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# RA, stress and the autonomic nervous system

## A chicken and egg conundrum?

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Most people living with RA find that it adds some degree of stress to dealing with their life on a day to day basis. But interestingly, when we as rheumatologists listen to our patients in the clinic, many feel not only that stressful events worsen their RA disease activity but even attribute the onset of RA to prior stressful events. NRAS has recently conducted a major UK wide survey to evaluate emotional wellbeing and mental health including psychological stress as a factor affecting patients with rheumatoid arthritis. Their report of the survey results will be launched in parliament on November 1st, 2018.

Similarly, over the past few years, researchers in the UK, Amsterdam and the US have focused attention on the science behind this question. At the May 2018 annual meeting of the British Society for Rheumatology in Liverpool, the findings of new studies were presented which may have begun to shed further light on this conundrum.

## Defining "immuno-autonomics"

This brain-stress-immune concept has been recently called "immuno-autonomics". It is the interface between stress, modulated within the brain by the autonomic nervous system (ANS), and functioning of the immune system. The ANS is an integral and relatively primitive subsection of the central nervous system (CNS) responsible for all automatic functions, including cardiovascular (heart rate, blood pressure), breathing, digestion, temperature regulation, sleep and fight-or-flight survival (adrenaline). It coordinates with production of hormones by the endocrine system (pituitary, thyroid and adrenal hormones) to manage any threats to wellbeing from outside the body or within it. While the endocrine system acts slowly, the ANS responds in milliseconds.

In general, the ANS is divided into two components: the sympathetic (fight-or-flight) and the parasympathetic (rest-restorative). At night during sleep, the parasympathetic system predominates and when physical and mental performance is called upon, the sympathetic system is aroused. When one component is more active, the other is less so, and the relative balance changes depending on time of day, activities and bodily needs.

For any given person, their ANS tendency towards a sympathetic or parasympathetic predominance is controlled by genetic factors, life experiences and immediate events, such as exercise, meals and stimulants, including caffeine. Stress intensifies the sympathetic component. Activities of healthy living activate the parasympathetic system, such as moderate exercise, a healthy diet, avoiding stimulants and nicotine, meditation, massage, acupuncture, cognitive behavioral therapy, mindfulness and other relaxation techniques.

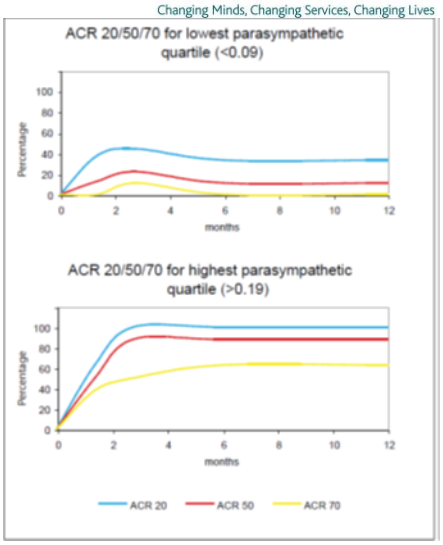
## Measuring the ANS state

The state of the ANS, and relative sympathetic versus parasympathetic activation, cannot be conveniently measured directly within the brain or the bloodstream. However, it can be quantified through assessment of its impact on one of the organs whose function it influences, and this is most often the heart. Resting pulse is controlled not necessarily by the heart itself, but in large part, by the brain, specifically the ANS.

Of course, resting heart rate is not static. For example, a resting pulse of 72 is not really a steady 72. It varies by milliseconds due to varying chest cavity pressure related to breathing, called respiratory sinus arrhythmia. This benign 'arrhythmia', or changes in rhythm, lead to a beat-to-beat heart rate variation. This is called heart rate variability (HRV) and is the most practical way to measure the state of the ANS.[2]

The phenomenon of HRV has been recognized for hundreds of years. But it is only more recently, over the last sixty years, that the complex mathematical assessments required to accurately quantify the ANS state have been refined. In fact, the Russian and United States of America space

programs have applied HRV to measure and improve human performance to survive the extreme physiological challenges of space travel. As a result, assessment of the ANS state has become an essential guide for training. Today, elite professional athletes and Olympians train with the most effective and very best performing tools to measure the ANS state. On the other hand, for patients, there have only been a few available options with the accuracy required for measurement of HRV for the purposes of medical research and optimizing care, usually in cardiovascular medicine. By contrast, most consumer-grade means of measuring HRV, for example, in cell phones, apps, Fitbit, etc., offer only limited reliability.




## Rheumatoid arthritis and stress

Inflammation caused by RA affects the brain and emotional wellbeing.[3] By studying the relationship between RA disease activity and mental and emotional wellbeing, we can investigate how RA influences mental health and the ability to respond to stress. But with the availability of a tool that can measure the "stress thermostat" setting in the body through accurate measurements of the ANS state, we can begin to explore to what extent stress can independently impact on RA disease activity.

Clinical research has showed that the best outcomes from anti-TNF treatment (etanercept or adalimumab) were associated with those people with RA and a parasympathetic predominant profile by HRV in a 52-week, double-blind, clinical trial.[4] Patients within the highest parasympathetic quartile achieved ACR20/50/70 outcome at 52-weeks of 100%/88%/65%. Those in the lowest parasympathetic quartile when initiating TNFi therapy achieved ACR20/50/70 outcome at 52-weeks of 40%/12%/0% (Figure 1). (ACR is the American College of Rheumatology and the numbers indicate the percentage, 20%, 50% or 70%, improvement that can be measured following an intervention. ACR20/50/70 are standard measures applied in clinical trials).

At the 2018 annual meeting of the British Society for Rheumatology in Liverpool, a study asked the question: "To what degree is anti-TNF outcome affected by factors rheumatologists can measure?" Traditional factors (rheumatoid factor, age, disease severity, gender, HAQ (Health Assessment Questionnaire), etc.) only explained 15% of the variability of treatment outcome. In contrast, and impressively, 35-60% of the variability in anti-TNF outcome at 52-weeks could be accounted for by measures of parasympathetic activity by HRV assessed over just 5 minutes.[5]

These interesting observations suggest that higher stress levels might diminish the chances of responding well to treatment. But which came first: the stress or the RA? Frieda Koopman at the

University of Amsterdam offered a suggestion in 2016. Her team monitored patients 'at-risk' for developing RA with factors such as positive blood tests, family history and joint aches (without inflammation). Over 32 months, 31% of at-risk individuals developed RA. An important risk factor was HRV high stress sympathetic state.[6]

## The future

Stress matters! New research will confirm or refute these early findings, however, investigators in the US and UK are also working on what is potentially an entirely new way to treat RA by using electrical pulses to optimize the ANS state of the body; resetting the stress thermostat, as it were. Parasympathetic signals influence the immune system through the vagus nerve. Pilot research to date has shown that stimulation of the vagus nerve reduced RA severity by 35%. This seems to work by reducing inflammatory cytokine levels – the same inflammatory cytokines, TNF, IL-1 and IL-6, that rheumatologists prescribe biologic agents to block.[7]

Treating a clinical condition called obstructive sleep apnea with continuous positive airway pressure (CPAP) in a person who also has RA resulted in a 35% reduction of RA joint count and CRP after 5 months.[8] Obstructive sleep apnea is the best studied condition known to be associated with ANS dysfunction. CPAP, when effective, restores normal ANS state and reduces the cardiovascular risk of obstructive sleep apnea. Very preliminary evidence also suggests that treatment of restless legs syndrome, which is thought to be associated with a high sympathetic state, could also enhance the outcome of anti-TNF treatment.[9]

## Conclusion

Of course, all early medical research studies should be viewed with caution. Immuno-autonomics is a new concept and additional validating research from independent sources will be required prior to drawing conclusions. However, we do know that stress does indeed affect many diseases such as heart disease. Cardiologists are concerned to reduce the impact of stress on their patients. Now, with the development of immuno-autonomics, rheumatology researchers are beginning to explore how measuring and managing ANS stress might help their patients, too.

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