

Editorial: Infiltrative Cardiomyopathy and Heart Failure

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Provisional

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Infiltrative cardiomyopathy (InfCM) is characterized by deposition of abnormal substances within the myocardium, leading to inflammation and subsequent fibrosis. The sequelae of abnormal extracellular substance deposition include ventricular diastolic and systolic dysfunction, coronary flow limitation and mechanical stress, all of which can have long-term irreversible effects. This pan-cardiac damage causes conduction blocks, arrhythmias, and progressive heart failure. Notoriously, InfCM is often diagnosed late or misclassified, resulting in a worse prognosis.

This research topic aimed to provide readers with new findings, opinions and perspectives on the diagnosis and management of InfCM. It also aimed to highlight novel approaches in the diagnosis and treatment of InfCM types such as Cardiac Amyloidosis (CA) and Cardiac Sarcoidosis (CS), using genetics, biomarkers, and imaging modalities. In total, there were 233 contributors to this research topic. After editorial review, 5 manuscripts were accepted for publication over 18 months. These highlight the depth and breadth of diseases classified under the umbrella term of “InfCM”. The selected manuscripts include 2 original research articles and 3 comprehensive review articles.

Echocardiography is often the gateway diagnostic imaging test for InfCM. Ferkh¹ et al show that echocardiographic measures can be used to differentiate various cardiomyopathies associated with ventricular hypertrophy or increased left ventricular (LV) wall thickness. They specifically demonstrated that a composite of echocardiographic parameters could help differentiate Cardiac Amyloidosis (CA) and Anderson–Fabry disease (AFD), from hypertensive heart disease (HHT). This study comprised of 209 patients, compared 120 CA (58 transthyretin amyloidosis [ATTR] and 62 light-chain [AL] amyloidosis), 31 AFD and 58 HHT patients; mean age 64.1 ± 3.7 years, 75% male. Common echocardiographic measurements were evaluated including LV) mass, LV global longitudinal strain (GLS), segmental strain and diastolic measures (e' velocity and E/e' ratio). The authors utilized a linear discriminant analysis to identify parameters specific to a particular disease state; these algorithms could potentially be utilized on ultrasound systems using artificial intelligence and machine learning techniques. The echocardiographic measurements employed in this paper are simple and widely accessible which facilitates their widespread use to aid early diagnosis.

The paper by Zhu et al.², evaluates the minimum clinically important differences (MCID) in heart failure questionnaires for patients with chronic heart failure. This study recruited 194 patients from 3 centers in China and used anchor-based and distribution-based approaches to estimate MCID. They found a minimum MCID of 3.6, 2.0, and 7.4 and maximum estimates of 9.5, 2.5, and 13 in the physical domain, emotional domain and total scores respectively. Interestingly, as this study includes 194 patients from 3 centers in China, patients were treated with a combination of traditional HF therapy as well as integrative Chinese medicine. These findings highlight the

need for wholistic evaluation of patient responses to heart failure therapies and the potential for discrepancies between physical and psychosocial parameters of improvement.

Three of the articles provide comprehensive reviews on the leading causes of InfCM giving an in-depth and up to date perspective.

Mohty et al.,³ discuss the landscape of CA in the Middle East, an area that the authors note is underrepresented in the global literature. The authors estimate there is a case burden of ~6,159 patients with ATTR-CA in Saudi Arabia alone, many of whom are not getting diagnosis or treatment due to lack of awareness, referral, and imaging modalities. The authors explain the poor rate of diagnosis by citing two recent surveys in Saudi Arabia which identify that the major barrier is lack of physician awareness and knowledge regarding symptoms of ATTR-CA. This presents an urgent opportunity to improve care in the region for patients with InfCM.

The review paper by Cherett et al.,⁴ evaluates sarcoid, with specific electrophysiology insights. Noteworthy aspects of this review is the discussion of the complexities of the diagnosis of CS according to the Heart Rhythm Society and Japanese Circulation Society expert guidelines. Both guidelines provide a clinical diagnostic pathway, which additionally requires a confirmatory histopathological diagnosis, generally from an extra-cardiac site combined with cardiac symptoms. In the case of isolated CS, a histopathological diagnosis of non-caseating granulomas (with no alternative cause) is needed from cardiac tissue, however this is difficult given the patchy nature of cardiac disease. They give an in-depth update of the role and utility of electrophysiology-guided targeted biopsy including electroanatomical (CARTO) mapping, which may help improve the diagnostic yield for a histopathological diagnosis of CS.

Averbuch et al.,⁵ provide updates on AFD, a disorder in which up to 50% of patients have cardiac involvement. AFD results in a reduced life expectancy and adverse cardiovascular events that usually occur in the 5th decade especially in males. Interestingly in AFD, the degree of increased LV wall thickness correlates with α -galactosidase activity levels. Notable updates include the use of cardiac magnetic resonance imaging, specifically T1 mapping techniques for the non-invasive diagnosis of AFD. In addition, novel therapies such as oral chaperone therapy (in patients with specific mutations of the alpha galactosidase gene) are presented. Existing future therapeutic options include substrate reduction therapy and emerging mRNA techniques are also highlighted.

Recent advances in treatment of InfCM underline the crucial need for sensitive and accurate diagnostic techniques, as well as awareness of markers of early disease. The suite of papers in this review series are timely and address these key issues.

Development of specific stabilizers for amyloid fibrils, mRNA based therapy to reduce abnormal protein production and gene editing technology (CRISPR) have now been shown to reduce transthyretin in hereditary ATTRs Recognition of CA and CS in United Network for *Organ* Sharing (UNOS) criteria have improved cardiac transplantation rates and outcomes. It is possible that early disease diagnosis combined with new disease -modifying treatments will eliminate the

need for cardiac transplantation in the long run. Despite these recent areas of progress, there is still a long way to go, with respect to knowledge about the natural history of disease in diverse ethnic cohorts, patient and physician education and access to specialized services. Research topics such as this one help to remind readers of these somewhat rare yet increasingly treatable conditions and provide updates in this fast moving and exciting field.

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