As excerpted from:

Autonomic function and arterial elasticity testing: A brief summary of the evidence for the use of heart rate variability, sudomotor function and pulse wave velocity tests in clinical practice.

Chronic Pain

Scientific studies have consistently shown that autonomic nervous system function is disturbed in chronic pain patients (Bruehl and Chung, 2004). Acute pain also impacts the autonomic nervous system in predictable and measureable ways (Koenig, 2014). In chronic pain, the balance between the two branches of the autonomic nervous system is disturbed, such that the sympathetic branch excessively dominates over the parasympathetic, resulting in all the negative long-term effects of low HRV (Tracy, LM, Ioannou L, et al., 2016). The relationship between the autonomic nervous system and both chronic and acute pain has important implications for the complete medical treatment of chronic pain.

As Koenig outlined in his 2013 review paper on the topic, "The systems controlling cardiovascular function are closely coupled to systems modulating the perception of pain (Randich and Maixner, 1984) and extensive interactions between the neural structures involved in pain sensation and autonomic control can be observed (Benarroch, 2001; Benarroch, 2006)." Koenig further stated in his 2016 review that, "The functional interaction of these systems is an important component involved in the endogenous modulation of pain, and there is strong evidence that the functionality of these networks is altered in patients with chronic pain" (Koenig J et al, 2016). Indeed, a recent study using simultaneous HRV and fMRI showed that bodily pain does in fact induce pain- processing brainstem nuclei to function in concert with autonomic nuclei in the production of the observed cardio-vagal pain response (Sclocco R, 2016).

Koenig's 2016 systematic review and meta-analysis, the most extensive review of the current evidence, concluded that chronic pain patients had significantly lower heart rate variability than healthy controls (Koenig J et al, 2016) and a separate experimental study the same year again confirmed this conclusion (Koenig J, Loerbroks A, 2016). Another study of 6,783 individuals published in 2018 likewise found that "beyond effects of age, sex and body mass index, the CP [chronic pain] group displayed significantly lower HRV" than the control group (Bruehl S, Olsen RB, et al., 2018).

Studies on the relationship between individual chronic pain illnesses and heart rate variability have additionally shown reduced HRV in particular diseases. These specifically studied conditions include:

- Chronic Low Back Pain (Storella RJ, 1998)
- Chronic Neck Pain (Kang et al., 2012)
- Chronic musculoskeletal neck-shoulder pain (Hallman DM, 2014) (Hallman DM and Lyskov E, 2012)
- Irritable Bowel Syndrome (Mazurak et al., 2012)
- Headache (Micieli et al., 1993) (Tubani, et al. 2003) (Koenig J et al 2016)
- Temporomandibular disorder (Maixner W, 2011) (Greenspan JD, 2013)
- Sciatica (Sodervall J, Karppinen J, 2013)
- Interstitial cystitis/bladder pain syndrome (Williams DP, et al, 2015)
- Chronic prostatitis (Cho DS, Choi JB, 2011)
- Chronic pelvic pain syndrome – in both men and women (Williams, 2015) (Cho, 2011) (Yilmaz, 2007)
- Complex Regional Pain Syndrome (Terkelson, er al., 2012)
- Fibromyalgia (Mork et al., 2013) (Meesus M, Goubert D, 2013)
- Rheumatoid Arthritis (Adlan AM, et al., 2017) (Provan SA, Olstad DS, et al., 2017)
- Spondyloarthritis (Provan SA, Olstad DS, et al., 2017)

The applications of HRV measurement in pain management are many. HRV is a sensitive quantitative measure of the body's experience of pain. When used as a monitoring tool, i.e. before and after changes in medications

or other treatments, HRV can act as a quantitative indicator of pain level change with treatment (Koenig, Jarczok, 2015). HRV also has tremendous potential to help evaluate pain in patients who cannot communicate well, such as very young children, the unconscious and those are suffering advanced illnesses like cancer, stroke, trauma or degenerative CNS disease and are unable to communicate (Maesel EK, 2016).

Reducing pain improves heart rate variability, indicating improved ANS balance comes with improved pain control (Storella RJ, 1999, Terkelson AJ, et al. 2012). Numerous studies have demonstrated that pain is inversely correlated with HRV such that, in general, the greater the pain, the lower the HRV (Koenig J, Flavay D, et al., 2016). Furthermore, a 2015 study found that analgesic intake reduced pain and improved HRV, concluding that effective analgesic self-medication may lead to more normalized HRV (Koenig J, Jarczok MN, et al., 2015). “These results further support the vagus nerve as an objective indication of pain severity and treatment efficacy in patients with persistent pain” (Koenig J, Jarczok MN, et al., 2015).

Stress and the Central Nervous System

Numerous studies have also found that imbalance in the autonomic nervous system can help explain the well-known link between psychological or physical stress, inflammation and the development of disease, particularly heart disease. Brosschot, Thayer and Yamamoto in their 2010 review asserted the theory of autonomic imbalance as the “final common pathway to increased morbidity and mortality from a host of conditions and diseases, including cardiovascular disease” and that this theory of autonomic imbalance may provide “a unifying framework within which to investigate the impact of risk factors, including psychosocial factors and work stress, on cardiovascular disease” (Thayer, et al., 2010). Dozens of papers including a 2013 review by Jarczok and Jarczok have shown that psychological stress reduces parasympathetic function (Jarczok MN, Jarczok M, et al. 2013). Another review analyzing data from 11,994 patients and published in 2015, again confirmed that lower heart rate variability is directly correlated to a higher cardiovascular risk of all types and also found evidence of the connection between stress, low HRV and high cardiovascular risk (Schuster AK et 47,099 normotensive individuals and found that low heart rate variability predicted greater risk of an individual developing hypertension over the 9 years of study follow-up (Schroeder EB, 2003). al., 2015). The authors noted, “A previous systematic review and a meta-analysis has described an association between workplace stress and reduced HRV in employees [Jarczok MN, 2013] We therefore included work- related stress in our statistical model. Interestingly, the associations between cardiovascular risk estimates and HRV measurements were even stronger post-adjustment” (Schuster AK et al., 2015). A study by Kang MG et al. likewise found that high job strain was significantly correlated to lower HRV score, as well as to higher risk of Metabolic Syndrome X (Kang MG et al, 2004). These and other studies have demonstrated that psychological stress also contributes to low HRV scores and thus to increased cardiovascular risk, risk of metabolic syndrome, and thereby cancer and all-cause mortality.

A number of papers by Thayer and colleagues convincingly make the argument for the “neuro-visceral model” of health regulation which posits the autonomic nervous system as the essential mediator between the brain’s perception of stress and the ultimate development of disease (Thayer and Lane, 2000, Thayer, 2009, Thayer and Sternberg, 2009). In this model, heart rate variability may be understood as an “index of central-peripheral neural feedback and CNS-ANS integration” (Thayer JF, Lane RD, 2009). [See Appendix C for diagram]
The cycle begins with the brain perceiving a stressor, or a “threat,” and then communicating the presence of a “threat” to the autonomic nervous system, which then signals the release of inflammatory cytokines. These cytokines alert the body to the perceived threat, and in the process raise the body’s global level of inflammation. A study from the field of psychoneuroimmunology put forward a parallel theory connecting negative emotions, inflammation and disease, writing “chronic, high level of inflammation that has been shown to contribute to eventual development of stress-related diseases (Rohleder N, 2014).

Many papers shown proposed that this inflammatory cytokine system is primarily regulated by the vagal nerve, the main output of the parasympathetic system. In a review of 13 studies looking at heart rate variability and inflammatory markers or cytokine production, author Haensel also concluded that HRV was indeed

(Haensel A et al, 2008). Using data collected from 1,255 participants, Cooper et al. demonstrated again that measures of HRV were inversely correlated with inflammatory cytokines. Both studies therefore concluded that the lower the HRV score, the higher the level of inflammatory markers (Cooper, et al. 2015). A 2016 study by Woody, et al. tested whether stress induced changes in HRV would predict increases in cytokine inflammatory markers (Woody A., et al. 2017). The study found that lower HRV did indeed predict higher inflammatory markers, a finding that supports the previous literature's model and establishes the predictive value of HRV for increased inflammation. These findings have significant implications for the use of HRV in the management and treatment of inflammation-related diseases.

It is furthermore important to note that the high prevalence of lowered HRV has been well-established in patients with mood and anxiety disorders (Thayer, Friedman, Borkovec 1996). Additionally, medications often used to treat these disorders, in particular tricyclic medications and the serotonin and noradrenaline reuptake inhibitors, have been shown to further reduce HRV (Kemp AH and Quintana DS, 2013) (Kemp AH, Fraguas R, et al., 2016). Mood disorders have also been shown to worsen HRV in existing cardiovascular disease patients (Aydin-Sunbul E, 2017) and a 2016 study found that lowered HRV was associated with worry, stress, tension and decreased positive affect (Verkuil B, 2016). Patients with epilepsy have also been shown significantly lower heart rate variability, a fact which is especially important as some antiepileptics can lead to cardiac arrhythmias (Lotufo PA, et al., 2012). Therefore, patients with known mood disorders, such as depression, bipolar disorder and others, as well as those with anxiety disorders and epilepsy, would benefit from HRV testing and resulting appropriate treatment and monitoring steps taken to mitigate the adverse cardiovascular effects of these conditions and their pharmacological treatments.

Distress-related immune dysregulation may be one core mechanism behind a large and diverse set of health risks associated with negative emotions" (Kiecolt-Glaser JK, 2002). Indeed, "inversely correlated with inflammatory markers in healthy individuals as well as in those with cardiovascular diseases"

Treatment and Follow Up

Improvement in autonomic function produces meaningful reduction in cardiovascular risk and all-cause mortality. Strategies producing significant improvement in HRV score and autonomic function include but are not limited to:

- Physical fitness, as indexed by lower exercise heart rate (Hamer and Steptoe, 2007) (Coote JH, 2015)
- Moderate to vigorous / endurance exercise (Rennie KL, 2003) (Carter JB, 2003)
- Effective self-administered medicinal pain control (Koenig J, Jarczok MN, 2015)
- Relief of chronic pain (Storella RJ, 1999)
- Attaining a normal BMI (Koenig J, Jarczok MN, Warth M, et al., 2013)
- Reducing central adiposity (Windham BG, 2012) (Poliakova N, 2012)
- Omega-3 fatty acid intake (Christensen, 2003) (O'Keefe Jr, 2006) (Sauder, 2013) (Mozaffarian, 2008)
- Stress reduction / improved coping mechanisms (Pal GK, 2014) (Blumenthal, 2005) (Nolan, 2005)
- Beta-blocker therapy (Lampert, 2003) (Malfatto, 2003)(Lin YL, 2001) (Lin JL, 1999) (Izzo JL Jr., 2012)
- Therapy with other rhythm control agents (Yarnabe, 2007)
- Statin therapy (Millar, 2014) (Riahi, 2002) (Vrtovec, 2005) (Gomes, 2010) (Christensen, 1999)
- Treatment with ACE inhibitors (Brinkley PF, et al., 1993) (Bonaduce D, et al., 1994)
- Smoking cessation (Minami, 1999) (Yotsukura, 1998) (Harte, Meston, 2014) (Cagirci G, et al., 2009).
- Zero to moderate alcohol use (Karpyak VM, 2014)
- Healthy sleep timing and duration (Neufeld EV, 2017) (Mezick EJ, 2014) (Spiegelhalder K, 2011)
- Ablative treatment of atrial fibrillation (Seaborn GE, 2014)

As is well known, individual response to treatment varies such that no one treatment is best for everyone. For those with sympathetic domination, initial steps towards balancing the autonomic nervous system may include better pain control, appropriate physical activity and weight loss. Beta-adrenergic blockers are also useful in improving heart rate variability and "are the only class of anti-arrhythmic drugs that definitively decreases the incidence of sudden cardiac death, cardiovascular death and all-cause death in patients who have ischemic

heart disease or hypertension." (Kennedy HL, 1997). Treatments to improve HRV with the goal of reduce inflammatory cytokines show promise and warrant further investigation. Pharmaceutical and even direct vagal nerve activation is also a promising new therapeutic approach in the treatment of cardiovascular diseases (Zhao M, 2012) (He X, 2015).

Conclusion

Knowing the profound and far-reaching effects of sympathetic-leaning autonomic nervous system imbalance, it is essential to test for this imbalance and provide treatments to correct it. Measurement of heart rate variability can also help indicate severity cardiovascular risk and whether additional diagnostic testing or specialist evaluation is needed.

Based on the extensive evidence, HRV testing is therefore clinically warranted in patients with personal or family history of heart disease, personal or family history of hypertension, personal or family history of diabetes, metabolic syndrome, known risk factors for developing heart disease (obesity, smoking, dyslipidemia, hypertension, sedentary lifestyle, chronic pain, mood disorders, high levels of physical and / or psychological stress), those with existing heart disease such as CVD and CHF, and a history of MI or stroke.

Follow up HRV testing to evaluate the efficacy of these treatments is essential. If medical treatments and lifestyle changes are not satisfactorily improving the patient's autonomic nervous system balance, and thereby reducing their risk for adverse cardiovascular outcomes like MI, stroke and sudden cardiac death, then the treatment should be adjusted, augmented or changed and the tests repeated as necessary.

Full bibliography and list of references available upon request.