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Commentary

Association of cardiovascular risks with sympathovagal imbalance in rheumatoid arthritis

Rheumatoid arthritis (RA) is the commonest inflammatory arthritis occurring throughout the world[1]. It is more prevalent in Indians and less prevalent in black Africans and Chinese. Both genetic and environmental factors are involved in the pathogenesis of RA. Cigarette smoking is a strong risk factor for RA[2]. Irrespective of the initiating stimulus, RA is characterized by infiltration of lymphocytes, plasma cells and macrophages into the synovium[3]. In RA, in the affected joints, activated lymphocytes secrete immunoglobulins including rheumatoid factor (RF) and macrophages release proinflammatory cytokines such as tumour necrosis factor- α (TNF-α). These chemicals act on synovial fibroblast, bone cells and chondrocytes to promote destruction of synovial membrane, bone, cartilage and soft tissues[4].

From the studies carried out among western population, it has been observed that sympathetic nervous system activity is significantly elevated in RA patients[5]. Spectral analysis of heart rate variability (HRV) in RA patients have revealed a decrease in high frequency (HF) power representing vagal inhibition in addition to an increase in low frequency (LF) power indicating sympathetic activation[6]. It was suggested that the increased incidence of sudden cardiac death in these patients could have been due to the decreased vagal drive to the heart[6]. The magnitude of cardiovascular autonomic imbalance was linked to cardiovascular risks in patients suffering from RA[7,8]. Reduction in HRV, prolongation in QTc interval and higher sympathetic and decreased vagal drive were proposed as significant risk predictors for onset of sudden cardiac death in RA[9,10]. The cardiovascular autonomic dysfunction was suggested to stem from the underlying proinflammatory cytokines in RA[11]. It was also observed that in chronic arthritis such as RA, decreased responsiveness of hypothalamic-pituitary-adrenal axis causes inadequate production of cortisol in relation to inflammation that consequently leads to increased sympathetic activity, increased circulating cytokines, decreased local synovial sympathetic innervation, altered metabolism of estrogen in the synovium and high expression of estrogen receptors in synovial cells; all leading to exacerbation of neuroendocrine abnormalities in RA[12].

In this issue, Yadav and colleagues[13] report on HRV analysis in RA patients in Indian population. Authors have studied in details the HRV indices and correlated with immunological and biochemical parameters. They observed a decrease in total power (TP) of HRV in RA patients, which indicates poor cardiovascular health of these patients, as TP in general reflects cardiovascular status of the subject[14]. There was significant decrease in all time domain indices (TDI) in patients compared to controls indicating considerable decrease in vagal drive of cardiac modulation. In addition, there was increased sympathetic activity in these patients that corroborated with their significantly high systolic blood pressure (SBP) compared to the SBP of age and gender matched controls. The most important finding was the significant correlation of rheumatoid factor (RF) with changes in LF and HF powers of HRV indicating the alteration in sympathovagal activity with the severity of the disease. Though already there are reports of similar kind on autonomic imbalance in western population, a report from Indian subcontinent is worth publishing as there is wide ethnic variations in HRV indices and autonomic functions[15]. This study highlights the cardiovascular risks of RA patients, as mortality in patients suffering from RA is primarily due to cardiovascular events rather than the disease *per se*. However, the major limitations of the study are the less sample size and absence of plasma biochemical assessment of sympathetic activity.

The morbidity and mortality in RA is attributed mainly to the cardiovascular complications of the

disease[16,17]. Cardiovascular events in RA are mainly due to the severity of inflammation and immunological reactions[18-20]. In recent years, RA has been considered as an independent risk factor for coronary artery disease[20]. Various studies have aimed to clarify important aspects of risk stratification and treatment options in patients with rheumatoid arthritis, and specific therapies are being evaluated that promise to reduce long-term cardiovascular risk in these patients. Chemicals released from the inflammatory cells in RA patients initiate and facilitate the cardiovascular damage. Hence, it is imperative to detect the mediators of inflammation linked to sympathovagal imbalance that impose cardiovascular risks in RA. As the mainstay of treatment in RA is anti-inflammatory drugs[4], this will also explore the possibility of use of specific drugs from the very beginning of the disease process to check the rise in inflammatory chemicals that could be harmful for cardiovascular functions. Spectral HRV analysis is a non-invasive and sensitive tool to assess autonomic fluctuations in health and disease[14]. Hence, future studies should aim to assess the individual contribution of various inflammatory markers to the genesis of sympathovagal imbalance assessed by HRV analysis in RA in larger samples.

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