Editorial

Heart rate variability analysis in rheumatology: past, present… and future?

M. Martinez-Lavin[1], A.J. Holman[2]

[1]National Institute of Cardiology Ignacio Chavez, Tlalpan, Mexico City, Mexico; [2]Pacific Rheumatology Associates, Inc. PS, Seattle, WA, USA.

Manuel Martinez-Lavin. MD
Andrew J. Holman. MD

Please address correspondence to:
Andrew J. Holman,
17837 First Avenue S, 6,
Normandy Park,
WA 98148, USA.
E-mail: andrew.holman@inmedix.com

ORCID iD: 0000-0002-2108-4392

Received on May 21, 2021; accepted in revised form on July 26, 2021.

Clin Exp Rheumatol 2021; 39: 927-930.

Key words: heart rate variability, immuno-autonomics, rheumatoid arthritis, autonomic nervous system, fibromyalgia

Competing interests: A.J. Holman holds equity shares in Inmedix. Inc. as CEO, but receives no salary or other compensation; M. Martinez-Lavin has declared no competing interests.

Just over 20 years ago, heart rate variability (HRV) analysis, was introduced to rheumatologists as a tool to assess autonomic nervous system (ANS) stress state (1). For much longer, patients in this field have voiced concern that stress flared their disease activity, contributed to impaired therapeutic responses, and may have even contributed to disease onset. Today, HRV has advanced in software, hardware, and applications to potentially offer a paradigm shift to integrate ANS stress state as a meaningful personalised, precision medicine component to achieve superior rheumatology care.

Heart rate variability analysis

Long before it was standardised by the Task Force of The European Society of Cardiology and The North American Society of Pacing and Electrophysiology (2), HRV was a tool primarily used by cardiologists to measure ANS state as a risk factor for cardiovascular disease outcomes. It is based on the correlation of ANS state with respiratory sinus arrythmia.

With inhalation, chest pressure falls to draw in air. Simultaneously, this reduced chest cavity pressure causes slight expansion of the ascending aorta. Local baroreceptors sense a relative reduction in blood pressure and signal the brain (through the ANS) to increase pulse rate. With exhalation, the reverse occurs.

Consequently, respiratory sinus arrythmia leads to 'variability' on an electrocardiogram (ECG) rhythm strip with accelerating and decelerating heart rate. Of particular importance, this phenomenon attributed to respiratory sinus arrythmia is gradually abolished with increasing sympathetic activity. Hence, HRV has become an indirect measure of ANS state modulated peripherally by the central brain and brainstem.

HRV outputs validated in 1996 include time and frequency domain calculations based on ECG rhythm strips as brief as 5-minutes. The simplest time domain output is the standard deviation (SD) of all beat-to-beat time distances (called N-N) as SDNN. This basic statistical calculation has been extended to include a cornucopia of additional outputs, including standard deviation of the standard deviation (SDSD), the root mean square of the standard deviation (RMSSD), and many more mathematical calculations (3).

Fast Fourier Transform of the data allows HRV frequency domain analysis which is reported as high frequency (HF), low frequency (LF) and very low frequency (VLF) and Total Power (HF+LF+LVF). HF (0.15–0.4 Hz) is overwhelmingly related to respiratory sinus arrhythmia and is considered a parasympathetic surrogate. LF (0.04–0.15 Hz) reflects mixed parasympathetic and sympathetic impact and VLF (0.003–0.04 Hz) remains controversial, although some authors suggest it reflects thermoregulation in response to ambient temperature changes (2).

A poignant limitation of classic HRV is lack of a specific measure for sympathetic state. While HF is accepted as a reflection of parasympathetic activity, LF is a mix and not reflective of pure sympathetic neuromodulation. In order to cope, many consider sympathetic activity as the inverse of HF, but while these two functions compete continuously for predominance and are inversely correlative, they are not perfectly inversely correlative. As an alternative, many authors rely on LF/HF as an indicator of ANS balance. (2).

Clinical application

In 1998, HRV demonstrated discrimination between patients with fibromy-

algia (FM) and age-matched controls (1). Between midnight and 4 am, patients with FM exhibited higher levels of sympathetic activity. Others corroborated this reporting (4), which resulted in a paradigm shift in the FM perspective among many researchers. Regardless of the pathophysiology to be eventually proposed, dysautonomic, hyper-sympathetic state would have to be reconciled in the pathophysiology of FM.

Advanced non-linear HRV analysis brought to light additional information on FM dysautonomia that was not evident using traditional linear HRV mathematical calculations. When compared to matched healthy controls, women suffering from FM have decreased multifractality in heart-beat time-series, unveiling deranged ANS resilience. In addition to decreased non-linearity, FM patients presented stronger anticorrelation in heart-beat directionality. In other words, women suffering from FM lose the healthy heart-beat harmonious swaying, potentially explaining the development of chronic fatigue (4).

It should be acknowledged that most rheumatologic research associating HRV parameters with symptoms have been cross-sectional in nature. Nevertheless, there are several longitudinal investigations in FM looking at non-drug therapy effect on symptoms and on HRV modification. In some of these studies, clinical improvement correlated with HRV changes. Tai Chi training (5), aerobic exercise (6), resistance exercise (7), or hydrotherapy (8) led to improved HRV parameters accompanied by decreased FM symptoms. Other prospective studies on FM have not found such correlation (9). Clearly, more research is needed in this area.

In 2000, Elenkov *et al*. published a compelling review with over 400 references for the connection between two "Super Systems"(10): the immune system and mutually direct and indirect wiring with the ANS. Examples include non-synaptic autonomic-sympathetic innervation of lymphoid organs, expression of adrenoreceptors on lymphoid cells, sympathetic control of lymphocyte traffic, catecholamine modulation of cellular and humoral immunity, and lymphocyte proliferation and maturation.

In 2002, Tracey presented the Cholinergic Anti-inflammatory Reflex (11) as an essential mechanism by which the parasympathetic vagus nerve modulates inflammation. The vagus is comprised of afferent (25%) and efferent (75%) fibres to monitor and attenuate systemic inflammation, respectively. Vagus nerve stimulation was eventually proposed as a potential complementary pathway to reduce inflammation with and without accompanying immunosuppression (12). In rheumatoid arthritis (RA), vagus nerve stimulation was reported to significantly reduce disease activity as well as reduce inflammatory cytokines (13).

Obstructive sleep apnea is also a well-documented sympathetic arousal illness leading to cardiovascular disease mortality. Effective treatment with continuous positive airway pressure (CPAP) reduces this dysautonomic risk of cardiovascular mortality and can be quantified with HRV. Shimizu reported a 54% prevalence of obstructive apnea among 94 predominantly Japanese women (85%) with RA (14). A subset of 7 patients with an apnea-hypopnea index >20 was treated with CPAP, without altering immunosuppressive therapy. Treatment of co-morbid obstructive sleep apnea in patients with RA resulted in a 35% decrease in joint count and C-reactive protein over 5 months. Deep breathing exercises to increase parasympathetic tone have also been proposed to improve management of RA and systemic lupus erythematosus (SLE) (15).

HRV has generally been used to assess the deleterious impact of an autoimmune disease on ANS function. Inversely, classic HRV has also been used to predict clinical course and has correlated with RA disease activity (16). In SLE, Thanou reported that HRV correlated with SLE flare and inflammatory cytokine levels (interferon, tumour necrosis factor-α) (17). In a case-controlled study of ankylosing spondylitis, a sympathetic predominant ANS profile by HRV correlated with the presence of peripheral joint disease, uveitis, and higher inflammatory markers, while BASDAI, BASFI and BAS-G did not (18).

Finally, Koopman evaluated patients at risk for developing RA, including family history, laboratory parameters and arthralgias without arthritis. After 30.7 months, 14 of 45 (31%) developed RA. A novel risk factor identified was ANS profile demonstrated by increased resting heart rate (hazard ratio 1.098: 95% CI 1.012–1.191, p=0.025) and decreased parasympathetic activity by HRV (19).

Next-gen HRV

Specific measures of sympathetic tone were not available in the 1996 time or frequency domain HRV analyses (2). Next-generation HRV incorporates a solution proposed by RM Bayevsky as 'Sympathetic', 'Parasympathetic' and 'Bayevsky's Tension index' outputs (20). Building on the basis of Fast Fourier Transform analysis and frequency domain calculations, these HRV outputs were developed independently in Russia and the former Soviet Union over many decades. Until recently, access to this technology was restricted to its use to enhance professional athletic and US Special Forces training. This new HRV is also supported by superior, precision location of the heartbeat. Hospital-grade ECG sample the ECG 200-330 times per second (Hz). Next-gen HRV samples the ECG at 8000 Hz to reduce error in beat isolation and measuring the time between beats. The QRS complex is 70–100 ms (milliseconds). Current standard 200–330 Hz ECG can add 2 ms of error to classic 1996 standard HRV (21).

While most clinicians and patients accept that ANS stress drives the activity of autoimmune and other diseases, most HRV studies have generated correlative rather than causal evidence. An exception is a prospective, 52-wk, double-blind study of patients with RA and psoriatic arthritis initiating tumour necrosis inhibition (TNFi). Bayevsky's outputs on day 0 correlated better with ACR20/50/70 than did 1996 HRV (22). Those subjects in the highest parasympathetic quartile achieved 52-wk ACR20/50/70 outcomes of 100%/88%/65%, respectively, while

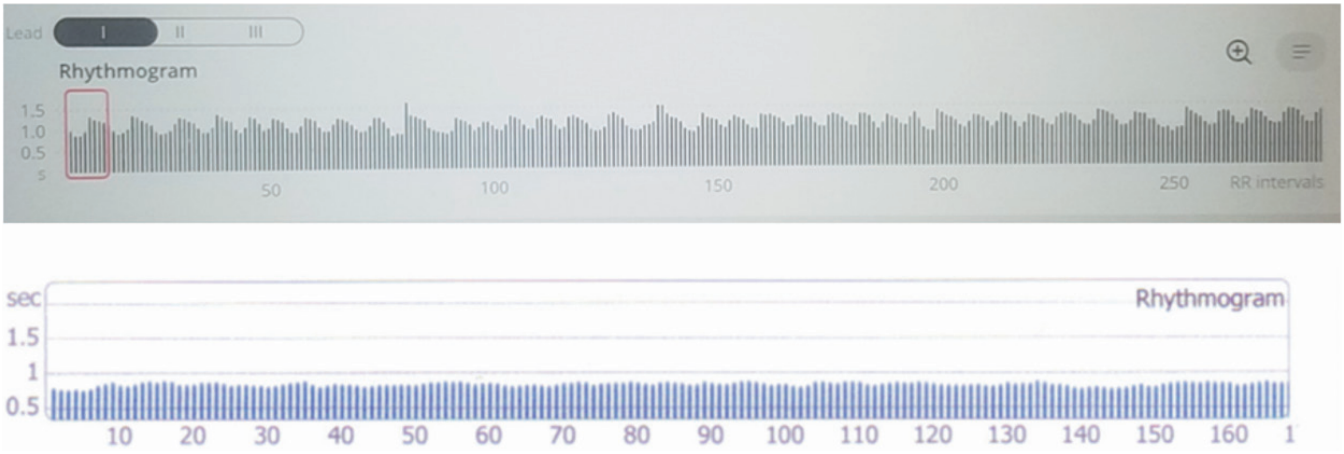

Fig. 1. A rhythmogram plots time between heart beats (y-axis) against time (x-axis).
Top: Prominent HRV reflecting high parasympathetic/low sympathetic state and active respiratory sinus arrythmia.
Bottom: blunted HRV reflecting low parasympathetic/high sympathetic state.
Data obtain with permission from Omegawave Oy, Espoo, Finland.

those in the lowest parasympathetic quartile achieved 52-wk ACR20/50/70 outcomes of 40%/12%/0%, respectively. For ACR70 at 52 weeks, receiver operating characteristic area under the curve (ROC-AUC) for Bayevsky's 'parasympathetic' and 'tension index' were 0.926 and 0.918, respectively. Total power and other 1996 HRV outputs, while statistically significant, lagged. Also, the previously noted application of vagus nerve stimulation to reduce in RA activity was evaluated in a randomised, prospective, double-blind trial (13). Nevertheless, additional longitudinal studies will be needed to determine whether these reports herald a correlative or determinative concept.

A future for immuno-autonomics?

Many efforts are currently underway – with vagus nerve stimulation, next-gen HRV, small molecule parasympathetic agonists, including α7-nicotinic acetylcholine receptor agonists – to mitigate how ANS stress state appears to drive RA, and perhaps other autoimmune diseases, to excess. This link between the immune system and the ANS, recently described as immuno-autonomics (23), may offer a novel opportunity to improve outcomes through complementary mitigation of adverse ANS stress state profile.

The Holy Grail of choosing the best treatment for the individual patients remains important, including stratification of TNFi efficacy (24). However, such efforts may also be potentially enhanced by reducing how adverse ANS state drives immune activity. Additional applications, already widely considered in cardiovascular disease, are also being tested in immuno-oncology, COVID-19 cytokine storm and post-acute sequelae of COVID-19 (PASC).

The future of medicine is, by definition, uncertain, and innovation comes often from unexpected sources. From oncologists, rheumatologists appropriated methotrexate, and now, we have our own immunosuppressants. From cardiologists, rheumatologists may next soon appropriate HRV. Only time and thoughtful, rigorous research will determine what may come of it.

References

1. MARTINEZ-LAVIN M, HERMOSILLO AG, ROSAS M, SOTO M: Circadian studies of autonomic nervous balance in patients with fibromyalgia: a heart variability analysis. *Arthritis Rheum* 1998; 41: 1966-71.
2. [No authors listed] Heart rate variability. Standards of measurement, physiological interpretation, and clinical use. Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. *Eur Heart J* 1996; 17: 354-81.
3. SHAFFER F, GINSBERG JP: An overview of heart rate variability metrics and norms. *Front Public Health* 2017; 5: 258.
4. REYES-MANZANO CF, LERMA C, ECHEVERRÍA JC *et al*.: Multifractal analysis reveals decreased non-linearity and stronger anticorrelations in heart period fluctuations of fibromyalgia patients. *Front Physiol* 2018; 9: 1118.
5. WONG A, FIGUEROA A, SANCHEZ-GONZALEZ MA, SON W-M, CHERNYKH O, PARK S-Y: Effectiveness of Tai Chi on cardiac autonomic function and symptomatology in women with fibromyalgia: a randomized controlled trial. *J Aging Phys Act* 2018; 26: 214-21.
6. SANUDO B, CARRASCO L, DE HOYO M, FIGUEROA A, SAXTON JM: Vagal modulation and symptomatology following a 6-month aerobic exercise program for women with fibromyalgia. *Clin Exp Rheumatol* 2015; 33 (Suppl. 88): S41-45.
7. FIGUEROA A, KINGSLEY JD, MCMILLAN V, PANTON LB: Resistance exercise training improves heart rate variability in women with fibromyalgia. *Clin Physiol Funct Imaging* 2008; 28: 49-54.
8. ZAMUNER AR, ANDRADE CP, FORTI M *et al*.: Effects of a hydrotherapy programme on symbolic and complexity dynamics of heart rate variability and aerobic capacity in fibromyalgia patients. *Clin Exp Rheumatol* 2015; 33 (Suppl. 88): S73-81.
9. VILLAFAINA S, COLLADO-MATEO D, DOMÍNGUEZ-MUÑOZ FJ, GUSI N, FUENTES-GARCIA JP: Effects of exergames on heart rate variability of women with fibromyalgia: A randomized controlled trial. *Sci Rep* 2020; 10: 5168.
10. ELENKOV IJ, WILDER RL, CHROUSOS GP, VIZI ES: The sympathetic nerve – an integrative interface between two supersystems: the brain and the immune system. *Pharmacol Rev* 2000; 52: 595-638.
11. TRACEY KJ: The inflammatory reflex. *Nature* 2002; 420: 853-9.
12. VAN MAANEN MA, VERVOORDELDONK MJ, TAK PP: The cholinergic ant-inflammatory pathway: towards innovative treatment of rheumatoid arthritis. *Nat Rev Rheumatol* 2009; 229-32.
13. KOOPMAN FA, CHAVAN SS, MILJKO S *et al*.: Vagus nerve stimulation inhibits cytokine production and attenuates disease severity in rheumatoid arthritis. *PNAS* 2016; 113: 8284-89.
14. SHIMIZU M, TACHIBANA N, HAGASAKA Y, GOTO M: Obstructive sleep apnea in RA patients and effect of CPAP on RA activity [abstract]. *Arthritis Rheum* 2003; 48 (Suppl): S114.
15. ROVSING C, ROVSING H, LIBORIUSSEN CH

et al.: Deep breathing increases heart rate variability in patients with rheumatoid arthritis and systematic lupus erythematosus. *J Clin Rheumatol* 2020 Mar 18 [Online ahead of print].

16. YADAV RK, GUPTA R, DEEPAK KK: A pilot study on short term heart rate variability & its correlation with disease activity in Indian patients with rheumatoid arthritis. *Indian J Med Res* 2012; 136: 593-8.
17. THANOU A, STAVRAKIS S, DYER JW, MUNROE ME, JAMES JA, MERRILL JT: Impact of heart rate variability, a marker for cardiac health, on lupus disease activity. *Arthritis Res Ther* 2016; 18: 197.
18. WEI CY, KUNG WM, CHOU YS, WANG YC, TAI HC, WEI JC: Cardiac autonomic function in patients with ankylosing spondylitis: a case-control study. *Medicine* (Baltimore). 2016; 95: e3749.
19. KOOPMAN FA, TANG MW, VERMEIJ J *et al*.: Autonomic dysfunction precedes development of rheumatoid arthritis: a prospective cohort study. *EBioMedicine* 2016; 6: 231-7.
20. BAYEVSKY RM, IVANOV GG, CHIREYKIN GG *et al*.: HRV Analysis under the usage of different electrocardiography systems prepared according to the order of the Committee of Clinic Diagnostic Apparatus and the Committee of New Medical Techniques of Ministry of Health of Russia (protocol №4 from the 11th of April, 2002).
21. OMEGAWAVE OY, Espoo Finland (product information)
22. HOLMAN AJ, NG E: Heart rate variability predicts anti-tumor necrosis factor therapy response for inflammatory arthritis. *Auton Neurosci* 2008; 143: 58-67.
23. TAYLOR PC, HOLMAN AJ: Rheumatoid arthritis and the emergence of immuno-autonomics [editorial]. *Rheumatology* (Oxford) 2019; 68: 2079-80.
24. TAO W, CONCEPCION AN, VIANEN M *et al*.: Multiomics and machine learning accurately predict clinical response to adalimumab and etanercept therapy in patients with rheumatoid arthritis. *Arthritis Rheumatol* 2021; 73: 212-22.