# Introduction

heumatic heart disease remains a considerable cause of Cardiovascular morbidity and mortality in developing countries where two thirds of world's population live.

Millions of children and young adults have rheumatic heart disease and nearly a third of these have mitral stenosis. Rheumatic heart disease is the etiology of mitral stenosis in most of the patients (1,2).

It is accepted that isolated MS does not impair left ventricular (LV) systolic function (3), but in some publications it has been shown that MS impairs LV systolic function <sup>(4,5)</sup>.

In the assessment of LV systolic function, a number of imaging techniques-such as echocardiography, MRI, scintigraphy and CT-have been used. In the echocardiographical assessment of LV function, the ejection fraction (EF), tissue Doppler imaging (TDI), Doppler strain, and 2D strain have been widely used<sup>(6)</sup>.

EF is the most widely used index of contractile function, but due to the visual component, assessment of endocardial excursion is subjective and has high inter-observer variability<sup>(7)</sup>.

2D strain is a novel technique which evaluates LV systolic functions more objectively and quantitatively, and does not have

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the limitations seen in EF, TDI, and Doppler strain; thus, it has become more commonly used in recent years<sup>(8)</sup>.

In the diagnosis of LV dysfunction due to MS, some studies have shown EF, TDI, and Doppler strain to be useful, However, studies related to the use of 2D strain, a more objective technique in the diagnosis of LV systolic function in MS, are very limited <sup>(9)</sup>.

In this study, we aimed to evaluate the role of 2D strain in the assessment of subclinical LV systolic dysfunction and the relationship between stenosis severity and LV dysfunction in patients with MS.

# AIM OF THE STUDY

The Aim of this study is to evaluate the effect of the severity of mitral stenosis on LV systolic function by 2D Strain using speckle tracking.

# Chapter 1

# RHEUMATIC HEART DISEASES

Ver the past decades, rheumatic heart disease (RHD) and its antecedent rheumatic fever (RF) have largely disappeared from wealthy countries, and the clinical caseload of RHD has shifted to older age groups. RHD has also been dwarfed by ischemic heart disease. Additionally, RF/ RHD control programs were successfully implemented in some low- and middle-income countries during the latter part of the 20th century, prompting the World Health Organization (WHO) and others to downscale their RF/RHD activities by the early 2000s<sup>(10)</sup>.

Yet, RHD continues unabated in poor countries and among vulnerable groups in wealthy ones<sup>(11)</sup>. A 2007 report on RHD among school children in Cambodia and Mozambique spawned a whole literature on echocardiography and RHD<sup>(12)</sup>.

The recent REMEDY study (Global Rheumatic Heart Disease Registry) documented high rates of disability and premature death across African and Asian countries<sup>(13)</sup>.

In 2015, a civil society movement, RHD Action, was launched to raise awareness and support countries looking to address RHD.

In May 2018, the World Health Assembly adopted a resolution to reinvigorate global and national RF/RHD prevention and control efforts<sup>(14)</sup>.

Because of this renewed interest, the science of RHD has evolved rapidly. A number of new or ongoing studies aim to provide answers to key questions. This Scientific Expert Panel seeks to summarize recent research on RHD from molecular mechanisms to health systems in one coherent, scientifically-grounded vision for the future of science, clinical medicine, and public health practice relating to RHD.

# WHAT IS RHEUMATIC HEART DISEASE, AND HOW BIG IS THE PROBLEM?

**PATHOGENESIS:** The major driver of acute RF is group A beta-hemolytic streptococcal (GAS) infection. Socioeconomic conditions leading to increased GAS exposure include household crowding, poor hygiene, and low access to medical services<sup>(15)</sup>. Why only a minority of persons (<6%) living in GAS-endemic areas develop RF is less understood.

Host factors: There are 2 theories of how GAS infection damages host tissues. The basis of the molecular mimicry theory is that molecules on the infecting organism are antigenically similar to molecules on host tissues. When the host immune response targets these molecules, both are damaged.

In the case of acute RF, 2 main streptococcal antigens have been implicated: the surface M protein, and GlcNAc, the immunodominant epitope of the group A Carbohydrate<sup>(16)</sup>. The "neo-antigen" theory, a more recent development, suggests that the GAS organism gains access to the subendothelial collagen matrix, where M proteins binds to the CB3 region of type IV collagen, creating a neo-antigen that induces an autoimmune response against collagen<sup>(17)</sup>.

In both theories, it is thought that the initial damage to cardiac tissues is due mainly to antibodies, with cellular responses subsequently implicated as the immunological cascade evolves. These antibodies recognize and activate valve endothelium to express adhesion molecules like vascular cell adhesion molecule 1, allowing CD4 T cells (and others) activated by GAS to invade the heart valve, encounter antigens, and become further activated. Over time, tissue break-down, partly involving autoantibodies and complement activation, releases additional endogenous antigens such as collagen, lamnin, myosin, and tropomyosin that may also serve as autoantigens, stimulating more CD4 T cells, which then produce Th1 and potentially Th17 cytokines, leading to further inflammation in the heart valve. Over time, successive episodes coupled to resolution leads to neovascularization and fibrosis (18).

#### **Clinical features:**

Aside from a subset of children in whom RF leads to severe carditis and early RHD, RHD is usually clinically silent (latent) until it manifests during adulthood. Many individuals in endemic countries present late in their disease process with 1 or more sequelae. The REMEDY study followed 3,343 individuals with symptomatic RHD presenting for care at academic centers in 14 countries. Most individuals were 15 to 49 years of age, and fewer than one-half recalled a history of RF. Heart failure, pulmonary hypertension, and atrial fibrillation were the most frequent medical complications. About 20% demonstrated decreased left ventricular ejection fraction, and about one-third had increased left ventricular end-diastolic diameter underscoring the consequences of late presentation.

Challenges in diagnosing acute RF are a major factor for preventing RHD. Strong evidence of mild presentation and the importance of subclinical carditis prompted revision of the Jones Criteria (the gold standard for RF diagnosis) in 2015 to better account for differences in population risk<sup>(19)</sup>.

While these criteria will likely increase case detection, barriers such as poor health seeking behavior, lack of pathology services, and clinical overlap with other endemic diseases (such as malaria in sub-Saharan Africa) limit the efficacy of a simple diagnostic shift within a clinical decision rule. Better RF diagnosis

will require the development of new laboratory tests that could replace clinical decision rules.

**Revised Jones criteria (low-risk populations):** Major and minor criteria are as follows:

Major criteria: carditis (clinical and/or subclinical), arthritis (polyarthritis), chorea, Erythema marginatum, and subcutaneous nodules.

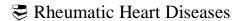
Minor criteria: polyarthralgia, fever ( $\geq 38.5^{\circ}$  F), ESR  $\geq 60$  mm and/or CRP  $\geq 3.0$  mg/dl, and prolonged PR interval (unless carditis is a major criterion).

Revised Jones criteria (moderate- and high-risk populations): Major and minor criteria are as follows:

Major criteria: carditis (clinical and/or subclinical), arthritis (monopolyarthritis or polyarthritis, or polyarthralgia), chorea, Erythema marginatum, and subcutaneous nodules.

Minor criteria: fever ( $\geq$ 38.5° F), ESR  $\geq$ 30 mm and/or CRP  $\geq$ 3.0 mg/dl, and prolonged PR interval (unless carditis is a major criterion).

ARF diagnosis (initial episode): The diagnosis of an initial episode of ARF requires two major criteria, or one major plus two minor criteria.



**Echocardiography and RHD:** The World Heart Federation (WHF) published the first evidence-based, standardized criteria for the echocardiographic diagnosis of RHD in 2012<sup>(20)</sup>.

2012 WHF criteria for echocardiographic diagnosis of RHD

#### A- Echocardiographic criteria for individuals aged ≤20 years

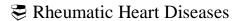
- > Definite RHD (either A, B, C, or D):
- A) Pathological MR and at least two morphological features of RHD of the MV
- B) MS mean gradient ≥4 mmHg
- C) Pathological AR and at least two morphological features of RHD of the AV
- D) Borderline disease of both the AV and MV
- ➤ Borderline RHD (either A, B, or C):
- A) At least two morphological features of RHD of the MV without pathological MR or MS
- B) Pathological MR
- C) Pathological AR

- Normal echocardiographic findings (all of A, B, C, and D):
- A) MR that does not meet all four Doppler echocardiographic criteria (physiological MR)
- B) AR that does not meet all four Doppler echocardiographic criteria (physiological AR)
  - C) An isolated morphological feature of RHD of the MV (for example, valvular thickening) without any associated pathological stenosis or regurgitation
  - D) Morphological feature of RHD of the AV (for example, valvular thickening) without any associated pathological stenosis or regurgitation

# Echocardiographic criteria for individuals aged >20 years

Definite RHD (either A, B, C, or D):

- A) Pathological MR and at least two morphological features of RHD of the MV
- B) MS mean gradient ≥4 mmHg
- C) Pathological AR and at least two morphological features of RHD of the AV, only in individuals aged <35 years
- D) Pathological AR and at least two morphological features of RHD of the MV



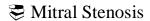
#### Morphological features of RHD

#### **Features in the MV:**

AMVL thickening  $\geq 3$  mm (age-specific) , Chordal thickening, Restricted leaflet motion, Excessive leaflet tip motion during systole

#### **Features in the AV:**

Irregular or focal thickening, Coaptation defect, Restricted leaflet motion, Prolapse.



# Chapter 2

## MITRAL STENOSIS

#### Etiology and epidemiology of mitral stenosis

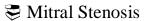
The mitral apparatus consists of the annulus, valve leaflets, chordae tendineae and papillary muscles. Mitral stenosis (MS) is characterised by a narrowed valve orifice and obstruction to left ventricular inflow.

Rheumatic MS, a delayed complication of rheumatic fever, is the most common etiology for MS worldwide, while degenerative MS due to mitral annular calcification (MAC) is increasingly encountered in developed countries<sup>(21)</sup>.

Uncommon etiologies include congenital MS and radiationinduced MS. Echocardiography can establish the diagnosis and elucidate etiology, severity and complications of the disease.

It is essential for treatment planning (medical, percutaneous or surgical) and useful in predicting response to therapy.

Mitral stenosis (MS) is characterised by a decrease in mitral valve (MV) orifice area leading to compromised left ventricular filling. The consequence is stagnation of blood proximal to the MV that results in elevated left atrial, pulmonary venous, and pulmonary artery pressures<sup>(22)</sup>.



Mitral stenosis most commonly occurs because of rheumatic fever or degenerative MV disease. Although rheumatic fever remains the predominant cause of MS worldwide, it has been largely replaced by degenerative MS in the developed countries<sup>(23)</sup>.

Historically, the diagnosis of MS was made based on clinical examination findings and, because most symptoms generally occur in later stages of the disease, the diagnosis was made late in the clinical course leading to increased morbidity and mortality. However, since the presence of echocardiography and other investigations, the disease is now diagnosed at relatively early stages allowing early intervention and fewer complications. Improvements in catheter-based interventions and surgical techniques have also contributed greatly to the reduction in MS-related morbidity and mortality<sup>(24)</sup>.

#### **Mitral Valve Anatomy**

The mitral valve (MV) apparatus is comprised of the mitral valve annulus, anterior and posterior MV leaflets, chordae, and anteromedial and posterolateral papillary muscles. It is the most complex of the cardiac valves and is commonly affected by disease. Recent advances in imaging (cardiac magnetic resonance imaging, computed tomography and 3D and strain echocardiography) have shed light on its complex structure and function.

The anterior and posterior leaflets have roughly the same area. However, they differ significantly in shape and annular attachment. The anterior mitral leaflet is a tongue-like structure and has a length to width ratio of roughly one. The posterior leaflet on the other hand has a semi-lunar shape and has a low height to width ratio. It occupies two thirds of the annulus which reinforces its framework and makes it more conducive to surgical repair. However, it may be more susceptible to pathologies that cause fixation of the leaflet, such as mitral annular calcification (MAC) and rheumatic disease.

The annulus is a saddle-shaped structure which acts as a framework for attachment of the MV leaflets. It has complex mechanical properties and enables the MV to operate as an effective "one-way door" by allowing deformation along the anteroposterior diameter during each cardiac cycle. The mitral annulus is the site for calcific changes that lead to degenerative MS. Compared to the normal annulus, the calcified mitral annulus is larger and flatter, has an increased anteroposterior diameter, reduced saddle height and reduced contraction along the anteroposterior axis (25).



#### **Etiological Types**

#### Rheumatic MS

Rheumatic MS is a delayed complication of acute rheumatic fever. Antibodies to streptococcal antigens cross-react with valve tissue, with damage to the valve accumulating over decades. While rheumatic disease can affect any of the heart valves, it most commonly involves the mitral valve.

The hallmark feature of rheumatic MS is commissural fusion which eventually leads to the classic "fish mouth" appearance of the valve orifice. Other anatomical lesions include chordal shortening and fusion, leaflet thickening and, later in the disease, superimposed calcification which may contribute to the restriction of leaflet motion. However, unlike annular involvement in degenerative MS, calcification in rheumatic MS primarily affects the leaflet tips.