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Editorial

Cutting the "Gordian Knot" — Cardiac Involvement in Primary Sjögren Syndrome

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Sjögren syndrome (SS) is a systemic autoimmune disease typically characterized by inflammatory involvement of the exocrine glands[1]. The association of SS with an increased risk of cardiovascular disease (CVD) including manifestations such as stroke and myocardial infarction has been demonstrated by numerous previous studies[1]. Bringing classical CVD risk factors under control through appropriate therapeutic interventions has traditionally been the primary approach that has been reiterated in most practice guidelines regarding the prevention of CVD in patients with SS[2]. Yet, it would appear that these measures are not adequate by themselves to halt progression to CVD in these patients, as demonstrated by previous epidemiologic evidence[3]. It would thus appear that more mechanisms that are as of yet unaccounted for play an important role in this context. This complex conundrum is reminiscent of the ancient Greek legend of the "Gordian knot," a knot tied by Gordius, the king of Phrygia, rumored to be impossible to untie except by one destined to rule Asia. Famously, Alexander the Great came upon a "unique" solution to this puzzle by cutting the knot with his sword, thus fulfilling the condition, although somewhat unconventionally.

Back to our modern reality, Nishiwaki, *et al*[4] in this issue of *The Journal*, present compelling evidence that cardiovascular magnetic resonance (CMR) can serve as the sword that can cut the metaphorical knot of CVD in patients with SS. In the Nishiwaki, *et al*[4] study, the authors utilized CMR to screen 52 female patients with primary SS without any previous history of coronary artery disease and/or CVD risk factors for silent cardiac involvement. CMR is uniquely suited for this purpose as it is a noninvasive imaging modality that does not employ ionizing radiation. In addition, apart from accurate and highly reproducible assessment of biventricular function, CMR can characterize myocardial tissues with regard to edema and fibrosis. This allows the identification and assessment of recent myocardial inflammation (high signal in T2-weighted imaging due to edema) as well as myocardial scarring related or unrelated to active inflammation [late gadolinium enhancement (LGE) in T1-weighted images 15 min after the injection of contrast agent]. Based on LGE distribution, it is possible to distinguish between myocardial scarring of ischemic and nonischemic origin (subendocardial or transmural fibrosis following the distribution of the coronary arteries vs subepicardial, intramyocardial, or diffuse subendocardial fibrosis not following the distribution of coronary arteries, respectively). It is worth noting that extensive evidence in a multitude of autoimmune rheumatic diseases already supports the notion that CMR can detect cardiac lesions not only in symptomatic but also in asymptomatic patients, during both the acute and the chronic phases of cardiac disease[5,6,7,8].

Nishiwaki, *et al*[4] report that CMR revealed myocardial abnormalities in 11 (21%) asymptomatic patients. In total, CMR identified myocardial fibrosis in 10 (19%) patients, 2 (20%) of whom showed high intensity on T2-weighted imaging, as is typically seen in active myocardial inflammation. The fibrotic tissue followed a linear or patchy intramyocardial and subepicardial distribution suggestive of nonischemic etiology. Interestingly, no patients had any signs of fibrosis of ischemic origin. Further, the presence of myocardial fibrosis was independently associated with salivary gland focus scores, but the study was not specifically powered to detect this association. Although these findings will require future independent validation, they have important clinical implications for daily practice and for future studies in primary SS. First, the presence of active inflammation, in the form of myocardial edema or previously healed cardiac lesions (areas of nonischemic fibrosis in the absence of edema), is of great concern, considering the established role of inflammation as an important driving force behind heart failure[9]. Second, although myocardial fibrosis is meant to serve as a reparative

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mechanism, it has the potential to adversely affect cardiac function and normal electrical conduction, and by extension to cause increased morbidity and mortality[10].

The authors document for the first time, to our knowledge, that a significant proportion of asymptomatic patients with primary SS and no CVD risk factors may manifest myocardial involvement of nonischemic origin. This has also been demonstrated in other autoimmune rheumatic diseases[11,12]. Collectively, these findings suggest that additional refinement of candidate selection for immunomodulation is required for better control of immune responses at the cardiac milieu, while at the same time demonstrating a prominent role for CMR-based screening and/or patient selection for treatment beyond clinical or echocardiographic examination. CMR figures prominently as the new and sophisticated player in the field of cardiology and a sharp sword in the clinician's arsenal. It is now up to us to wield this powerful weapon in clinical practice and in future research so that the "Gordian knot" of CVD in autoimmune rheumatic diseases, and SS in particular, can finally be cut as in the legends of old.

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