54] and serves as a primary scaffold for platelets, fibrin, and erythrocytes to adhere to, thus forming a link between inflammation and thrombosis. Intracoronary thrombus aspirate samples from patients with acute myocardial infarction revealed

that high mobility group box 1 proteins, which were presented to neutrophils by activated platelets, induced the formation of NET.[55] This highlights the interaction between neutrophils and platelets in atherothrombosis and postulates that NET could contribute to plaque rupture. The quantity of NET formation in coronary artery thrombus in patients with STEMI has also been shown to correlate positively with enzymatic and magnetic resonance imaging (MRI) measured infarct size and negatively with ST segment resolution.[56] One suggested theory is that coronary NET may be propagating thrombosis and inflammation distally into the area of infarction causing further myocyte necrosis, leading to dysfunction of the microvasculature.[57] Another study of thrombus aspirates in STEMI patients undergoing PCI revealed neutrophils release NET which, in turn, expose active tissue factor in infarct-related areas, but not in non-infarcted regions.[58] This suggests that local release of NET in sites of plaque rupture contribute to atherothrombosis via the delivery of active tissue factor. Nucleosomes and double-stranded DNA, which are key components of NET, have been shown to be independently associated with severe coronary atherosclerosis[59] and this has led to nucleosomes and double-stranded DNA being used as surrogate markers of NETosis.

Atherosclerotic plaque rupture exposes its prothrombotic contents (modified lipids, highly inflammatory cells, and necrotic core) to circulating blood, resulting in platelet and coagulation cascade activation, which ultimately leads to atherothrombosis via fibrin deposition and entrapment of blood cells.[60] Activated neutrophils are major contributors to arterial thrombosis after plaque rupture. Circulating neutrophils express tissue factors on their cell surfaces and their activation can lead to the generation of thrombin and subsequent clot formation.[61] As discussed earlier, neutrophils also release tissue factors through NET and functional tissue factor bearing NET have been identified at culprit artery sites of patients with STEMI.[58] Activated neutrophils within atherosclerotic plaques can also inactivate tissue factor pathway inhibitor, which is an important regulator of tissue factor-induced blood coagulation, via the release of proteases at the site of vessel injury.[62] ROS generated by activated neutrophils within atherosclerotic plaques also cause platelet activation. This accentuation of prothrombic processes by neutrophils can lead to significant clinical outcomes in ACS. In particular, activated circulating neutrophils promote microvascular obstruction via neutrophil plugging and microthrombi formation in the microcirculation, leading to increased infarct size.[63] The proinflammatory state in ACS leads to increased neutrophil-platelet adhesion with CRP and IL-6 levels strongly correlating to neutrophil-platelet aggregate formation detected by flow cytometry.[64] Moreover, an abundance of highly activated neutrophil/platelet aggregates has been identified in aspirated coronary thrombus in STEMI patients undergoing primary PCI.[56] These neutrophils express adhesion markers such as CD11a, CD11b, and CD66b, all of which increase adhesiveness of neutrophils to platelets, facilitating aggregate formation that can further contribute to microvascular obstruction.

POTENTIAL THERAPEUTIC OPTIONS

As the role of neutrophils in cardiovascular disease is increasingly appreciated, potential treatment strategies targeting NET release and breakdown have been studied. Deoxyribonuclease (DNAse), an enzyme that breaks down NET, has been shown in a clinical study of STEMI patients to accelerate lysis of coronary thrombi.[56] The study demonstrated that DNAse levels correlated negatively with coronary NET burden and cardiac MRI-measured infarct size. DNAse treatment in a murine model of myocardial ischaemia resulted in decreased infarct sizes and infiltration of neutrophils in infarcted myocardium, as well as reduced circulating nucleosome levels, an indirect measure of NETosis.[65] Another therapeutic agent targeting NET are PAD inhibitors. PAD are enzymes involved in citrullination of histones and the use of Cl-aminidine, a peptidomimetic pan-PAD inhibitor, in apolipoprotein E-deficient mice resulted in significantly reduced atherosclerotic lesion areas.[66] Colchicine, an anti-inflammatory agent, has been shown to acutely suppress caspase-1 activity and inhibit inflammasome activation in monocytes from ACS patients. Similarly, targeting the neutrophil inflammasome or inhibiting its assembly could also be a therapeutic strategy in reducing the athero-inflammatory cytokine IL-Iβ.[11,13]

In summary, there are abundant data demonstrating the role of neutrophils in ACS. This knowledge presents opportunities to develop novel diagnostic and prognostic biomarkers and therapeutic agents that specifically target neutrophil activation and/or downstream mediators.

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ECTOPIC BEATS: HOW MANY COUNT?

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ABSTRACT

Premature atrial and ventricular contractions, or ectopic beats, are frequently detected on routine electrocardiogram monitoring. They are often considered to be benign with no pathological significance; however, the literature suggests that higher ectopic burdens may have clinical importance. This paper reviews the current literature and provides the treating physician with an understanding of when ectopic beats should be deemed significant and when treatment may be appropriate.

Keywords: Premature atrial complex (PAC), premature ventricular complex (PVC), ectopy, ectopic beat, atrial fibrillation (AF), stroke.

INTRODUCTION

Premature atrial and ventricular contractions, or ectopic beats, are frequently detected on routine electrocardiogram (ECG) monitoring. They are often considered to be benign with no pathological significance; however, data suggest that higher ectopic burdens may have clinical importance.

PREMATURE ATRIAL COMPLEXES

Worldwide, stroke is a leading cause of mortality and the burden of disease on healthcare services is steadily increasing.[1] Approximately 30–40% of ischaemic strokes are cryptogenic in nature with no clear pathological cause;[2] it is thought that many could be secondary to subclinical or asymptomatic atrial fibrillation (AF). There is growing evidence that premature atrial complexes (PAC) may be associated with the development of AF, and therefore with an increased risk of stroke.

Haïssaguerre et al.[3] investigated the link between PAC and the onset of AF. They identified individuals with frequent episodes of paroxysmal AF and mapped which rhythms commonly preceded the onset of AF. The trigger was often a PAC originating from a pulmonary vein, and radiofrequency ablation of this area of ectopic activity led to decreased recurrence in arrhythmic activity.[3]

Haïssaguerre et al.'s[3] findings prompted further research toward the link between higher burdens of PAC and the risk of developing AF. Wallmann et al.[4] recruited patients who had suffered an acute ischaemic stroke without prior documented AF and performed 7-day Holter monitoring at baseline, 3 months, and 6 months. Patients were then grouped according to their total burden of PAC over the 7-day period. A higher burden of PAC was classified as ≥70 within the first 24-hour period. In individuals with a higher burden of PAC, 26% had AF, which was five-times more than those in the low burden group.[4]

The Copenhagen Holter study[5] investigated AF prevalence and its effect on morbidity and mortality and was one of the largest studies of its kind in healthy individuals. Investigators contacted all men aged 55 years, and all men and women aged 65, 70, and 75 years in two different areas of the city. Individuals with previous cardiovascular ill health were excluded, leaving 678 participants who went on to complete 48-hour ambulatory ECG monitoring. In 2010, Binici et al.[6] used these data to explore the link between excessive atrial ectopy and the primary endpoints of death or stroke, and secondary endpoint of AF. Excessive atrial ectopic activity was defined as ≥30 PAC per hour or a single run of ≥20. Over a median follow-up period of 76 months, it was found that excessive PAC

were associated with a >60% increase in the risk of death or stroke, and a 2.7-fold increase in the development of AF.

Using a more clinically applicable approach, Larsen et al.[7] took data from the same study in an attempt to further clarify the link between higher burdens of atrial ectopy and stroke with a longer follow-up period (median: 14.4 years). Individuals were also risk stratified using the CHA_2DS_2VASc scoring system (congestive heart failure, hypertension, aged >75 years, diabetes, previous stroke or transient ischaemic attack, vascular disease, aged 65–74 years, female sex).[8] It was found that those with increased atrial ectopic activity had an increased adjusted risk of stroke (hazard ratio [HR]: 2.02; 95% confidence interval [CI]: 1.17–3.49), and a significantly higher risk of stroke (p=0.0002) was identified in subjects with excessive PAC (≥30 per hour or a run of ≥20). Subjects with both excessive PAC and a CHA_2DS_2VASc score >2 had an absolute risk of stroke equal to 2.4% per year.[7]

The intervention arm of the EMBRACE trial[9] was used to investigate the prevalence of subclinical AF in patients who had suffered either a transient ischaemic attack or cryptogenic stroke. Recruits underwent 24-hour ambulatory ECG monitoring and, if AF was not detected on initial monitoring, they were then assigned to 30-day external loop recording. The overall 90-day AF detection rate was 16%, and the probability of detecting AF increased with higher atrial ectopic activity. Patients with <100 PAC/24 hours had a probability of AF detection of <9%, whereas the probability increased to 40% in those with a burden of >1,500 PAC/24 hours.[9] This again serves to highlight the need for much longer periods of monitoring, especially in patients with higher PAC burdens.

PREMATURE VENTRICULAR COMPLEXES

Higher burdens of premature ventricular complexes (PVC) post myocardial infarction are associated with a poorer prognosis.[10] Traditionally it has been thought that the use of anti-arrhythmic therapy in such patients may reduce the risk of sudden cardiac death; however, findings from CAST[11] demonstrated that suppression of ventricular ectopy with Class 1a anti-arrhythmic agents was in fact associated with higher rates of death due to their proarrhythmic properties.

In patients with underlying structural heart disease, PVC can trigger ventricular arrhythmia,[12] but in individuals with structurally normal hearts they are often considered a benign process that does not require treatment or intervention.[13] However, Engel et al.[14] showed the presence of ventricular ectopics on resting ECG to be significant. Patients with resting ventricular ectopy had a significantly increased risk of all-cause and cardiovascular mortality. They also categorised patients by heart rate and showed mortality to increase with heart rate and to double in the presence of PVC.[14] This increased adrenergic drive was proposed as a possible mechanism for incidental heart failure in tachycardia-driven PVC states.

The presence of PVC has been linked with incidental heart failure. In the ARIC study, Agarwal et al.,[15] found that participants, who at baseline had no heart failure or coronary artery disease, had an increased risk of incidental heart failure if PVC were present on baseline ECG. Further work by Agarwal et al.[16] demonstrated that the presence of PVC was associated with nearly a two-fold risk of systolic heart failure.

A high frequency of PVC may result in left ventricular systolic dysfunction. In 2010, Baman et al.[17] sought to quantify what burden of ventricular ectopy was associated with an increased risk of developing an ectopic-induced cardiomyopathy.[17] They took patients with persistent ventricular ectopy despite best medical therapy, and calculated their PVC burden and left ventricular ejection fraction (LVEF) pre and post ablation. PVC-induced cardiomyopathy was defined as an improvement in LVEF of ≥15%. The investigators identified that a total PVC burden of >24% per 24 hours was associated with an increased risk of developing a cardiomyopathy with almost 80% sensitivity and specificity for the diagnosis of PVC-induced dilated cardiomyopathy. However, the minimal burden of PVC seen with cardiomyopathy is 10% over a 24-hour period.[17] The affect that a PVC has on ventricular filling and contractility, as well as the reversal in left ventricle systolic function seen post ablation, could make this a possible mechanism for left ventricle dysfunction in higher burdens of PVC.[18]

Penela et al.[19] further highlighted the importance of suppressing ventricular ectopy in patients with systolic function poor enough to mandate primary prevention implantable cardioverter defibrillator (ICD) implantation. Patients with high ectopic burdens who met the criteria for ICD implantation had the ICD withheld and instead underwent

ventricular ectopic ablation. They were followed up at 6 and 12 months. The investigators found that at 12 months the LVEF had increased from a baseline of 28% ± 4% to 42% ± 12% at 12 months after PVC ablation.[19] This emphasises the need for consideration of PVC ablation in those patients with indication for ICD and the potential for LVEF to recover, such that indication for ICD implantation can be reassessed at 12 months.

Dukes et al.[20] further investigated the association between PVC burden and myocardial dysfunction. Participants with normal LVEF and no history of heart failure were studied; 1,139 were randomly assigned to 24-hour ambulatory ECG monitoring. Baseline echocardiography was performed and 842 participants went on to have repeat echocardiography after 5 years. Over the study period, it was shown that a two-fold increase in PVC burden from baseline was associated with a statistically significant greater chance of reduction in LVEF. Patients with known systolic dysfunction and higher burdens of ventricular ectopy showed a higher incidence of congestive cardiac failure (HR: 1.08; 95% CI: 1.03–1.17) and higher burdens of ventricular ectopy were also associated with increased mortality.[20]

The use of ambulatory monitors in many studies is reflected in clinical practice, as patients are often monitored for either 24 or 48 hours. Loring et al.[21] demonstrated that 75% of patients that reach a PVC burden of ≥20% will do so within 24 hours of monitoring. However, only 53% of patients who reached a PVC burden of 10% did so in the same 24-hour timeframe.[21] The yield continued to increase throughout the 14 days of monitoring; thus, leaving the possibility that almost half of this 10% PVC burden group may go undetected within a 24-hour monitoring period.

Increased ventricular ectopic activity is often seen during exercise stress testing; however, its clinical significance is poorly understood. Identifying the relationship between adverse outcomes and frequency of exercise-induced PVC has proven difficult. Schweikert et al.[22] reported greater thallium perfusion defects with higher ectopic burdens, but these findings have not been shown to correspond with angiographic severity of disease.[22] Other studies have suggested that whilst a causal link between exercise-induced ectopy and coronary artery disease does not exist, it may be a marker for increased risk of exercise-induced ventricular arrhythmia.[23]

Jouven et al.[24] performed exercise testing in 6,106 asymptomatic male volunteers and measured ventricular ectopic burden. Excessive ventricular ectopic activity was defined as >10% of all ventricular depolarisations during a 30-second ECG recording or a run of ≥2 consecutive PVC. Frequent ventricular ectopy was identified in 138 participants and, over a 23-year follow-up, was associated with an increased risk of death from a cardiovascular cause (relative risk: 2.67; 95% CI: 1.76–4.07).

Frolkis et al.[25] retrospectively examined a large cohort of 29,244 patients who had previously undergone exercise testing. Frequent ventricular ectopy was defined as >7 PVC per minute, or the presence of bigeminy, trigeminy, ventricular tachycardia, or fibrillation. Frequent ventricular ectopy was identified in 3% of individuals during exercise and 2% during recovery. Over a mean follow-up of 5.3 years, frequent ventricular ectopic activity in recovery was associated with a higher rate of death when compared with ectopy seen on exercising (11% versus 5%; HR: 2.4; 95% CI: 2.0–2.9; p<0.001). An assessment of LVEF had been made on 6,421 participants and a higher proportion of patients with ventricular ectopy during recovery had a LVEF of <40% (27% versus 18%).

Morshedi-Meibodi et al.[26] retrospectively examined ventricular ectopic activity in 2,885 individuals who had undergone exercise testing as part of the Framingham offspring study. Their definition of excessive ventricular ectopic burden differed from Jouven et al.'s[24] as only 0.1% of participants would have met the required standard. They instead used a model based on the median number of ventricular ectopics measured in participants whilst exercising, which was one ectopic every 4.5 minutes (0.22 ectopics/minute), and excessive activity was seen in 792 (27%) participants. Their primary endpoint was 'hard' cardiovascular disease, which included angina symptoms, myocardial infarction, and sudden cardiac death. It was concluded that there was no association between high PVC burden and any of the 'hard' cardiovascular disease endpoints; however, there was an increase in all-cause mortality over a follow-up period of 15 years.

DISCUSSION

AF and atrial flutter are the most common arrhythmias associated with ischaemic stroke. There is now growing evidence supporting an association between atrial ectopic activity and the development of atrial arrhythmias. Individuals with

high atrial ectopic burdens are at a greater risk of stroke and death, possibly due to co-existing AF. Patients with AF and a CHA_2DS_2VASc score of two have an annual stroke risk of 2.2% and should be appropriately anticoagulated unless contraindicated. Data presented in this review suggest that individuals with a high PAC burden of >30 per hour and CHA_2DS_2VASc score of two also have an increased risk of stroke. Randomised trials are needed to assess whether anticoagulation (and the inherent risks that come with it), suppression of atrial ectopics, or modification of other risk factors decrease stroke risk in patients with high PAC burden. Clinical suspicion of undiagnosed AF should be higher in patients with a high CHA_2DS_2VASc score, an atrial ectopic burden of ≥30/hour, or an episode of ≥20 PAC. More extended periods of ambulatory monitoring, including implantation of loop recorders, may increase the chance of diagnosing asymptomatic AF.[27]

As many as 50% of cases of congestive cardiac failure are labelled as idiopathic, yet many may be secondary to excessive ventricular ectopic activity.[28] In a meta-analysis, Zang et al.[29] demonstrated an improvement in LVEF following ablation of PVC. The mean burden of PVC referred for an ablation was 24.0% and the overall increase in LVEF post ablation was 7.7%.[29] Patients with high PVC burdens should therefore be considered for regular echocardiographic assessment and those who show deterioration in LVEF should be assessed for treatment with catheter ablation. The significance of ectopic burden during exercise testing, or in the recovery period, is as of yet unknown. Data does suggest a link to all-cause mortality over long follow-up periods, but there is no current evidence to suggest that suppression of PVC in this setting would be beneficial. As such, catheter ablation of PVC in this setting is an untested area and, in symptomatic patients, clinicians may first wish to employ a less invasive approach, such as anti-arrhythmic therapy.

CONCLUSION

Higher burdens of PAC are associated with a greater risk of developing AF. High frequency of PVC is associated with a reduction in LVEF and subsequent heart failure, which may be reversible with ablation. In all cases, longer periods of monitoring allow a greater yield of information and better prediction of those higher risk patients. Longer periods of monitoring of ≤2 weeks should become commonplace.

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ARRHYTHMOGENIC CARDIOMYOPATHY: GENETIC PATHOLOGY, INFLAMMATORY SYNDROME, OR BOTH?

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ABSTRACT

Arrhythmogenic cardiomyopathy (ACM) affects mainly young athletes <35 years old and has a potential risk of malignant arrhythmias and sudden death. Different post-mortem and clinical studies have been conducted in North America, Asia, and Europe, with sharp differences in incidence and sex-associated pattern. Alterations in desmosome proteins, such as desmoglein, plakophilin, ion channels, or intracellular calcium handling proteins, have been highlighted as the principal cause of ACM, but the pathology has shown more complexity than initially described. This short review summarises the principal and more recent findings about ACM, mainly those related to inflammatory phenomena reported in the literature. Viral infections, especially enterovirus, have been associated with ACM and may be implicated in myocardial apoptosis, structural cardiac changes, and sudden death. *Bartonella henselae* and *Sarcocystis* infection have additionally been reported in ACM patients. Information regarding the role of proinflammatory cytokine or T cell infiltration and their possible role in sudden death is scarce, with increasing evidence of proinflammatory infiltrate associated with fibro-fatty ventricular patches related to biventricular affectation and worse outcomes. Nevertheless, findings taken from other sudden death-causing cardiomyopathies, such as viral myocarditis and Chagas disease, allow us to propose proinflammatory cytokines, such as tumour necrosis factor and interleukins 17 and 2, as possible serological markers of sudden death and/or ventricular dysfunction in order to conduct further research and identify diagnosis/prognosis markers for ACM.

Keywords: Arrhythmogenic cardiomyopathy (ACM), arrhythmias, sudden death.

INTRODUCTION

Historical Antecedents and Definition

Arrhythmogenic cardiomyopathy (ACM), previously called arrhythmogenic right ventricular cardiomyopathy or arrhythmogenic right ventricular dysplasia, was classically defined as a fibro-fatty substitution of ventricular myocardium. Recent advances have given a more complete view of its pathophysiology, including genetic and electrophysiological criteria to classify the disease. Therefore, we can consider ACM as a ventricular arrhythmogenic syndrome with a structural substrate associated to intercalated disc protein mutations. The possible role of ionic disturbances in lethal arrhythmias make it challenging to specify a precise definition and adopt a rational approach to prevention and therapeutics and this should be acknowledged.

Initially, ACM was reported mainly in the right ventricle,[1] but may also implicate the left ventricle, as well as both ventricles simultaneously. ACM principally affects young men and can cause sudden death by ventricular arrhythmias,[2] especially in athletes, which is not always associated to structural changes in ventricular walls. As a result of these variables, we can classify ACM into ionic and non-ionic-associated origin by the presence or absence of structural ventricular changes. In this review, we explore the possible role of inflammation as a concomitant cause in ACM, a mechanism poorly explored in the literature and one that possibly should be included in further classifications.

ACM was first described early in the 1980s. Initially, it was reported as hypokinetic cardiomyopathy associated with non-ischaemic tachycardia.[1] Progressively, ACM was described as being in association with lethal arrhythmias,[3] functional myocardial involvement,[4] and biventricular affectation.[5,6] The clinical and electrocardiographic spectrum of ACM was described by Nava et al.[7,8] as well as the genetic involvement in arrhythmia genesis.[9-13] In the next sections, we briefly describe the most recent advances in the comprehension of the pathophysiology of ACM.

Predisposing Factors

Sex, physical activity, and incidence

ACM incidence patterns have been addressed by several authors. A French study reported ACM in 2.8% of 361 autopsies of sudden cardiovascular death.[14] A 2016 multicentre European Cardiomyopathy Pilot Registry (1,155 patients) reported an incidence of 5.29% among all cardiomyopathy phenotypes studied.[15] There are several differences reported in ACM clinical presentation, especially regarding sex-dependent patterning. In a study published in 2008, male patients had a higher incidence of sustained ventricular tachycardia, ventricular fibrillation, or sudden cardiac arrest as initial manifestations, with larger epicardial right ventricle unipolar low-voltage zone, and longer local abnormal ventricular activity.[16] In another study, the sexes differed in prevalence of abnormal electrocardiogram (ECG) (69% versus 52%) and presence of late potentials; men had larger right ventricular dimensions and practised competitive sports more frequently.[17] However, the same study reported that sex was not associated with a high incidence of life-threatening ventricular arrhythmias or with a poor outcome.[17] On the contrary, in an extensive post-mortem study among 842 athletes in the USA with autopsy-confirmed cardiovascular diagnoses, male sudden deaths were almost four-times more common than among females, but ACM was more common in females (13% versus 4%).[18] Additionally, total and free testosterone levels were significantly increased in males with malignant arrhythmias compared to males with a favourable outcome, whereas oestradiol was significantly lower in females with malignant arrhythmias compared to females with a favourable outcome.[19] Interestingly, neither ventricular arrhythmias, ACM duration (mean: 6.5±5.6 years), nor heart failure incidence were significantly increased during pregnancy.[20] Finally, the prognostic significance of marked cardiac dilation, reduced deformation, or small patches of delayed gadolinium enhancement in non-symptomatic athletes is unknown; however, cardiac imaging for the assessment of athletes with symptoms, an abnormal ECG, or a positive family history is extremely useful.[21]

Geographical Origin

As previously stated, high endurance sports have been associated with sudden death in young athletes and the two most common conditions leading to sudden cardiac death in athletes <25 years old are hypertrophic cardiomyopathy and ACM.[22] Excessive right ventricle wall stress during exercise has also been reported as an inductor of a pro-arrhythmic state resembling ACM.[23] However, there is scarce information about the incidence of ACM in African or Latin American young athletes. Interestingly, non-athletic individuals (n=210) showed evidence of ACM in an African survey,[24] although the authors suggested possible under-registration in low-income countries. On the contrary, in a post-mortem survey with 38 Korean athletes, with a mean age of 27±5 years, ACM was reported in 42% of cases, and no relationship to vigorous physical or competitive activity was observed.[25]

There is a need to address the scarcity of information on ACM incidence in other locations outside Europe, especially in Latin America, because information is principally restricted to Europe, especially Italy, and the USA, with some sporadic reports in Asia and Africa. Sudden death is very often under-represented in countries where healthcare services are deficient, and high endurance athletes are not always assessed after sport practice, making it necessary to establish a survey for pro-arrhythmogenic substrates in young people. Additionally, individuals need to be assessed to identify if genetic factors, such as regional genetic patterns of polymorphisms, are involved in these possible differences.

Pathophysiology

Non-ionic handling related mutations

Several pathophysiological mechanisms have been suggested for ACM. One of the most cited causes are alterations in the structure and functionality of intercalated discs.[26] It has been reported that desmoglein 2 (DSG2) gene mutations, which code for the desmosomal cadherin desmoglein, cause

ACM affecting cell adhesion, suggesting this is a major pathogenic mechanism in *DSG2*-related ACM.[27] Additionally, mutated desmin, impairment in filament formation,[28] remodelling of connexin43,[29] and plakophilin-2 mutations[30] have all been reported as possible causes of pathogeny in ACM. Interestingly, the presence of miR-130a-mediated translational suppression of desmocollin and downregulation of connexin43,[31,32] important proteins in spreading of cell to cell communication, cause cell to cell disturbances, which may be linked to structural degeneration reported in ventricular tissue in ACM patients. Additionally, they can generate a pro-arrhythmogenic substrate for alterations in action potential conduction.

Ionic or calcium handling disturbances

Other studies have focussed their attention on ionic signalling disturbance in heart cells. Remodelling of cardiac sodium channels has been proposed as an arrhythmia-inductor in ACM[33] and is associated with changes in Nav1.5, an integral membrane protein and tetrodotoxin-resistant voltage-gated sodium channel subunit.[34] The *SCN5a* mutation, expression of which is abundant in working myocardium and conduction tissue, has been detected in Chinese patients with ACM,[35] reinforcing suggestions that ion channel dysfunction in arrhythmogenesis plays a role in the onset of ACM. Additionally, intracellular calcium handling through activation of calmodulin dependent protein kinase II and calcineurin A has recently been reported as a novel pathophysiological mechanism,[36] as well as phospholamban-associated R14Del gene mutation[36] and cardiac ryanodine receptor.[37] Phospholamban mutation carriers have ACM characteristics, including important right ventricular involvement, and more often low-voltage ECG, inverted T waves in the left precordial leads, and left ventricular involvement.[38] It is well known that the presence of malignant arrhythmias in ACM patients with non-structural alterations,[39] especially in young people and children, which may be plausibly linked to ionic and calcium handling disturbances, are often associated in other cardiac sudden death causes. Nonetheless, the high variability in clinical and clinical-pathological presentation of ACM makes the analysis of possible causes challenging.

Possible concomitant causes

One of the most intriguing issues is the role of inflammation in arrhythmogenic right ventricular cardiomyopathy development, as well as primary and/or secondary causes. Viral infection, alcohol consumption, and autoimmunity are some of the most common causes of chronic cardiomyopathy. The possible role an inflammatory response plays in ACM pathogenesis has not yet been fully addressed, nor the presence of concomitant degenerative heart disease as an inductor of ACM. As such, the next section summarises the findings associated with myocarditis in ACM compared with heart inflammation/degeneration related to other aetiologies.

EVIDENCE OF INFLAMMATION IN ARRHYTHMOGENIC CARDIOMYOPATHY: INFECTIOUS OR AUTOINMMUNE ORIGIN?

Several reports of autopsied human hearts have suggested the presence of inflammatory infiltrate in subjects diagnosed with ACM. ACM with biventricular involvement was associated with the presence of T cell infiltration in 50% of cases (n=16).[40] In another study, scattered foci of lymphocytes with myocardial death were observed in 67% of cases.[41] Patients with fibro-fatty left ventricular involvement observed histologically and macroscopically had inflammatory infiltrates significantly more often than those from patients with isolated right ventricle involvement (73% and 88%, respectively, versus 30%),[42] suggesting an association between global heart affectation and inflammation. In concordance with these findings, adipose infiltration of the right ventricle was associated with lymphocytes in 5.5% of cases in a review of autopsies of sudden death.[43]

Cytokine disturbance has been described in patients with ACM. Higher levels of pro-inflammatory cytokines patients' interleukin (IL)-1β (1.22±0.07 versus 0.08±0.01 pg/mL; p<0.0001), IL-6 (3.16±0.44 versus 0.38±0.04 pg/mL; p<0.0001), and tumour necrosis factor (TNF)-α (9.16±0.90 versus 0.40±0.06 pg/mL; p<0.0001) in ACM were reported, while levels of the anti-inflammatory cytokine IL-10 were not significantly different (1.36±0.15 versus 1.20±0.30 pg/mL; p=0.74).[44] Interestingly, increased TNF and IL-6 was recently reported in high sudden death risk patients with Chagas disease, an arrhythmogenic infectious cardiomyopathy.[45] Additionally, T-lymphocytes were reported as the main infiltrate cell types in patients with ACM.[40] However, studies assessing the molecular pattern of myocarditis in ACM are scarce and the issue needs to be more deeply addressed.

Concomitant viral infections in ACM have been associated as a cause of inflammation and worsening of ACM outcome. Enteroviral sequences were detected in myocardial samples of seven ACM patients and adenovirus 5 in another two patients from 12 analysed by polymerase chain reaction.[46] Enteroviral RNA with homology to Type B coxsackieviruses was detected in three of 8 ACM patients (37.5%).[47] Other studies, however, failed to find any viral genome in the heart of ACM samples,[48] suggesting multifactorial causes of cardiac pathology. Additionally, several reports have addressed cardiomyocyte apoptosis that may possibly relate to other viral infections. Right ventricle, chamber-specific apoptotic process in ACM patients was reported.[49] In other studies, apoptosis was detected by TUNEL in biopsied heart specimens;[50] endomyocardial biopsies[51] and myocardial damage were closely related to apoptosis in both children and adults.[52] Also, disruptions of the plasma membrane and dissociation of intercellular junctions were associated with discharge of intracellular lipid droplets into the interstitial space,[53] suggesting that apoptosis may be related with desmosome dysfunction. Finally, mRNA for p53, a protein related to apoptosis, was upregulated compared to those with dilated cardiomyopathy and healthy controls.[54]

Other pathogens have also been co-associated to arrhythmogenic cardiomyopathy. Six patients with ACM (12%) had positive (>1:256) immunoglobulin (Ig)G titers in the immunofluorescence test with *Bartonella henselae*, a proteobacteria that may cause endocarditis in patients with non-ACM familiar antecedents[55] and has been related to sudden death.[56] Additionally, cardiac sarcoidosis arrhythmias have been reported that are similar to ACM and have a high threshold of defibrillation.[57] However, there is very limited information about the functional relationship among viral/bacterial infection, especially if it is possible to establish a direct connection with pathogen invasion or if it is plausible that cellular/humoral autoimmune responses may play a role in ACM pathophysiology.

OTHER ARRYTHMOGENIC PATHOLOGIES AS POTENTIAL COFACTORS AND MODELS FOR ASSESSMENT OF THE ROLE OF INFLAMMATION

Based on the reports analysed here, ACM appears as a complex and multifactorial example of cardiovascular disease. A genetic background may be potentiated by external factors, such as viral infections, which also may explain the wide range of clinical presentations of ACM and the relative early presentation. This issue is of great importance, with the spread of several viruses and protozoan with myocarditis and/or arrhythmogenic potential (*Trypanosoma cruzi*, Chikungunya, Zika, and Dengue viruses as just a few examples) or autoimmune myocarditis. As such, we considered it important to analyse the reported relationship between cardiac inflammation linked to infection and arrhythmias. It is relevant in two complementary senses: knowing the nature of possible inflammatory substrates, potentially associated with ACM, and improving comprehension of pro-arrhythmogenic mechanisms associated with cardiac inflammatory pathology to explore possible approaches to future research and clarify the role of inflammation in ACM.

Viral Myocarditis

Viral myocarditis is becoming increasingly recognised as a contributor to under-reported mortality, and is thought to be a major cause of sudden cardiac death in the first two decades of life.[58] Several viruses, such as Epstein–Barr,[59] hepatitis E,[60] and enterovirus,[61] among others, have been suggested as aetiological agents of myocarditis. Immune system modulation has a deep impact on evolution of viral myocarditis in different experimental systems. T helper-17 and regulatory T balancing,[62] IL-4 modulation of interferon-γ-mediated T cell response,[63] NF-κβ transcription factor,[64] and IL-2 T cell dependent activation[65] have been addressed in the literature, showing the impact of different branches of inflammatory responses in viral myocarditis. Viruses are often pantropic, and this may generate a proinflammatory cardiac milieu and potentially lead to exacerbated cardiac damage. As previously mentioned, information about immune response in ACM is scarce; therefore, cardiac immune response during viral myocarditis may represent a guide for understanding pathogenesis of ACM and to design experimental approaches to study possible inflammatory markers associated to ACM sudden death. Finally, the global spread of non-endemic viruses (Dengue, Zika, and Chikungunya) with cardiac inflammatory potential increases the necessity for full comprehension of comorbidities associated with ACM.

Chagas Disease

Chagas disease, caused by intracellular protozoan *T. cruzi* is the most important infectious myocarditis worldwide. Initially confined to the American continent, it has begun to spread via immigration to developed countries, mainly to Europe and the USA,[66] representing a comorbidity to ACM to consider. Malignant arrhythmias, often asymptomatic until the fatal final episode, are the principal cause of death in Chagasic patients.[67] Interestingly, a proinflammatory cytokine profile has been associated with high sudden death risk during chronic phases of Chagas disease.[45] Additionally, TNF-blocking agents have shown pro-arrhythmic activity in acute experimental murine models,[68] but in other cases have shown an ability to reduce the correct QT interval,[69] and TNF signalling may be linked with cardiac action potential conduction.[70] IL-17 mediated response has also been shown to play a role in cardiac inflammation during acute Chagasic myocarditis and parasite control, with apparent results about their potential beneficial[71] or detrimental role,[72] which is important considering the reported deleterious role in autoimmune myocarditis models.[73] Thus, the relationship between arrhythmias and myocarditis/sudden death may be an important area to analyse in regard to the role of cytokines and inflammatory infiltrate in cardiac remodelling and/or sudden death in ACM. However, the notable possibility of under-registration of ACM should be considered for the Latin-American population and the possible association between both pathologies.

Autoimmune Myocarditis

Autoimmune myocarditis (AM) is often a consequence of subsequent systemic autoimmune diseases, one of the causes of sudden death in young people. Cardiac involvement during auto-immune and/or auto-inflammatory diseases includes the pericardium, myocardium, endocardium, valvar tissue, and coronary arteries.[74] AM is characterised by sinus tachycardia, QT prolongation, atrioventricular conduction defect, and ventricular arrhythmias[74] and is one of the potential differential diagnosis for ACM.

An interesting aspect of AM that is often ignored is the role of regulatory T immunity in the progression of heart inflammation. Impairment in the thymus negative selection of anti-myosin specific CD4 T cells may have different outcomes depending on the context of antigen presentation to activated T cytotoxic cells. The normal process would be the major histocompatibility complex (MHC) Class II antigen presentation of cardiac myosin by non-activated dendritic cells, leading to T cell anergy or apoptosis induced by regulatory T cells. However, if there are associated proinflammatory stimuli that allow an eventual activation of cardiac resident dendritic cells, the MHC II antigen presentation process would lead to a strong T helper-1 and T helper-17 response and consequent myocarditis.[75] This could plausibly explain the comorbidity observed in AM with different viral infection.

Cytokine, humoral, and cellular responses for AM reflect the inflammatory milieu in the heart. IL-17 is a key factor for understanding autoimmune cardiac inflammation. Retinoic acid receptor-related orphan nuclear receptor γt was upregulated at 21 days post-inoculation of cardiac myosin and IL-17 T cells were recruited at the site of the inflamed heart.[76] In this sense, IL-17A-deficient mice were protected from post myocarditis remodelling and did not develop dilated cardiomyopathy.[77] Additionally, the PKCβ/Erk1/2/NF-κB signalling pathway was related to cardiac fibrosis[73] in AM and neutralisation of IL-17 was able to abolish proinflammatory reaction in a model of viral myocarditis.[78] These findings also highlighted the possible role of IL-6 as a key regulator of shift to T helper-1, 2, and 17.

CONCLUDING REMARKS

Although it seems clear that ACM has a primary genetic origin, the role of possible associated factors is far from being fully understood. It is especially true for inflammation and its possible implications in development of the cardiomyopathy, as well as the possible applications of inflammatory serological markers as auxiliary tools for diagnosis/prognosis. Additionally, the information about ACM incidences in Africa or Latin America need to be expanded to determine if there are regional genetic patterns involved in the pathophysiology of ACM. Inflammation of the myocardium has been identified as a concomitant cause of ACM, with T cells infiltrating patients with biventricular affectation; however, the causal effect is not yet well described. Identification of T cell subsets predominant in cardiac infiltrate has proven to be useful in other models of cardiac inflammation/arrhythmias to understand pathophysiology and to propose possible inflammatory markers. In fact, based principally on findings reported to autoimmune or

infectious arrhythmogenic myocarditis, IL-17, TNF, and IL-2 emerge as candidate markers for studying the inflammatory role in ACM. Alternatively, the body of research on viral myocarditis is growing and it has possibly been under-considered in the analysis of pathophysiology of ACM. Viral infections with cardiomyopathic potential are widely distributed and may represent a potential proinflammatory stimulus that can aggravate the outcome of ACM, as have been reported in other kinds of autoimmune myocarditis. The relative scarcity of reports on inflammation in ACM and their potential role in the devastating consequences highlight the particularly urgent need to develop a clear protocol of cardiovascular evaluation for young, high-endurance athletes, including inflammatory biomarkers to prevent fatal episodes of ventricular arrhythmias.

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CARDIAC CACHEXIA SYNDROME

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ABSTRACT

Heart failure is a chronic, progressive, and incurable disease. Cardiac cachexia is a strong predictor of poor prognosis, regardless of other important variables. This review intends to gather evidence to enable recognition of cardiac cachexia, identification of early stages of muscle waste and sarcopenia, and improve identification of patients with terminal heart failure in need of palliative care, whose symptoms are no longer controlled by usual medical measures. The pathophysiology is complex and multifactorial. There are many treatment options to prevent or revert muscle waste and sarcopenia; although, these strategies are less effective in advanced stages of cardiac cachexia. In these final stages, symptomatic palliation plays an important role, focussing on the patient's comfort and avoiding the 'acute model' treatment of aggressive, disproportionate, and inefficient care. In order to provide adequate care and attempt to prevent this syndrome, thus reducing its impact on healthcare, there should be improved communication between general practitioners, internal medicine physicians, cardiologists, and palliative care specialists since heart failure has an unforeseeable course and is associated with an increasing number of deaths and different levels of suffering.

Keywords: Sarcopenia, cachexia, palliative care (PC), cardiology, heart failure (HF).

INTRODUCTION

Heart failure (HF) is a progressive organ failure disorder, characterised by dyspnoea, fatigue, depression, and fluid retention, and affects ≤2% of the Western population.[1,2] It is a dynamic situation that, in the later stages, has high mortality rates. It is associated with several hospital readmissions due to its chronic and progressive disease evolution.[3-6] There is a gradual loss of functional capacity and self-sufficiency of the patient, which is portrayed by a pattern of sudden worsening without complete recovery (Figure 1).[7-8] In general, elderly patients with HF have other comorbidities, which cause different outcomes for these patients.[9]

Patients with HF tend to have a poor quality of life, especially those with a higher score in the New York Heart Association (NYHA) Functional Classification, weak socioeconomic status, and lack of social support.[7-9] The benefits of palliative care (PC) are often forgotten. Such care, which goes far beyond symptomatic control, should be considered in an appropriate manner according to the patients' needs.[7,8,10] Given that we are facing an incurable and irreversible illness, there cannot be a rigid division between curative care and overall care designed to maximise comfort (Figure 2).[8-12] This model balances the life-prolonging therapy with PC through most of the disease trajectory. When the active therapy is a viable option, minimal PC interventions are initiated. Once life-prolonging therapy becomes less of an alternative, PC becomes the primary method of clinical management.[8-12] The proper palliation of symptoms should not be delayed until the last days or hours of life.[13] The importance of PC and its inclusion in the therapeutic approach of HF is stated in the guidelines of the American Heart Association (AHA), the American College of Cardiology (ACC), the International Society of

Heart and Lung Transplantation (ISHLT), and the European Heart Association (EHA).[14-16]

In the later stages of HF, it is important to identify patients with end-of-life HF (HF in the last 12 months of life) in order to offer appropriate care for the patients' needs.[17] Always acting on the basis of an acute care model, characterised by aggressive, disproportionate, and inefficient care, is not suitable in these clinical settings.[18,19] Known scales, such as CARING or Gold Standard Framework, present global and specific deterioration indicators allowing the identification of patients with end-of-life HF.[20,21]

Cardiac cachexia (CC) is defined as the loss of >5% of body weight over 12 months in the presence of HF.[21,22] This pathological entity affects around 5–15% of patients with HF and is generally present in NYHA III or IV functional classes. CC corresponds to a strong predictive factor of poor prognosis in HF, independent of other important variables, such as age, functional class, ejection fraction, and physical capacity, although it is related to them.[7-9,22,23]

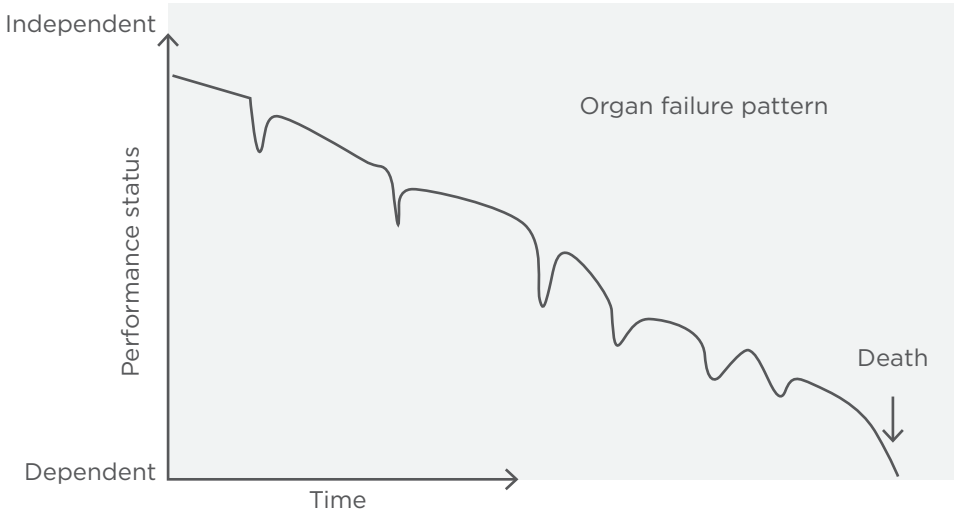

Figure 1: Progression model of heart failure towards the end of life.

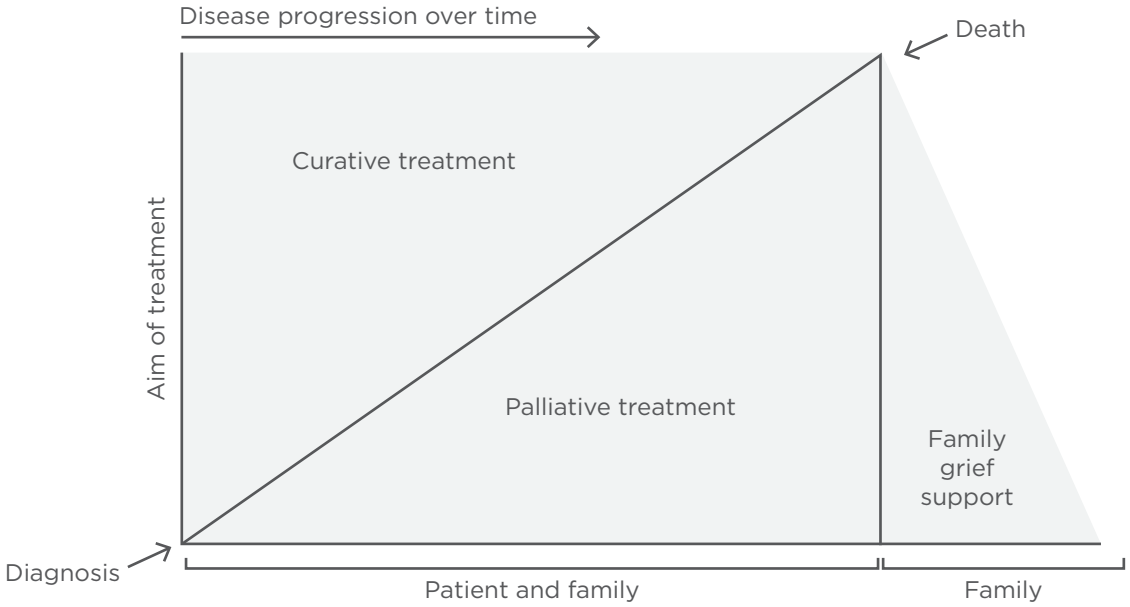

Figure 2: Multifactorial interactions between curative and palliative care.
There is compatibility between curative treatment, which permits life extension, and palliative care for symptomatic relief and quality of life; therefore, both approaches should be combined. Family/caregivers should also be included during the disease progress.

CC pathophysiology is complex and multifactorial and, when fully established, it is hard to treat and reverse the process.[21-26] The palliative approach to this class of non-oncological terminal patients has proven to be suboptimal.

The objective of this review is to gather evidence to correctly recognise CC and contribute to the improvement of clinical practice; namely, identification of early stages of muscle waste and sarcopenia, and better recognition of a patient with CC and terminal HF who is in need of PC due to their symptoms being no longer controlled by the usual medical measures.

PATHOPHYSIOLOGY OF CARDIAC CACHEXIA

Sarcopenia is defined as muscle wasting associated with functional impairment. It is characterised by a progressive and generalised loss of skeletal muscle mass in the limbs that exceeds two standard deviations of the mean of a healthy young reference and may be seen as a precursor of cachexia.[20,21] Sarcopenia is found in 19.5% of patients with HF, and 68.0% of patients show muscle waste and reduced capillary density. If there is no intervention in cases of HF, there is a progressive loss of skeletal muscle mass and, in the latter stages, fat and bone mass loss leads to fully established CC.[21-25] CC is present in 5–15% of advanced HF patients, and the mechanisms involved in the pathophysiology are multifactorial, involving reduced food intake, gastrointestinal malabsorption, neurohormonal disorders, overexpression of proinflammatory cytokines, increased oxidative stress, and an imbalance between anabolic and catabolic states.[22-36]

Reduced Food Intake

Several factors may be involved in the reduction of food intake, such as unsavoury diets due to low sodium content, severe depression, and visceral vascular congestion.[29-31] Some drugs commonly used to treat HF may also be related to a reduced food intake; for example, captopril can cause palate changes; digitalis is sometimes responsible for anorexia and vomiting; and diuretics used in a vigorous way may lead to zinc and potassium depletion, which in turn reduces the intestinal motility and causes palate changes.[15] The proinflammatory body status and the abnormal increase in serum levels of leptin and adiponectin are also responsible for anorexia. Early satiety due to hepatomegaly with gastric compression and the occurrence of dyspnoea at rest in NYHA Class IV functional class patients contribute to a reduced food intake.

Functional Modifications in the Gastrointestinal Tract

Vascular splanchnic congestion and collagen accumulation in the intestinal mucosa are typical findings in these patients. Such mucosal changes lead to a thickening of the gastrointestinal wall, reducing the number of intestinal villi and increasing the distance between the capillaries and the enterocytes. The accumulation of these modifications leads to intestinal malabsorption with a reduction in lipoprotein absorption.[32] Additionally, there is an increasing concentration of the intestinal bacterial flora and higher adhesion of the biofilm to the sigmoid mucosa. Increased paracellular permeability leads to bacterial translocation with the release of endotoxins (lipopolysaccharides), which in turn stimulates the production of tumour necrosis factor (TNF)-α and other proinflammatory substances, contributing to a state of systemic inflammation.[29-32]

Neurohormonal Activation

In HF, activation of the sympathetic nervous system (SNS) occurs, raising the levels of noradrenaline and cortisol. This adrenergic stimulus promotes a cellular catabolic state and peripheral vasoconstriction that exacerbates splanchnic congestion. Permanent activation of the SNS leads to increased basal energy expenditure and activation of the renin-angiotensin-aldosterone system.[32-34] As proven by animal models, angiotensin II, a significant mediator in CC development, induces muscle wastage by activating the ubiquitin-proteasome system (UPS), leading to apoptosis, a reduction in protein synthesis, and appetite impairment.[28-34]

Imbalance Between Anabolic and Catabolic Metabolism

The preservation and maintenance of skeletal muscle depends on the delicate balance between catabolic and anabolic mechanisms. The imbalance of these chemical processes forms the basis of the pathogenesis of sarcopenia and CC. The anabolic mediators are reduced, such as growth hormone, testosterone, insulin-like growth factor 1, ghrelin, and insulin. The major negative chemical processes concerned are the UPS,

autophagy, apoptosis, inflammation, and oxidative stress.[21-28] Proinflammatory cytokines, such as TNF-α, interleukin (IL)-1, IL-6, glucocorticoids, and adiponectin, play a cardinal role in muscle wastage by reducing the intracellular anabolic pathways. The activation of the UPS leads to lysosomal proteolysis by ubiquitination. Autophagy, a catabolic process that involves the lysosomal system, seems to be regulated by transcription factors (e.g. nuclear factor kappa B [NF-κB]), reactive oxygen species, and TNF-α. All of these elements lead to a disproportionate oxidative stress response, which in turn raises angiotensin II levels. It seems that the loss of mitochondria and mitochondrial dysfunction may also be implicated in the increase of cell-damaging oxygen free radicals.[35-38]

CLINICAL REPERCUSSIONS OF CARDIAC CACHEXIA

The clinical consequences of CC syndrome are related to muscle proteolysis, weight loss, and systemic inflammatory status, including changes in the cardiovascular and respiratory function; depletion of muscle mass due to atrophy, apoptosis, or necrosis, lowering the number of mitochondria and capillaries and increasing the predisposition for anaerobic metabolism with lactic acid production; impairment of urinary acidification and concentration; predisposition to pressure ulcers due to decreased healing capacity; gastrointestinal tract dysfunction; multifactorial anaemia due to nutrient malabsorption, systemic inflammatory status, iron deficiency and reduced erythropoiesis; and a decline in immunity, leading to a higher risk of infection. Due to the occurrence of these major metabolic alterations in CC, HF symptoms worsen.[32-38]

TREATMENT APPROACHES

It is difficult to establish a specific and effective therapy for CC syndrome due to its multifactorial pathogenesis. Physicians should be aware of muscle waste and sarcopenia even when the therapeutic options are effective and the full establishment of CC is delayed.

CC cannot be treated solely with an increase in nutritional uptake; exercise is also an important therapeutic approach. A combination of both strategies is recommended, including appropriate rehabilitation nutrition. Aerobic and resistance exercise training has the potential to reduce cytokine expression and increase anti-apoptotic factors, having an anti-inflammatory effect and improving functional capacity, therefore enhancing muscular regeneration.[22,31,39-43] In patients with advanced HF, advanced age, or frailty, who are unable to tolerate daily aerobic and resistance exercise, neuromuscular electrical stimulation (NMES) might be an option.[39,40] It has been demonstrated that NMES has the same anti-inflammatory properties as aerobic and resistance exercise training. In animal models, high frequency NMES (>50 Hz) induces an anabolic metabolic state due to an increase in glycolytic capacity, protein synthesis, expression of insulin-like growth factor 1, and muscle fibre size, which is also related to resistance training. Low frequency NMES (<20 Hz) has a similar activity to aerobic training exercise, inducing endurance and reducing autophagy.[39,40] Although rehabilitation nutrition is of extreme importance, there is no dietary standardisation; it is characterised by an increase in protein uptake and an adequate vitamin supply of both soluble and lipo-soluble vitamins (vitamins A, D, E, and K).[31,39-42]

The pharmacological treatment approach for CC involves appetite stimulators, anti-inflammatory drugs, hormones, and anabolic stimulants. In the appetite stimulators category, treatment with megestrol acetate (160 mg twice daily) and L-carnitine (4 g per day) have both proven to increase body mass in clinical trials. Megestrol acetate is a derivative of progesterone widely used by oncologists, not only for the treatment of hormonal-related cancers but also as an appetite stimulant when appropriate.[39-42]

Since inflammation is a major contributor to sarcopenia, immunomodulatory and anti-inflammatory therapies were thought to be a logical option. Small clinical trials with pentoxifylline, thalidomide, methotrexate, and immunoglobulins showed no sustained benefit as pharmacological treatments.[34,39,41] Clinical trials with beta-blockers demonstrated a delay in the development of CC and promoted a partial improvement in those with CC, since the drugs limit activation of the SNS.[39,41,42]

Ghrelin is a hormone produced by the stomach and acts on the pituitary gland to release growth hormone, which, in turn, reduces anorexia. It constrains the production of proinflammatory factors and induces the production of IL-10,

a potent anti-inflammatory cytokine. Clinical trials demonstrated that ghrelin lead to an increase in body weight, body fat mass, and lean tissue mass, which ultimately permit appropriate exercise training.[24,34,39,41]

Anabolic steroids are effective at reverting and treating muscle wasting, although the risks associated with their administration surpass the possible benefits. Selective androgen receptor modulators have the same anabolic characteristics as treatments with testosterone, without the associated side effects on the skin, hair, and prostate. Enobosarm, an example of this new pharmacological drug class, has tissue-specific anabolic and androgenic activity, which improves lean muscle mass and physical function.[24,34,36,39,41]

In animal models, espindolol is a beta-blocker that increases body weight, lean tissue, and fat mass without affecting cardiac function, having a more favourable effect on preventing muscle waste than other beta-blockers. The ACT-ONE trial demonstrated these beneficial effects in cancer cachexia. The COPERNICUS trial proved that carvedilol reduced cachexia development and stimulated a partial reversal of cachexia in patients with severe HF.[24,34,36,39,41,42]

PALLIATIVE APPROACH

Discussing end-of-life issues with patients is challenging, especially with patients who often have a limited understanding of the nature and seriousness of their condition. Many patients defer to their clinicians for important decisions, choosing a more passive role.[43-49]

The PC approach is directed at improving the patient's quality of life and addressing their family's challenges related to their refractory symptoms. Routine comprehensive symptom assessment with validated instruments enables the prevention and relief of suffering and allows treatment of physical and psychological symptoms.[8-12,16,17] Suitable acknowledgement of the shift from curative care to comfort care allows appropriate end-of-life care to be provided for both the patient and their family.[8-12,16,17,43-49]

When CC is fully established, it is fundamental to explain to caregivers and family members that clinical reversibility is less probable and emphasise the importance of the patient's comfort.[34,39] In these situations, the main medical practices that should be involved are general practice, internal medicine, cardiology, and palliative medicine. There should be a collaborative approach including physicians, nurses, therapists, psychologists, dietitians, social workers, and other health professionals to improve communication and understanding of the patient's objectives to a have a better end-of-life.[43-47] This methodology has shown to improve survival through patient education, including promotion of self-management skills, improving medication and dietary compliance, encouraging daily weighing and exercise, assuring close follow-up, and introducing end-of-life issues.[8-10] Clear communication between the medical team, family members/caregivers, and the patient is vital to shared decision-making and various assumptions about the palliative approach should be demystified.[2,8,10]

The most frequent symptoms in advanced HF with CC are refractory dyspnoea, fatigue, anorexia, nausea, constipation, asthenia, and depression.[44] Symptomatic palliation, which aims to reduce total suffering, comprises several strategies, both pharmacological and non-pharmacological.

Table 1: RADboud Indicators for PAlliative Care (RADPAC).

The RADboud indicators for PAlliative Care (RADPAC)	
Congestive heart failure	• The patient has severe limitations and experiences symptoms even while at rest; mostly bedbound patients (NYHA IV functional class) • The patient has frequent hospital admissions (>3 per year) • The patient has frequent exacerbations of severe heart failure (>3 per year) • The patient is moderately disabled or dependent; requires considerable assistance and frequent care (Karnofsky score ≤50%) • The patient's weight increases and fails to respond to an increased dose of diuretics • A general deterioration of the clinical situation (oedema, orthopnoea, nycturia, dyspnoea) • The patient mentions "end of life approaching"

NYHA: New York Heart Association.

Non-pharmacological measures aim to help the patient adapt to the progressive losses that they will experience and include adjustments in the home, massages, acupuncture, and others.[19,35]

In the absence of a response to first line treatment efforts for refractory dyspnoea, including diuretics, post-load reduction drugs, and inotropes, progressive and titrated doses of morphine may be administrated for symptom relief, favouring the oral route.[16-19] Non-pharmacological measures consist of directing fresh air towards the face with a fan, reducing the room temperature, opening windows, breathing humidified air, and elevating the head from the bed.[35,43-50] Benzodiazepine may also be administrated to mitigate any associated panic symptoms.[16-18]

In the case of depressive symptoms, selective serotonin reuptake inhibitors may be used as a first therapeutic line option as they offer good efficacy and limited side effects. Behavioural therapy and psychotherapy also play relevant roles in symptom relief, as well as adapted exercises under specialised supervision.[43-50]

Common causes for nausea in advanced CC include a reaction to opioids and other medications, hepatic congestion, and ascites.[43,44] Various antiemetic drugs with different mechanisms of action exist that can be used in situations of nausea, such as metoclopramide, haloperidol, first or second-generation antipsychotics (e.g. prochlorperazine and olanzapine), and serotonin agonists (e.g. ondansetron, granisetron). These pharmaceutical drugs can be used in combination to enhance their effects.[22,43] In terminal HF, constipation is multifactorial and, in most situations, is related to dehydration, immobility, and side effects of certain drugs, but is generally overcome with laxatives or emollient drugs.[43,48,50]

In the end-of-life setting, glucocorticoids may be included in the symptomatic treatment of anorexia due to their role in temporarily increasing the appetite and energy.[43] Regarding dehydration towards the end of life, clinical studies have demonstrated the lack of benefit of artificial hydration on patient quality of life or survival, with a high risk of worsening overload symptoms.[51,52]

In a study of ambulatory patients with various progressive organ failure diseases, around 60% of patients preferred discussions about their prognosis and future losses in the early stages of disease, rather than the last days of life, allowing adjustment of their expectations and acceptance.[52] For a timely referral, the health professionals who care for these patients should be able to recognise indicators of the need for a palliative approach. United Kingdom Primary Health Care developed a model that allows an appropriate recognition of patients with chronic pathology in need of PC, named RADboud indicators for PAlliative Care (RADPAC), as shown in Table 1.[49-53]

As seen in many hospitals, patients with terminal HF and CC are treated in internal medicine wards, often without sufficient supportive care. In order to provide adequate care and attempt to prevent this syndrome, thus reducing its impact on healthcare, there should be a clearer communication between general practitioners, internal medicine physicians, cardiologists, and PC specialists since HF is a chronic and progressive disease with an unforeseeable course and is associated with an increasing number of deaths and different levels of suffering.

CONCLUSIONS

CC is a major prognosis factor of HF, influencing survival and quality of life. The pathophysiology is complex and multifactorial. There are many treatment approaches to prevent or reverse initial cases of CC. Nonetheless, physicians should be attentive and try to prevent this syndrome by having a multidisciplinary team including nutritionists, experts in rehabilitation, and experts in PC. In end-of-life situations, comfort should be the main concern and inadequate therapeutic measures that do not offer any benefit should be terminated.

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