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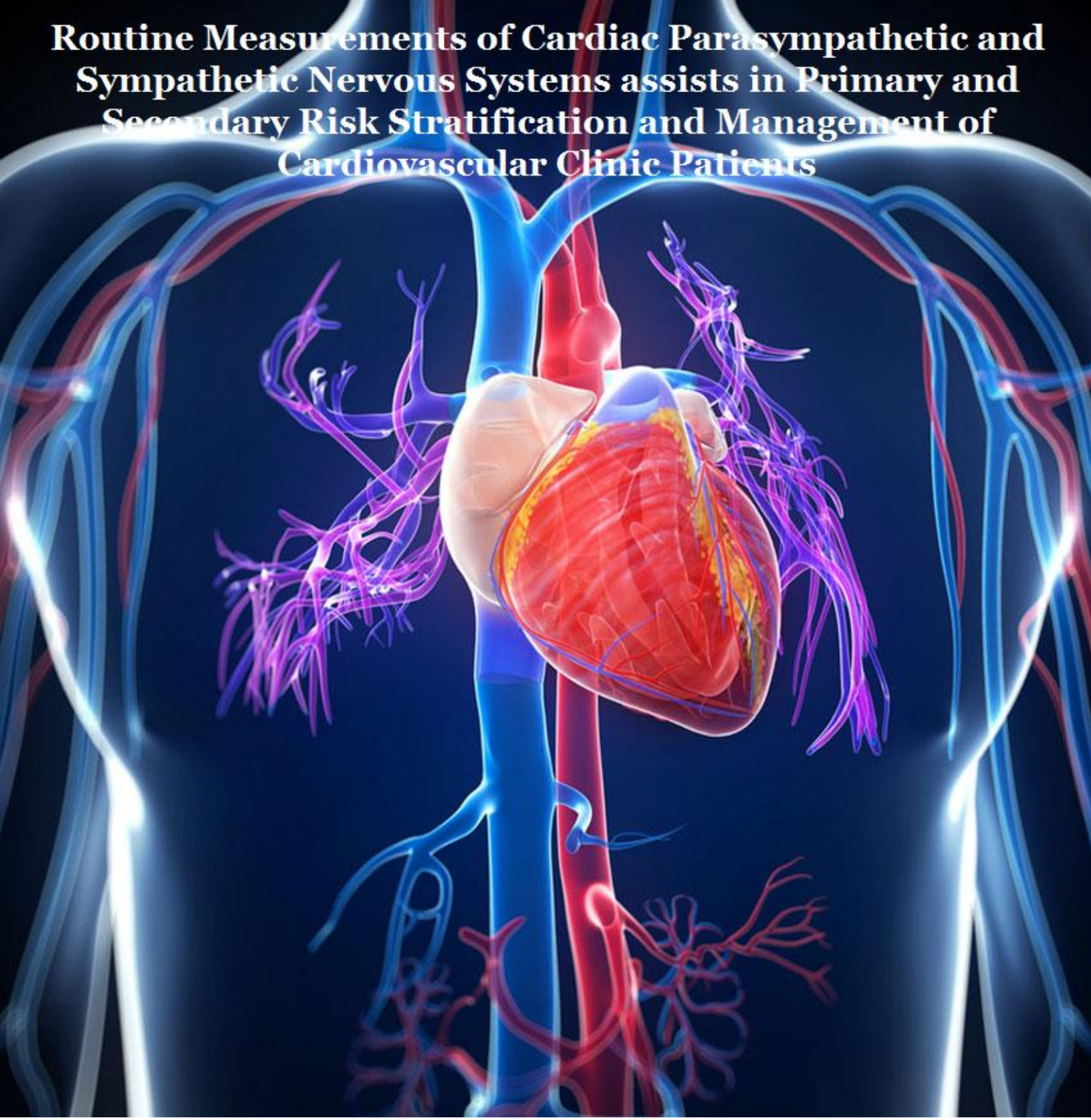

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Research Article

Routine Measurements of Cardiac Parasympathetic and Sympathetic Nervous Systems assists in Primary and Secondary Risk Stratification and Management of Cardiovascular Clinic Patients

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Abstract

Objective: To review our studies of the ease and importance of parasympathetic and sympathetic (P&S) measures in managing cardiovascular patients.

Background: The autonomic nervous system is responsible for the development or progression of hypertension (HTN), orthostasis, coronary disease (CAD), heart failure (CHF), and arrhythmias. Finally, new technology provides us with rapid, accurate P and S measures critically needed to manage these patients much more successfully.

Methods: Using the ANX 3.0 autonomic monitor, P&S activity was recorded in 4 studies: 163 heart failure patients in total, mean follow-up (f/u) 12-24.5 months; 109 orthostasis patients, f/u 2.28 years (yr), and 483 patients with risk factors or known HTN, CAD, or CHF, f/u 4.92 yrs. All were on guideline-driven therapy.

Results: Fifty-nine percent (59%) of CHF patients had dangerously high sympathovagal balance(SB) or cardiac autonomic neuropathy (CAN), and Ranolazine markedly improved 90% of these, improved left ventricular ejection fraction in 70% of patients on average 11.3 units, and reduced MACE (acute coronary syndromes, death, acute CHF, ventricular tachycardia/fibrillation[VT/VF]) 40%. Sixty-six-percent (66%) of orthostatic patients corrected with (r) alpha lipoic acid ([r]ALA); non-responders had the lowest S-tone. In the 483 patient study, SB>2.5 best predicted MACE when compared to nuclear stress and echocardiography (sensitivity 0.59, OR 7.03 [CI 4.59-10.78], specificity 0.83, positive predictive value 0.64, and negative predictive value 0.80).

Conclusion: Parasympathetic and sympathetic measures significantly improve care of cardiovascular patients.

Keywords: cardiac parasympathetic; cardiac sympathetic; coronary diseases; heart failure

Abbreviations: P&S-Parasympathetic and Sympathetic, HTN-Hypertension, CAD-Coronary Disease, CHF-Congestive Heart Failure, SB-Sympathovagal Balance, CAN-Cardiac Autonomic Neuropathy, MACE-Major Adverse Cardiac Event, ACS-Acute Coronary Syndromes, VT-Ventricular Tachycardia, VF-Ventricular Fibrillation, (r)ALA-(r) Alpha Lipoic Acid, CI-Confidence Interval, SE-Sympathetic Excess, ACE-Is-Angiotensin Conversion Enzyme Inhibitor, AR-Adrenergic Receptor, ARB-Angiotensin Receptor Blocker, ECHO-Echocardiogram, PE-Parasympathetic Excess, SW-Sympathetic Withdrawal, BP-Blood Pressure, CRPS-Chronic Refractory Pain Syndrome, HRV-Heart Rate Variability, RA-Respiratory Activity, RFa-Respiratory Frequency area, LFa-Low Frequency area, FRFFundamental Respiratory Frequency, RSA-Respiratory Sinus Arrhythmia, E/I-Exhalation/Inhalation, ROC-Receiver Operating Characteristic, LVEF-Left Ventricular Ejection Fraction, MPI-Myocardial Perfusion Imaging, AR-Adrenergic Receptors, CRT-Cardiac Resynchronization Therapy, ACC/AHA-American College Cardiology/American Heart Association, HFrEF-Heart Failure Reduced Ejection Fraction, HFpEF-Heart Failure Preserved Ejection Fraction, RANCHF-Ranolazine-Treated Heart Failure, NORANCHF-No Ranolazine-Treated Heart Failure, NYHA-New York Heart Association, OMTOptimal Medical Therapy, BNP-Brain Natriuretic Peptide, NOH-Neurogenic Orthostatic Hypotension, sBP-Standing BP, NOI-Neurogenic Orthostatic Intolerance, JNC-Joint National Committee, LDLLow Density Lipoprotein, CWT-Continuous Wavelet Transforms, FFT-Fast Fourier Transforms, MUCH-Masked Uncontrolled Hypertension, MOST-Management of Outpatients using Sympathovagal Balance Trial, CCTA-Coronary Cat Scan Angiogram, ETT-Exercise Tolerance Test, DE-Dobutamine Stress Echocardiography, 2DE-2-Dimentional Echocardiogram, WNL-Within Normal Limits.

Introduction

High Sympathetic (S) tone and cardiac autonomic neuropathy (CAN; defined as critically low resting Parasympathetic [P] tone, P < 0.10 beats per min.2 [bpm2]) have been associated with acute coronary syndromes (ACS), congestive heart failure (CHF), malignant ventricular arrhythmias, and increased mortality [1,2,3,4,5,6,7,8]. Good P-tone is cardio-protective [9]. Despite knowing this, we don't use Parasympathetic and Sympathetic (P&S) measures routinely, if at all, to help risk stratify and medically manage our patients. Historically, the reason for this may be due to the difficulty generalizing non-invasive autonomic measures to typical clinical populations. Heretofore, non-invasive measures of autonomic activity, including those based on beat-to-beat cardiac activity, are all measures of only total autonomic activity, forcing assumption and approximation to theorize P&S activity. However, we've found the user-friendly accurate, relatively inexpensive, easily mastered ANX 3.0 P&S monitor (formerly ANSAR Medical Technologies, Inc., now TMCAMS, Inc., Atlanta, GA, USA) assessment quite valuable. The P&S Monitor is based on technology developed, validated and verified by the first joint Bio-Medical Engineering program group from MIT and Harvard [10,11,12,13,14]. This article briefly reviews some of the studies we've completed as well as mentioning ongoing and future trials.

High S-tone and low P-tone at rest is relative and assessed by Sympathovagal Balance (SB: SB = [resting S]/ [resting P; normal is 0.4 < SB < 3.0]) [15]. High SB, indicating (resting) S-excess (SE) is associated with chronic inflammation, chronic high BP, hyperlipidemia, heart diseases, diabetes and other disorders that lead to heart disease, anxiety and other stress related disorders. High SB, or resting SE, is a net, cumulative result of: 1) persistently high levels of catecholamines, including norepinephrine and epinephrine, 2) persistent over-activation of the angiotensin-renin-aldosterone system, and more. Symptoms and P&S responses to stimuli, help to differentiate catecholaminergic from angiotensin effects, for example. High SB may be medication induced such as with excessive utilization of inhaled beta-2 agonists for pulmonary disorders [16,17,18]. Beta-adrenergic and alpha-adrenergic blockers, angiotensin-blockers (ACE-Is and ARBs) are known to reduce resting S-tone. Implanted cardiac devices and cardiac rhythm therapy also effect the sympathetics by forcing them to entrain to the therapy. Low SB, indicating (resting) P-excess (PE) is associated with depression, syncope, excess-gut motility, and is relieved with very low-dose anti-cholinergics. P-tone is a measure of the net, cumulative result of both nicotinic and muscarinic receptors. When treating the symptoms of these disorders, titrating to normalize SB is a goal.

There are also proper dynamic or challenge P&S balances. Challenge imbalances may lead to resting imbalances and complicating or confounding resting imbalances. For example, upon assuming a head-up posture (e.g., standing) the proper dynamic balance is a slight decrease in P-tone quickly followed by a modest increase S-tone. This defeats the effect of gravity causing a shift in blood to the lower extremities and vasoconstricts the lower vasculature to support standing. A decrease in S-tone at this time (sympathetic withdrawal or SW) is associated with orthostatic dysfunction and may cause secondary, high, resting BP as a compensatory response to the decrease in BP associated with orthostatic dysfunction. Typically, the high resting BP is considered the primary and treated as such, yet the patients become more lightheaded and then become non-compliant. This is because the medication induced lower resting pressure, which results in poor diastolic coronary and brain perfusion caused by the decline in standing BP, and the patient's body defeats the therapy to maintain proper perfusion. Low prolonged coronary diastolic pressure (and associated perfusion) due to SW with prolonged, high systolic pressure, as measured by high resting BP, may lead to heart failure. P&S monitoring helps to document these complications and guide therapy.

Another possible imbalance from the stand example is a challenge P-excess (PE) [15]. PE may also lead to secondary SE and confound the treatment of high BP, for example. Challenge PE [19] is associated with difficult to control BP, blood glucose, various hormone levels, increased weight, difficult to describe pain syndromes (including CRPS), unexplained arrhythmia (palpitations) , seizures, temperature dysregulation (both response to heat or cold and sweat responses), and symptoms of depression or anxiety, fatigue, exercise intolerance, sex dysfunction, sleep or GI disturbance, lightheadedness, cognitive dysfunction or "brain fog", or frequent headache or migraine. Challenge PE may also be treated with very low-dose anti-cholinergics, or if heart disease, high BP, or some other form of SE, PE may be treated with the double cocktail: carvedilol whose central alpha effect lowers PE. A better understanding of P&S pathophysiology provides more information to reduce morbidity and mortality risk and improve patient outcomes [15].

Methods

The ANX 3.0 P&S function monitor (hereafter designated "P&S Monitor") computes simultaneous, independent measures of P&S activity based on continuous time-frequency analyses of heart rate variability (HRV) with concurrent time-frequency analyses of respiratory activity (RA). The following variables were recorded (although not all are detailed in the results section): 5 min. seated resting BP and P&S activity (measured as Respiratory Frequency area [RFa] and Low-Frequency area [LFa], respectively) [10,11,12,13,14]; Exhalation/Inhalation (E/I) ratio and RFa were computed in response to 1 min. of deep breathing (paced at 6 breaths/min) [14]; Valsalva ratio and LFa & RFa were computed in response to a short series of Valsalva maneuvers (10 to 15 sec. each); and HR, BP, LFa, RFa and 30:15 ratio were computed in response to 5 min. of head-up postural change (quick stand followed by quiet 5 min. standing).

Sympathovagal Balance (SB) is computed as LFa/RFa (reported means are averages of ratios, not ratio of averages). P-activity (RFa) was defined as the spectral power within a 0.12 Hz-wide window centered on the fundamental respiratory frequency (FRF) in the HRV spectrum [10,11,12,13,14]. FRF was identified as the modal peak from the time-frequency analysis of RA. Effectively, FRF is a measure of Vagal outflow as it affects the heart, as in Respiratory Sinus Arrhythmia (RSA). S-activity (LFa) was defined as the remaining spectral power, after computation of RFa in the low-frequency window (0.04 – 0.15 Hz of the HRV spectrum) [10,11,12,13,14]. The 30:15 ratio is the ratio of the 30th R-R interval after a quick head-up postural change(standing) to the 15th R-R interval after standing. The 30:15 ratio reflects the reflex bradycardia after standing that is dependent on sympathetic vasoconstriction. The Valsalva ratio is the ratio of the longest R-R interval to the shortest R-R interval during a 15 sec. Valsalva maneuver. The E/I ratio is the ratio of the heart beat interval during peak exhalation over that during peak inhalation during paced breathing. The E/I ratio is a thresholded measure of more or less Vagal (P) tone, as are the 30:15 and Valsalva ratios.

In the first study, statistics, including means, standard deviations, and student t – tests, were performed under SPSS v 14.1. Student t-tests were performed as 2-tailed with equal variance. Significance values were determined on the null hypothesis that the pre- and post-treatment P&S values were equal.

In the second study, continuous data were assessed for normality with normally distributed data and analyzed using Student t-tests. Non-normally distributed data were assessed using a Mann-Whitney test. Dichotomous data were analyzed using the Chi-square test or Fisher's-Exact Test. We determined that 50 patients per group were needed to have a sufficient sample size using an alpha of 0.05, difference of means of 6 units and expected standard of deviation of 15 units with a power of 80%. All statistics were performed under SPSS v 1.4. Student t-tests were performed as two-tailed with equal variance. Significance values were determined on the null hypothesis that pre- and post- treatment values were equal.

In our third study, Receiver Operating Characteristic (ROC) analysis was determined. SB > 2.5 and LVEF < 0.34 best predicted major cardiac

events (MACE: acute coronary syndromes, acute CHF, malignant ventricular arrhythmias, cardiovascular death). The p-value of a SB > 2.5 vs. LVEF < 0.34 or reversible defect(s) on myocardial perfusion imaging (MPI) was computed by uncorrected chi-square test.

In our fourth study, continuous data were assessed for normality with normally distributed data using Student t-tests and non-normally distributed data using a Mann-Whitney U test. Dichotomous data were analyzed using the chi-square test or Fisher's exact test. A p-value of 0.05 or less was considered significant. Student t-tests as two-tailed with equal variance. Significance values were determined on the null-hypothesis that the pre- and post-treatment values are equal.
All patients signed informed consents.

Results

Congestive Heart Failure

In CHF, S is increased due to enhanced stimulatory input, increased adrenal catecholamine output, as well as reduction of restraining influences, including reduced vagal input, although beta-1 adrenergic receptors (AR) are down regulated due to chronic stimulation. Beta- 2 AR, muscarinic and nicotinic receptor function remain intact [20,21]. Patients responding to cardiac resynchronization therapy (CRT) demonstrate improved P&S function, whereas non-responders do not [22,23].

In our first study [24], 54 ACC/AHA guideline-treated chronic CHF patients (54% HFrEF, 46% HFpEF) were randomized to adding Ranolazine (RANCHF) vs. continued usual care (NORANCHF). Demographics between these groups matched well; the mean beta blocker dose was higher in the NORANCHF cohort. Fifty-nine percent (59%) of the patients in each group initially had high SB, CAN, or both. At 1 yr., 94% of RANCHF patients improved P&S measures; 88% normalized high SB and corrected CAN. Only 50% of NORANCHF patients improved (p= 0.056). Individually, only 18% of NORANCHF patients normalized high SB vs. 83% of RANCHF (p= 0.013). Four (4) NORANCHF patients (15%) demonstrated SB responses that became abnormally high. At 1 yr., resting P-activity was 0.50 bpm2 in RANCHF patients vs. 0.38 bpm2 in NORANCHF (p= 0.004). Improvement of P&S measures in RANCHF patients were independent of brain natriuretic peptide (BNP) and impedance cardiogram results, suggesting a direct effect of RAN on P&S function. This was confirmed by similar improvements in P&S measures in a 30 patient control group without known cardiac disease that had initial "CHF-like" profiles.

In our second study [25], 109 ACC/AHA guideline-treated NYHA class 2-4 chronic CHF patients (84 HFrEF, 25 HFpEF; 54 RANCHF, mean follow-up 24.5 mo.; 55 NORANCHF, mean follow-up 22.8 mo., were matched for age, gender, and history. Ninety-eight percent (98%) of patients took a beta blocker (slightly higher dose in NORANCHF); HFpEF RANCHF patients har more patients with HTN and chronic renal insufficiency. Seventy percent (70%) of RANCHF patients increased LVEF an average 11.3 units (p=0.018 for HFrEF RANCHF, initial mean LVEF 0.30); LVEF in NORANCHF patients decreased 1 unit from initially 0.30. RAN MACE (cardiac death, acute CHF, VT/VF) occurred in 31.5% vs. 38.2% MACE in NORANCHF (an 18% reduction). Again, RAN improved P&S measures. SB decreased in RANCHF (p=0.019) while increasing in NORANCHF patients (p=0.039). In the total population, final SB was 3.5 in MACE patients vs. 2.28 in patients without. This led us to do our third study.

In our third study (unpublished data) we followed 483 patients for a mean of 4.92 yr. (127 with CAD risk factors, 224 with CAD, 132 with chronic CHF). We compared SB > 2.5 to reversible myocardial imaging defect(s) or LVEF < 0.34 as a predictor of MACE (ACS, acute CHF, VT/VF, cardiac death). SB independently outperformed them (p=0.001) with a sensitivity of 0.59, OR = 7.03 (CI: 4.59-10.78), specificity of 0.83, PPV = 0.64, and NPV = 0.80. Thirty-one percent (31%) of patients had a SB > 2.5. There were 3 patterns of high SB (P&S measures taken every 6 mo.): acute, chronic, and intermittent. An acutely high SB (20%) is the most ominous.

In our fourth study [26], in a cohort of 109 patients with low standing S-response (known as Sympathetic Withdrawal [SW] as opposed to the normal increase in S-activity with stand), 29 were found with neurogenic orthostatic hypotension (NOH, fall in standing BP (sBP) of at least 20/10 mmHg), and 60 with neurogenic orthostatic intolerance (NOI, fall in sBP of -6 to -19 mmHg). Both groups were given (r) alpha lipoic acid ([r] ALA), at a mean dose range of 993-1500 mg/d. A third, control, group included 20 patients with either NOH or NOI. All patients were followed for a mean of 2.28 yr. Sixty-six percent (66%) of NOH patients responded (standing change in BP ranged from -28/-10 mmHg to 0/+2 mmHg [p=0.0129 for systolic, p=0.0456 for diastolic pressure changes]). Sixty-seven percent (67%) of NOI patents responded as well (standing change in BP ranged from -9/+1 mmHg to +6/+2 mmHg; [p≤0.001 for systolic, ns for diastolic, pressure changes]). The control group had no changes in BP. If maintaining a diastolic BP at least 60 mmHg to preserve coronary perfusion were taken into account, 88% of patients would be responders. Although all patients treated with (r) ALA increased their S-response to stand, responsiveness depended upon the resting S-tone: those with the lowest resting S-tone (indicating advanced autonomic dysfunction) responded the least.

Sympathovagal Balance

High S-activity contributes to MACE through hemodynamic stress, coronary vasoconstriction, cardiac electrical instability, endothelial dysfunction, and LDL cholesterol oxidation. Alternatively, MACE acutely increases S-activity and responsiveness. Therefore identifying high SB should help predict the risk of developing MACE as well as diagnosing its presence. Logically, normalizing SB will help to prevent MACE and reduce its mortality and morbidity.
SB > 2.5 increases the odds of suffering MACE seven-fold. Dutifully prescribing ACC/AHA and JNC 8 guidelines for prescribing beta blockers for chronic HFrEF, CAD, and hypertension is insufficient to insure optimal SB, which likely plays a significant role in the continued disturbing rates of MACE in our patients. In fact, death rate per 100,000 treated hypertensives is increasing. Now we may and should measure SB, and adjust pharmacologic therapy accordingly. Ranolazine reduces SB and MACE in chronic CHF, likely by its effect on cardiac sodium channel 1.5 and P&S sodium channel 1.7 [24,25]. We were the first to report Ranolazine reduces ACS in CAD [27].

Sympathetic Withdrawal and Orthostatic Dysfunction

Orthostatic hypotension occurs in 10-30% of the elderly, associated with significantly increased mortality and morbidity. Resting P&S activity falls with aging. Chronic disease accelerates the aging effect. The P-nervous system (comprised primarily of the Vagus Nerve outside the brain) is more exposed, and therefore, more susceptible to insult, including increased oxidative stress that occurs with age. As a result, the P&S nervous systems become uncoupled, with P-activity declining faster than S-activity. This imbalance leads to autonomic dysfunction and ultimately autonomic neuropathy. A first sign of autonomic dysfunction is orthostatic dysfunction, including SW which typically precedes any decline in BP upon standing.

SW (as in NOH) is a leading cause of orthostatic dysfunction. We typically, pharmacologically, treat symptomatically with Midodrine, Fluodrocortisone , Desmopressin, or occasionally with expensive Droxydopa (Northera) or other drugs. (R)ALA, an over-the-counter powerful antioxidant supplement (ALA is produced in the body and production declines with age), treated the cause of NOH and NOI successfully in 66% of patients by increasing S-responses with stand

(relieving SW). Hopefully, treating the cause will slow this disease's progression and reduce mortality and morbidity, as well as treatment complications such as supine/sitting high BP and fluid overload. P&S activity should be measured in all orthostatic patients without venous stasis or medication-related orthostatic dysfunction.

A concern of orthostatic dysfunction is the possibility of low coronary perfusion. If coronary diastolic BP is below 60 mmHg then the heart is hypo-perfused, as is the brain. As a result, an "adrenaline storm" is released and systolic pressure is increased. This increases cardiac demand and cardiac stress. A resulting increase in systolic pressure over 130 mmHg (resting) may produce pulse pressures (> 70 mmHg) that are associated with poor prognoses. Prolonged, this condition may precipitate, and certainly may exacerbate, heart failure. In this way SW may be associated with heart failure. Without a means of recognizing SW, therapy would typically be directed to reducing systolic pressure and thereby pulse pressure. However, this may exacerbate the orthostatic dysfunction and exacerbate coronary hypo-perfusion, as well as lead to non-compliance, or unstable or difficult to manage BP as the body attempts to maintain coronary and brain perfusion. Similarly, if the orthostatic drop in BP is treated as the primary, as with vasopressors, it may further increase systolic pressure, increasing pulse pressure, thereby exacerbating heart failure as well.

Cardiovascular Autonomic Neuropathy

CAN is defined as very weak, resting P-activity; regardless of resting S-activity. CAN is a normal part of the aging process. It simply means that the typical elderly person has a higher morbidity and especially mortality risk than the typical younger person. However, this is not to dismiss CAN. As soon as CAN is demonstrated, a full cardiac work-up is recommended, if for no other reason than to establish a baseline. The other reason not to dismiss CAN is that it should always be risk stratified. CAN is risk stratified by SB. Given that "a little more (resting) P-activity is cardio-protective" [28], low-normal SB ($0.4 < SB < 1.0$) is the recommended normal for CAN patients [15]. CAN with high SB (>2.5) is considered high risk and is associated with MACE, including stroke. CAN with high SB suggests that P-tone is insufficient to prevent an S-mediated ventricular tachy-rhythm from progressing to fibrillation. CAN with low SB (<0.4) is also associated with increased mortality risk. Low SB is associated with depression and may indicate a suppressed immune response or, in some cases, "Broken-Heart Syndrome."

In advanced disease cases, the traditional clinical assumption is that (resting) P-activity is significantly weaker than resting S-activity. This is unfortunate for several reasons. First, it has led to the belief that Autonomic Neuropathy, specifically CAN is untreatable. Second, together with the belief that P-activity cannot be measured, the standard clinical assumption has led to the belief that there is no upper limit to "healthy" Parasympathetic activation. Yet depression is known to be associated with too much P-activity. Third, together with the second reason, this assumption has led to the belief that, short of exercise intolerance, low HR or low BP, more Sympathetic (aka., Adrenergic) blockade is better; this applies to beta-blockers, anti-hypertensives, etc., despite no specific evidence to support this theory.

With P&S Monitoring, CAN is treatable. First, regardless of age or disease, CAN should be risk-stratified by relative amounts of resting P&S activity (SB, as above). CAN evaluation should be a high priority in therapy planning:

- If CAN with high SB is demonstrated, consider sympatholytics based on history, titrated against normalizing SB and thereby normalize mortality risk. Choice of sympatholytic treatment is based on patient history. For example, if BP is high then consider anti-hypertensives, or if BP is normal to low or HR is high, then consider beta-blockers. As with diabetics, Carvedilol is often the preferred beta-blocker for CAN with high SB.
- If CAN with low SB is demonstrated, consider low-dose anti-cholinergics (very low-dose anti-depressants – low-dose to minimize morbidity risks), depending on other medical history, titrate to normalize SB and thereby normalize mortality risk. Choice of anti-cholinergic is based on patient history. For example if BP is high then consider very low-dose SSRI, or if BP is normal to low then consider very low-dose SSRI or tri-cyclic.
- If CAN is present with normal resting SB with a recent cardiac work-up, then mortality risk is normal, and the resting autonomic state of the patient is well managed. Any (resting) abnormality may be due to end-organ dysfunction. If there has not been a recent cardiac work-up, then one is recommended.

For chronic patients, CAN has been found to carry the same 50% increase in the five-year mortality rate as in diabetics [29,30]. More recently, some data suggests that CAN represents a 50% increase in the two-year mortality rate. In addition to geriatric patients, CAN may be normal for post-MI, post-CABG, and CHF patients, as well as other chronic diseases. CAN is associated with other risk factors [31,32], including 1) low ejection fraction [33,34]; 2) poor cardiac output [35]; 3) arrhythmias [36], 37]; 4) cardiomyopathies [38,39], including chronic heart failure [40]; 5) poor circulation [41], coronary artery disease with or without angina [42]; 6) greater mortality [1]; and 7) greater morbidity [43], including silent myocardial infarction and early cardiac death [43,44]. Often, very low P-activity (CAN) leads to the need for an implanted cardiac device.

Discussion

P&S Monitoring was chosen for two reasons. First, P&S Monitoring includes spectral analyses based on the time-frequency analysis technique of continuous wavelet transforms (CWT), rather than the frequency-only analysis technique of the fast Fourier transforms (FFT). Although including short-term FFT is accurate for stationary signals, it results in a compromise in time and frequency resolution because fixed length windows are analyzed. Therefore, the FFT (including the short-term FFT) involves are two weak assumptions: the P&S signals are not stationary (even at rest or during quiet standing) and the time-frequency compromise is not static in addition to the fact that it is a compromise. The P&S-tone values from P&S Monitoring are computed from nonstationary, continuous, independent RA and HRV signals. CWT permits automatic adjustment of the window length to the features of the signal. As a result, time-frequency resolution is superior [11,12,13,14] to all prior HRV studies.

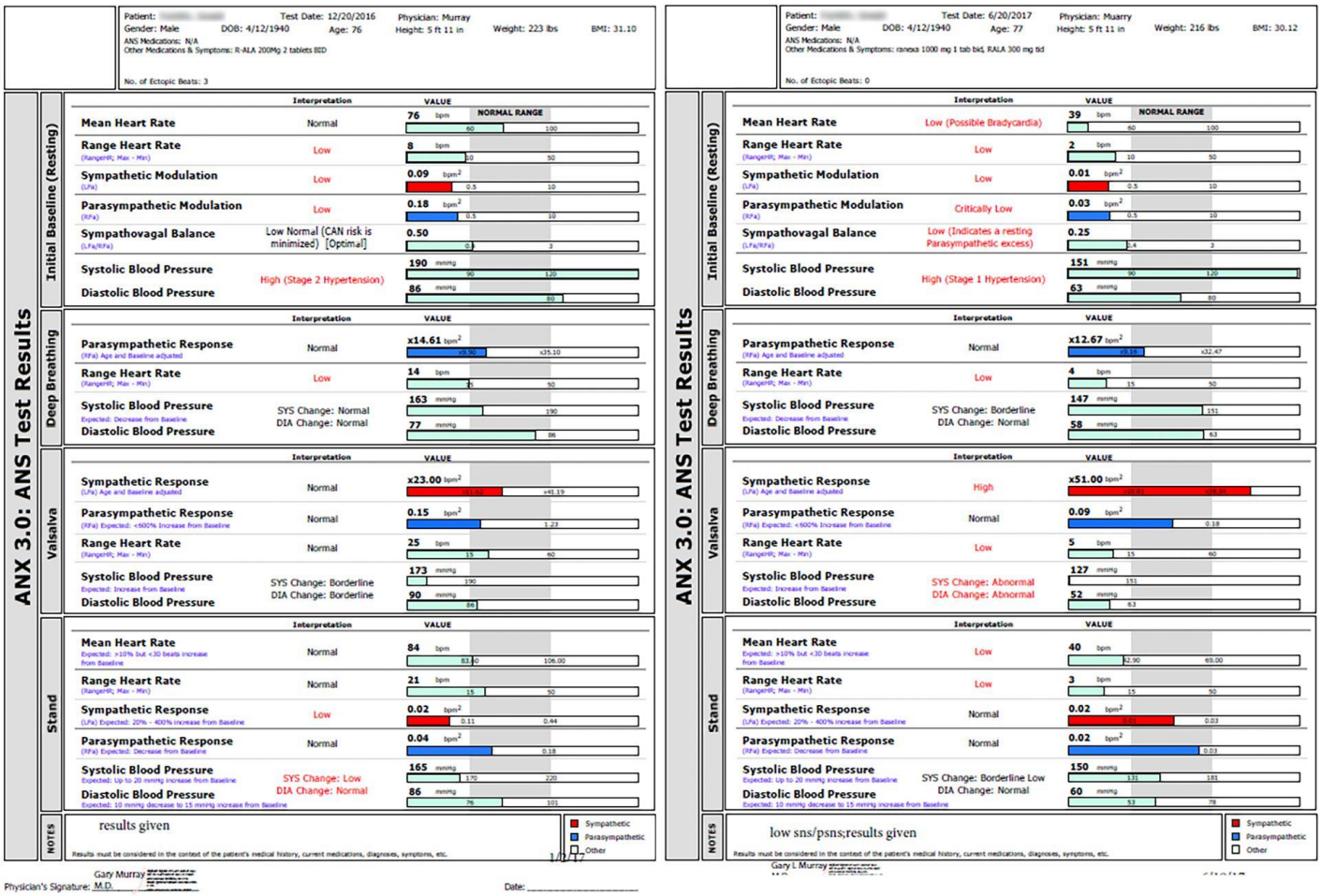
Second, P&S Monitoring is the only non-invasive technique that (mathematically) independently and simultaneously quantifies P-activity without assumption and approximation. Other autonomic measures based on beat-to-beat cardiac activity (e.g., HRV, beat-to-beat BP and Pulse Wave Velocity measures) assume that P-activity is always located within the 0.15-0.40 Hz frequency range (a wide window to improve the capture of P-activity). Instead, P&S Monitoring measures a second, independent measure of P&S activity: RA using impedance plethysmography. The first measure is of the heart (HRV), the second measure is of the lungs (RA). While it is true that RSA is generated from RA (via pulmonary baroreceptors and the Vagus Nerve), measuring RA is not a direct measure of P-activity. RA is a second independent measure of the autonomic nervous system and therefore fully satisfies the algebraic requirement necessary to fully characterize a system with two independent components.

With these two independent measures as verified and validated by the MIT/Harvard team [11,12,13,14], P&S Monitoring localizes and quantifies P-activity, and thereby S-activity, over the period of observation without the need for assumption and approximation. Conceptually, the P&S Monitoring process, in effect, measures RSA even when it is not possible to visualize it from the cardiogram. Given that RSA is purely parasympathetic in etiology [11,12,13,14], conceptualizing the measurement of RA as a measure of RSA helps to understand the process that provides a direct measure of P-activity. The process is based on the measure of the FRF [11]. For example, if the patient's respiratory

rate (FRF) is slow, P could be contained within the low frequency range (0.04-0.15 Hz), e.g., S-range of HRV [10]. The low frequency range represents S-activity as modulated by P-activity [11]. Slow respiration leads to higher low frequency HRV activity misinterpreted as increased S-response unless FRF is determined. For the first time, simultaneous time-frequency analysis of HRV and RA accurately identifies P, unscrambling S & P activity. This technological breakthrough allowed us to correctly measure SB and CAN.

Conclusions

P&S abnormalities, including high SB, CAN, and low S-responses to standing (head-up postural change) are common. They cause and contribute to the mortality, morbidity, and cost of medical care, including for CAD, chronic CHF, and NOH. Despite our ability to easily diagnose and address these P&S abnormalities, we seldom, if ever, do. Our patients deserve better.



Hypertensive patient on losartan 100mg, amiodipine 10mg daily, given additional cionidine, r-alpha lipoic acid based upon the autonomic profile

Figure 1: Hypertensive patient on losartan 100mg, amiodipine 10mg daily, given additional cionidine, r-alpha lipoic acid based upon the autonomic profile

Future Trials

Hypertension

We have begun to investigate P&S abnormalities contributing to hypertension, considering the question "When is high blood pressure a symptom and better treated as secondary?" By 2021, worldwide, 1.5 billion or 1/3 of the world's population will be hypertensive. Currently, only 35% of patients are clinic-controlled, 30% have masked-uncontrolled high BP (MUCH), and after 1.5 yrs. of treatment, 25% return to uncontrolled status. Often, we find high BP to be compensatory to decreases in BP upon head-up posture, such as with SW in NOH or NOI. Apparently this is to help maintain coronary and brain perfusion. This form of hypertension is often relieved organically once SW and thereby orthostatic dysfunction is relieved [45]. Another P&S finding associated with high BP that does not seem to respond to standard therapy is associated with high S-activity secondary to high P-activity. Typical therapy seems to exacerbate the high P-activity, thereby forcing higher S-activity (since P-activity establishes the threshold around which S-responds). As a result, BP becomes more labile or the patient seems unresponsive. It may be that treating the abnormal P-excess and normalizing P-activity, may organically normalize the S-response and thereby normalize BP. We plan to compare P&S-assisted therapy (Figure 1) to JNC 8.

Coronary Disease

We plan a multicenter, randomized, prospective study: Management of

Outpatients using Sympathovagal Balance Trial (MOST) to compare P&S-guided therapy to usual care (Figures 2, 3). Our hypothesis generating findings include the observation that SB > 2.5 seems to be a better predictor of MACE (ACS, acute CHF, VT/VF, cardiac death) when compared with reversible myocardial imaging defect(s) or LVEF < 0.34 in the same patients

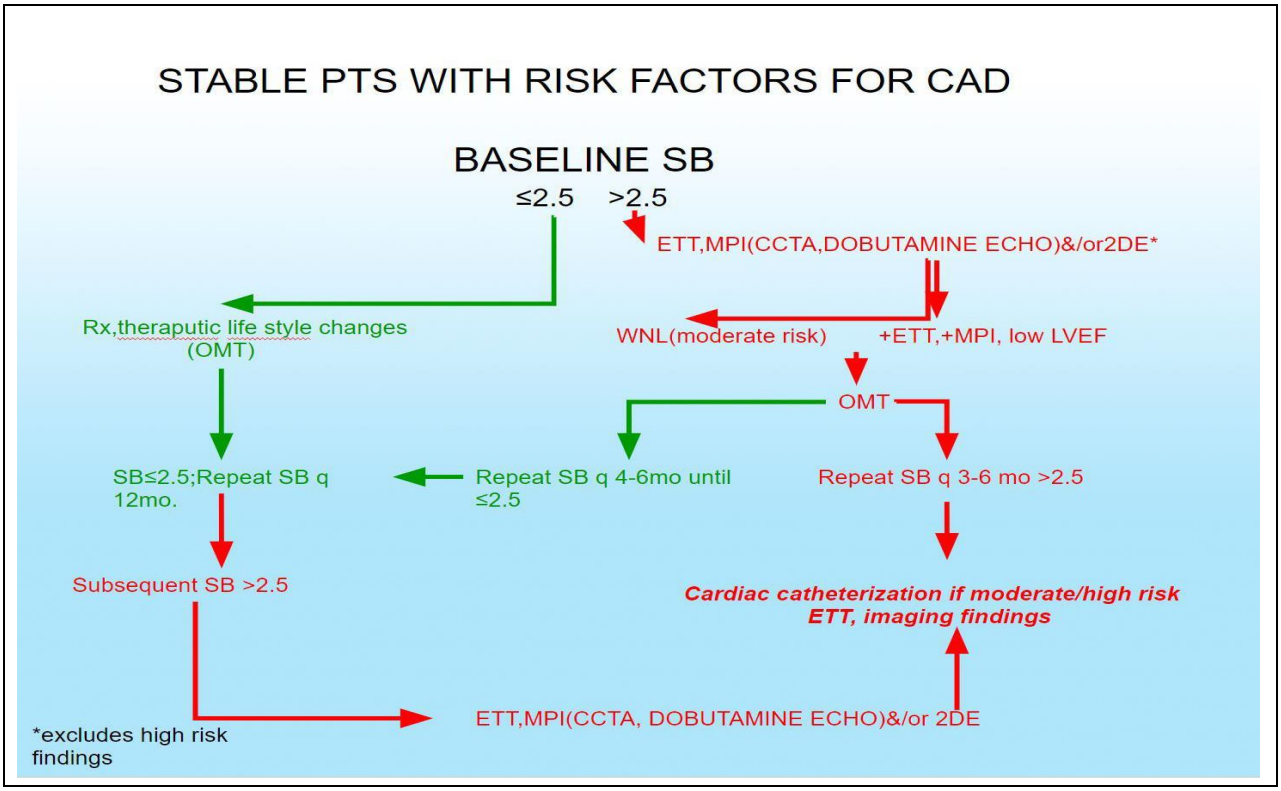


Figure 2: Stable PTS with risk factors for CAD

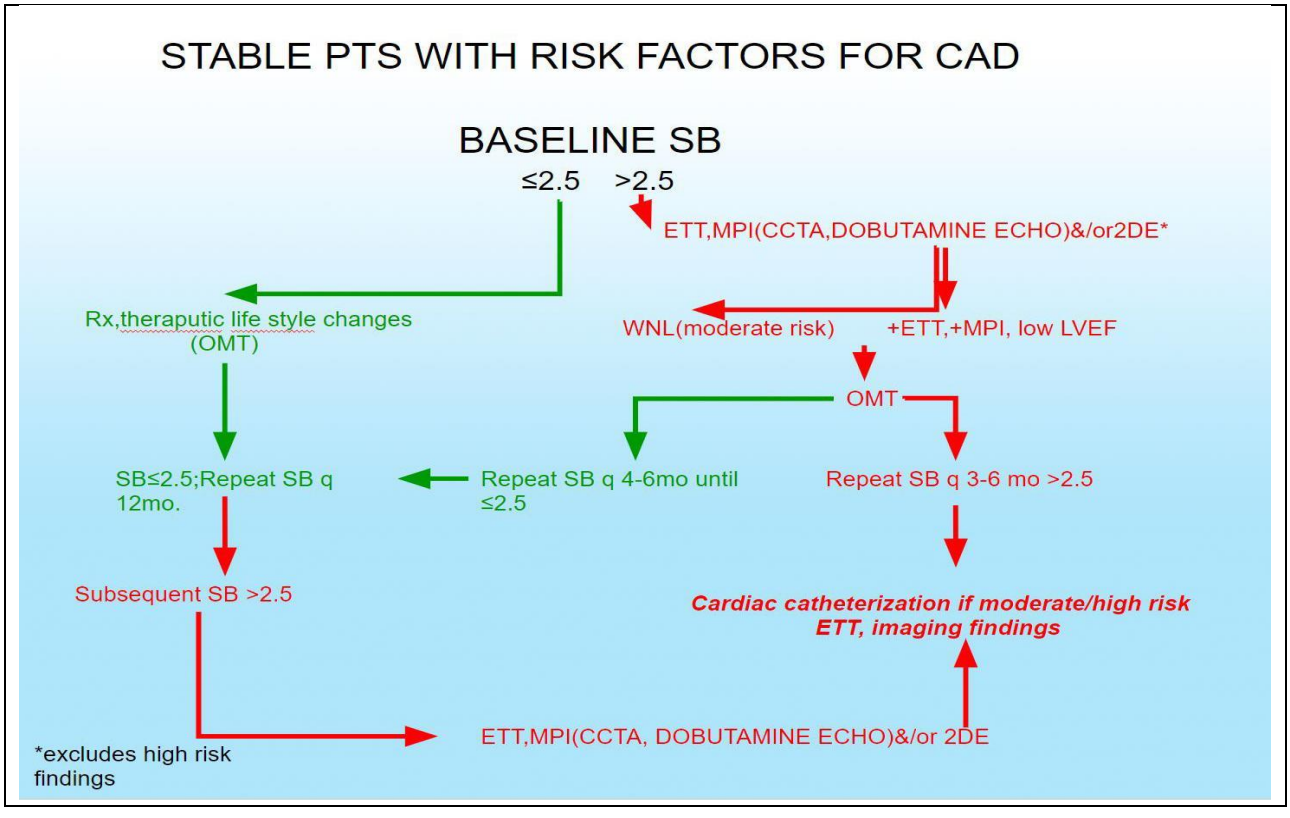


Figure 3: Stable CAD, CHF PTS Baseline ETT, MPI (CCTA, DE) &/or 2DE*

Disclosures

Gary L. Murray: none. Joseph Colombo: inventor of P&S Monitoring, part-owner and CTO & Senior Medical Director, TMCAMS, Inc., Atlanta, GA-USA

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