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CLINICAL COMMENTARIES

CARDIOVASCULAR RESEARCH Onlife

Can we diagnose acute rheumatic fever early to maximize the success of secondary prophylaxis in rheumatic heart valve disease?

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Rheumatic heart valve disease (RHVD) is a major burden in resource-poor settings around the world and the leading cause of cardiovascular death in children and young adults.[1] Valve replacement surgeries remain an integral part of RHVD treatment. However, such interventions are not available to the majority of affected RHVD patients.[2] Severe disease causes substantial disability in young adults during the most productive years of their lives, impacting economic growth.[2] Awareness of RHVD has increased recently as newly implemented echocardiography-based screening has improved diagnostic accuracy, further revealing the immense disease burden. Recently, advocacy groups are making efforts to identify and remove barriers to translation of existing knowledge into programmes and practice to combat RHVD.[2]

Valvular damage is a harmful post-infectious sequela of acute rheumatic fever (ARF), resulting from abnormal inflammation triggered by group A streptococcal (GAS) pharyngitis.[3] Chronic autoimmune responses represent the driving mechanisms in RHVD pathogenesis.[3] Recurrent GAS infection is a strong determinant of progression from acute carditis to severe chronic RHVD, and therefore, its early and accurate detection could allow prompt clinical intervention and improvement of disease outcomes.[4] Yet, ARF is infrequently diagnosed and RHVD only detected in its advanced stages. Although no pharmacological therapies exist to treat established RHVD, patients benefit from secondary antibiotic prophylaxis (e.g. penicillin G benzathine) since it can prevent recurrent GAS infection and incremental valve damage.[5] Host immune responses to bacterial re-exposure promote the expansion of autoantigen-reactive effector cells.[3] Unfortunately, numerous challenges exist that prevent implementation of this simple and inexpensive antibiotic intervention—the major difficulty being to identify and track patients with ARF and early RHVD (*Figure 1*).[6]

Echocardiographic screening can detect early mild valvular changes that do not cause symptoms and are often undetectable by standard auscultation, termed 'latent' RHVD.[6] The criteria for the diagnosis of latent RHVD were standardized in 2012 and can be applied to individuals younger than 20 years old.[7] Based on that framework, Beaton *et al.*[6] conducted a controlled randomized clinical trial in Ugandan patients (5–17 years) with latent RHVD, dubbed Gwoko Adunu pa Lutino, in which participants were assigned to receive either injections of penicillin G benzathine every four weeks or no prophylaxis. The trial population was recruited from primary and secondary schools, and disease progression was monitored by echocardiogram for a 2 years following enrolment.[6] This study sought evidence that secondary antibiotic prophylaxis could modify the natural history of disease and thus improve RHVD outcomes. A standard consensus panel was assembled to evaluate fifteen echocardiographic images from each patient based on the 2012 World Heart Federation Criteria.[7]

A total of 102 200 children and adolescents were screened; 926 were assessed to be eligible for the trial and 799 completed the study, 399 in the prophylaxis group and 400 in the control group.[6] RHVD patients who received secondary prophylaxis showed a significant reduction in disease progression compared with the control group. The authors estimated that 13 children or adolescents would need to be treated to prevent disease progression in 1 person (7.7%) over the course of 2 years of treatment.[6] Disease regression was not observed in either group.[6] As antibiotic therapy prevented disease progression in a subset of patients, the study provides new evidence in favour of echocardiographic screening to diagnose latent ARF in high endemic areas.

While particular benefits of this diagnostic approach are apparent, the study also highlights a persisting knowledge gap regarding methods that could detect ARF before latent RHVD develops, i.e. before valvular tissue damage occurs or when it may still be reversable. Discovery of early ARF biomarkers could significantly improve disease diagnosis and increase the success rate of secondary prophylaxis.

Given the persisting high prevalence of ARF and the shortcomings of prevention strategies in resource-poor countries, RHVD is expected to remain prevalent for the near future. Basic research efforts must advance towards elucidating the cellular and molecular mechanisms of ARF/RHVD, not only to identify accurate disease biomarkers but also effective therapeutic targets to prevent disease progression. Regrettably, such studies are extremely scarce. Our research group is committed to advancing the translation of basic research findings into the patient care arena by integrating studies of

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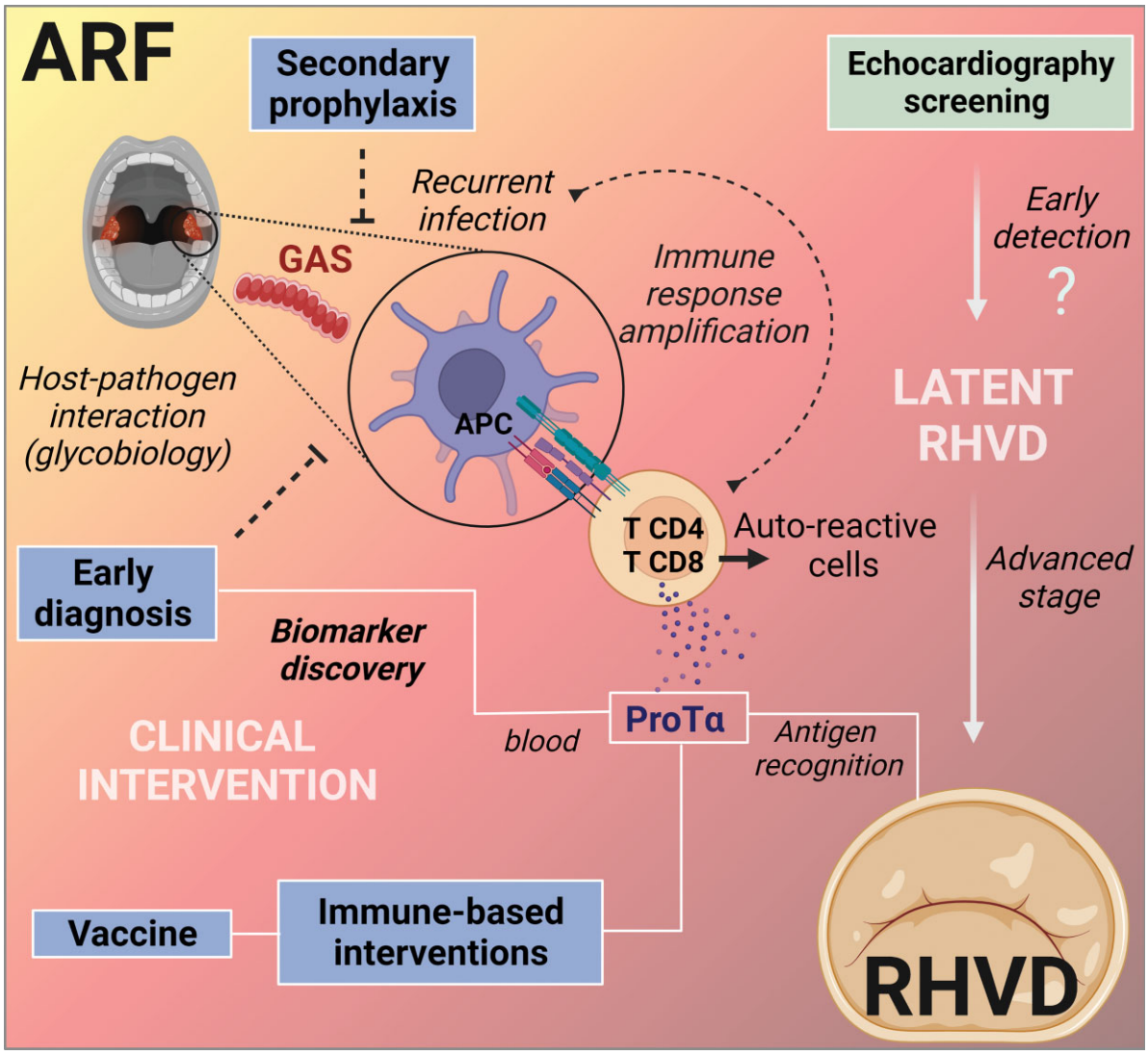

Figure 1 Schematic representation of the mechanisms of the pathogenesis of ARF and RHVD. Following GAS invasion of the pharyngeal epithelium, antigen presenting cells (APCs) recognize and process bacterial antigens and present them to T cells (CD4 and CD8 T cells). Some of these cells became auto-reactive clones and can recognize epitopes in heart resulting in valve dysfunction. T cells are sources of the immunostimulatory protein ProTα, which is elevated in blood of patients with RHVD and thus can serve as potential biomarker of RHVD. ProTα facilitates CD8 T cell recognition of cross-reactive collagen epitopes in RHVD and therefore could be a target for immune-based interventions. Echocardiographic screening can detect early mild valvular changes that termed 'latent' RHVD that could progress to permanent heart valve damage. Secondary prophylaxis can prevent recurrent GAS infection and incremental valve damage associated with amplification of pathogenic immune responses by antigen re-exposure. Discovery of ARF biomarkers could significantly improve early disease diagnosis and increase the success rate of secondary prophylaxis and clinical intervention.

mitral valve pathology, the immunobiology of systemic inflammation and the clinical presentation of RHVD.[8] For example, we recently demonstrated that prothymosin alpha (ProTα) is elevated in blood of patients with RHVD, and that its aberrant expression in valve lesions facilitates CD8 T-cell recognition of cross-reactive collagen epitopes in a manner that informs the large female predominance in RHVD (*Figure 1*).[9]

Although GAS is universally susceptible to penicillin G benzathine treatment, pain associated with intramuscular injection and retention of patient compliance for long-term treatment are some of the obstacles to achieving adequate secondary prophylaxis outcomes.[10] Furthermore, secondary prophylaxis might not imply lifelong protection. Considering the socio-economic conditions where RHVD develops, advancement of GAS vaccines, for which mechanistic ARF biomarkers could aid in safety evaluation, represents an ideal strategy to control disease burden in endemic countries. Identification of specific molecular RHVD drivers could further open possibilities for immune-based interventions to resolve or control the ongoing self-reactivity that drives cardiovascular pathology in this leading public health challenge.

Conflict of interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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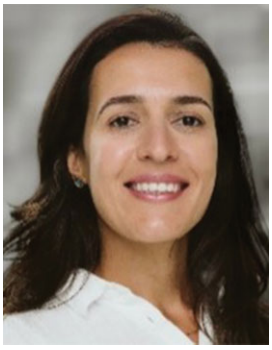

Biography: Livia S.A. Passos is a Research Fellow at Brigham and Women's Hospital, Boston, USA. During her academic career in Brazil, she investigated immunoregulatory mechanisms in tropical infectious diseases. After her PhD, she joined the group of Dr. Elena Aikawa to study cellular and molecular mechanisms that underlie RHVD. She focuses on understanding the pathogenic immune responses that lead to heart valve dysfunction in RHVD.

Biography: Victor Nizet is Distinguished Professor of Pediatrics and Pharmacy at the University of California, San Diego. His laboratory performs interdisciplinary research on bacterial molecular pathogenesis and innate immunity, with an eye toward development of novel therapies and vaccines. Over the past two decades, elucidating virulence mechanisms and host responses to group A streptococcus infection has been a key field of investigation.

Biography: Robert Levine is Professor of Medicine, Harvard Medical School, whose laboratory uses non-invasive imaging to study mechanisms of heart valve disease in collaboration with basic scientists, including Elena Aikawa, Livia S.A. Passos and Victor Nizet, the genetics of mitral valve prolapse, and RHVD pathophysiology with Maria Nunes and Walderez Dutra in Brazil.

Biography: Elena Aikawa is a Professor of Medicine at Harvard Medical School and the Naoki Miwa Distinguished Chair in Cardiovascular Medicine at Brigham and Women's Hospital (BWH) in Boston, Massachusetts, USA. She is also Founding Director of the Heart Valve Translational Research Programme at BWH. Her research focus is on the development of new therapies to prevent and treat heart valve disease. Recently she used systems approaches, involving multi-omics and network medicine, to identify novel therapeutic targets.

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