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How CMR Contributes to the Emerging World of Precision Medicine and Patient Stratification in Cardiology and Heart Failure

Dear readers and colleagues,

What a fabulous welcome to 2021, with a comprehensive review and series of global expert perspectives on state-of-the art CMR imaging in non-ischaemic cardiomyopathy in the SCMR edition of MAGNETOM Flash. Leading CMR investigators and clinicians have contributed to this edition from all corners of the world – Europe, Asia, North, and South America, providing insights into clinical applications, pragmatic challenges as well as technical developments and future directions.

Cardiomyopathy, with clinical presentations from heart failure to arrhythmia, is a massive burden across the globe, impacting patients and families through well-acknowledged mortality and morbidity, but also with major economic impact. It is a syndrome characterised by classic clinical history and physical findings. Mostly due to necessity related to our historic inability to differentiate the many underlying pathophysiological mechanisms with prior diagnostic technologies, patients have been bucketed together. The rather gross separation of heart failure patients into those with reduced versus preserved ejection fraction by echocardiography illustrates this well. In this edition, the enormous opportunity for CMR to transform the clinical stratification of heart failure patients in a way that more closely aligns with underlying biology is highlighted. This will have important benefits to patients immediately through the ability to identify early myopathic processes, help risk stratify and guide management, as well as diagnose potential secondary causes of heart failure amendable to targeted treatment approaches.

In addition, there are broader long-term and "big picture" benefits of improved phenotyping of cardiomyopathy, stratifying the enormous and heterogeneous syndrome into biologically relevant groups and allowing for more focused development of therapies relevant to specific mechanisms, with flow on effects such as improved ability to measure response to therapy in more powerful clinical trials.

Biomarkers, whether they are imaging or blood based molecular markers, are most powerful when they closely reflect underlying biology. Measures of inflammation and fibrosis within the myocardium, as well as patterns of distribution, now possible through technical advances with CMR, as highlighted in this edition of MAGNETOM Flash, have opened up a new eye for cardiologists, and combined with improved blood measures, offer the hope of improved "precision" medicine far beyond what we could "see" with echocardiography. They are obviously of direct relevance to cardiomyopathy and heart failure – reflecting specific mechanisms as well as being of value for risk stratification and measuring response to therapy. In order to get the most out of this valuable information, multi-disciplinary strategic leadership across the whole pipeline is required, helping us bring together fundamental molecular and cellular biology with clinical and imaging phenotype. Stratification of patient groups in this manner is our best chance of translating potential new therapies targeted to specific subgroups of non-ischaemic cardiomyopathy. With CMR as a tool, we can learn from the massive steps that the oncology field has been able to take once molecular characterisation was possible to stratify tumours

mill. She was awarded a National Health and Medical Research Council (NHMRC) Excellence Award for Top Ranked Practitioner Fellow (Australia), commencing in 2018. In 2019 she received the prestigious NSW Ministerial Award for Cardiovascular Research Excellence. Gemma is committed to the advancement of her field and serves as a member of the Editorial Board of leading international cardiovascular journals Circulation and Cardiovascular Research, as well as being a founding editorial board member for Redox Biology, and an Associate Editor for Heart, Lung and Circulation. Her research and clinical perspective and leadership are recognised by her membership of the Scientific Board of Cardiac Society of Australia and New Zealand (responsible for International Relations), and her appointment to the Expert Advisory Panel for NHMRC Structural Review of Grants Program (2016–17), and as well as the Clinical Committee of the Heart Foundation. She is committed to the promotion and advocacy of cardiovascular research, working as President of the Australian Cardiovascular Alliance with a national team to secure $220 Million Federal funding for the Mission for Cardiovascular Health, as well as a member of the NSW CVD Advisory Committee. She now chairs the Mission (CV) Expert Advisory Panel. She is a graduate of the Australian Institute of Company Directors and serves/has served as a non-executive Director on multiple community Boards.

previously lumped together, and now treated with a diverse range of biological agents targeted to specific mechanisms.

Magnetic resonance spectroscopy perhaps offers the most physiologically relevant insight to cellular function in the myocardium and has offered enormous hope for over a decade. Levelt and colleagues from the UK [1] provide a state-of-the-art update on its use as a clinical tool for the prognosis and diagnosis of diabetic heart disease, where the common problem of diabetes mellitus can cause similar clinical syndrome through multiple mechanisms, with potential impact on prognosis and management. These include impaired cardiac high energy phosphate metabolism, coronary microvascular dysfunction, and ectopic lipid deposition. Increased oxidative stress and dysregulated cellular metabolism drives alterations to Na+ and Ca2+ handling, impacting contractility, relaxation and susceptibility to arrhythmias [2]. Magnetic resonance spectroscopy methods, particularly those based on interrogating ^{1}H and ^{31}P metabolites, have now been shown to add an additional layer of information to clinical imaging data. The challenges of upscaling this potentially powerful clinical investigation tool are discussed. The most significant deterrents include the need for dedicated hardware, expert input during acquisition compared to standard imaging, dedicated time for the pre-scan adjustments, and exceptional sensitivity to cardiac and respiratory motion. Technical advancements that make spectroscopy more reproducible in a wide array of clinical settings may help in the next decade.

The importance of bioimaging signatures with parametric mapping in addressing the diagnostic challenges of myocarditis is expertly laid out by Dr. Abidin [3] from Malaysia, including with very pragmatic and representative cases. As she summarizes, although late gadolinium imaging is a sensitive technique to detect focal myocardial damage, it lacks the ability to differentiate the state of the disease activity, especially in myocarditis. Furthermore, "the incorporation of bioimaging signatures with parametric maps and LGE imaging, using our standardized exam card, allows for shorter examination time and provides a productive and highly reproducible technique for diagnosing myocarditis" [3]. Examples are also given by Dr. Mavrogeni from Greece, on integrating advances in CMR inflammatory measures into the diagnosis, risk stratification and management of patients with autoimmune rheumatic disease involving the heart [4].

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The purpose and approaches of whole-heart high-resolution late gadolinium enhancement are summarized by Dr. Cochet and colleagues from France [5]. Initially developed to assess fibrosis in the very thin walled left atrium [6], the technique is recognised to achieve much higher spatial resolution, but with the disadvantage of longer scan time. A pragmatic approach is taken in the application of the technique to the assessment of the left ventricle, highlighting that HR-LGE is not required in every

patient. However, patients with a number of key conditions have been shown to benefit, particularly when traditional CMR imaging is normal or inconclusive. These include patients with myocardial infarction with non-obstructive coronary arteries (MINOCA- where HR-LGE resulted in a change in the final diagnosis in 26% of the patients), ventricular arrhythmia, and it has been increasingly used in planning and assessment of patients with pulmonary vein isolation for atrial fibrillation. Dr. Nezafat et al. also shares the experience of clinicians at Beth Israel Deconess Medical Center where they have applying free-breathing 3D LGE for high resolution LGE imaging for over a decade [7].

Pragmatic experiences and approaches to applying 4D Flow MRI in clinical practice are well described by Dr. Avery and colleagues from the USA, and Dr. Monti from Italy. Whilst initial practical implementation has been to assess complex congenital heart disease, and large vessel abnormalities, including the aortic endovascular graft described by Dr. Monti [8] due to its ability to assess blood flow velocity and wall shear stress, there is also the real hope that 4D Flow can play a role in improving the speed and reproducibility of routine haemodynamic measures [9], and ultimately, although with need for considerable technical advances, provide measures of cardiac energetics previously only available through complex invasive pressure volume relation measures to easily applicable to the clinical setting [10].

Artificial Intelligence and machine learning approaches are emerging as excellent approaches to better cluster patient populations and derive more tightly circumscribed patient cohorts. Such unbiassed segmentation of patient populations has the advantage of reaching beyond our existing knowledge, potentially identifying new risk markers, and groups who may be linked by common mechanisms. CMR data, with its improved quantitation of physiologically and pathophysiological relevant myocardial function, along with more traditional clinical measures make for a perfect substrate for new discovery and approaches to longstanding and common cardiovascular problems as recently discussed by Bhuva and colleagues in Circulation: Cardiovascular Imaging [11], and is very relevant to consideration of this SCMR edition of MAGNETOM Flash.

A major challenge for the cardiovascular field in developing and translating new therapies has been the high bar set, with primary endpoints focussed on mortality. Whilst being careful not to lower the ultimate bar, validated surrogate measures that reflect underlying disease activity have the potential to play an important role in working towards a staged regulatory process, reducing the cost and improving the power of early phase trials and ensuring efficiency. This may have some impact in reversing the current trend away from cardiovascular clinical trials related to high costs and perceived high risk.

With rapid improvements in CMR and other tools that improve our clinical phenotype and understanding of contributing factors to an individual's heart failure syndrome, we need to continue to invest in rigorous assessment and implementation for new diagnostic pathways, with a particular focus on the benefit to the patient. *Does new information translate to improved care and outcome?* For this, global leadership, aligning new developments with efficient and innovative clinical trial platforms, and guideline experts are required to ensure we have a strong evidence-base to guide clinical implementation. Dr. Schulz-Menger and colleagues from Germany have provided a considered commentary regarding the evolution of guidelines that play a critical role in the implementation of CMR as a diagnostic tool for non-ischaemic cardiomyopathies [12], driving clinical quality and minimising clinical variation. As they astutely state "it has become more and more evident, that the quantification of cardiac function and myocardial structure is crucial for a diagnostic decision. This major step will also challenge the community as a significant effort is needed to ensure quality assurance including standardization" [12]. Whilst there may be some argument against widespread use of CMR from the "payers" in the system, the economic savings that can be made by early accurate diagnosis of underlying pathophysiology as well as risk stratifying features also needs to be clearly identified and placed in the equation.

Whilst it is invigorating to observe the progress in technology and clinical application of CMR as it pertains to heart failure and non-ischemic cardiomyopathy, we need to continue to wrestle with the immense challenge of implementing equitable access to evidence-based clinical pathways and diagnostic tools. For CMR this includes collaborative approaches to improve access to hardware, sequences, technical and clinical expertise in clinical settings around the globe, as well as efforts to accelerate acquisition and sharpen reproducibility in non-expert hands. This is highlighted by the powerful final sentence in the review by Dr. Abidin "Now the task is to make parametric mapping with CMR technically available across the globe" [3]. Improvements in remote support, as presented by Bac Nyguyen [13] from Norway, is one critical ingredient in this ambition.

In conclusion, this SCMR edition of MAGNETOM Flash provides its broad readership with an excellent overview regarding the emerging role of CMR with more stratified approaches to common clinical cardiology challenges. Better stratification by underlying mechanistic markers – both imaging and blood based – will be the central ingredients to making the next advances in prevention, early detection and treatment of many cardiovascular conditions. CMR and the non-invasive window that it provides into myocardial pathology, without the need for myocardial biopsy, will

undoubtedly be a central player in both better diagnosis management of individual patients as well as advances in the field through coordinated stratification and targeting of novel therapies in more efficient and powerful trials. Ongoing partnerships between academia and industry, as well as clinical guideline and policy experts are required to ensure we maximise the huge potential going forward.

Gemma Figtree

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