TITLE

The Critical Role of the Autonomic Nervous System (ANS) in the Development and Progression of Cardiovascular Diseases: For the First Time, Easily Assessed and Applied to Patient Management

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The ANS has a profound influence on the development and progression of the major cardiovascular diseases hypertension (HTN), coronary artery disease (CAD), congestive heart failure (CHF), neurogenic orthostatic hypotension (NOH), and is a major factor in sudden cardiac death (SCD) of Type 2 Diabetics (DM II). New technology, the 3.0 ANX AUTONOMIC MONITOR (Physio PT, Atlanta, GA USA), has, for the first time, provided accurate measurement of parasympathetic (P) and sympathetic (S) activity, whose sum equals heart rate variability(HRV), that is easily, quickly acquired in either an office or hospital setting. This article reviews our studies that suggest pharmacologic therapies of P and S abnormalities which reduce mortality and morbidity of these illnesses. How this new technology differs from all previous methods of HRV measurement and can be used in the daily practice of cardiology is also explained.

INTRODUCTION

In the 2nd century A.D., Wang Shu Ho stated, "If the heartbeat gets as regular as the knocking of the woodpecker or the dripping of the rain on the roof, the patient will die within 4 days". One century ago, the critical role of the ANS in health and disease was prophesized. In 1990, HRV (HRV = S + P) was 1st used in clinical cardiology, emphasizing reduced HRV is associated with a poor prognosis in all major cardiovascular diseases. In 2000, HRV was included in SCD risk stratification. High S and critically low P are associated with life-threatening ventricular arrhythmias, congestive heart failure (CHF), and acute coronary syndromes (ACSs). However, ANS testing is very rarely used in today's patient management. Why not?

Until recently, ANS measurement in the frequency domain yielded only total ANS activity, resulting assumptions and approximations of the independent contributions of S and P to total HRV. Since HRV = S + P, both must be accurately identified mathmatically. Furthermore, once in possession of this inaccurate S and P information, what were we told to do with it? So we needed accurate information and knowledge of S and P application to patient management in order to utilize this powerful tool.

ACCURATE MEASUREMENT OF S AND P

A technologic breakthrough was developed, validated, and verified by the 1st joint Bio-Medical Engineering program group from Massachusetts Institute of Technology and Harvard [1-5], and is now available for user-friendly routine clinical use. It is P&S Monitoring using the ANX 3.0 MONITOR(Physio PT, Atlanta, GA USA)=. The breakthrough quantifies the independent contributions of S and P to total HRV through two simultaneous measurements: (1) ECG monitoring which establishes total HRV (Low Frequency area [0.04-0.15 Hz] under the HR time-frequency spectral curve), simultaneously with (2) Impedance Plethysmography which independently quantitates P (a 0.12 Hz-wide window area under the HRV spectral curve centered on the modal peak of the time-frequency Respiratory Activity (RA) spectral curve; HRV due to RA is solely P-dependent). Therefore, S = HRV − P; where P is no longer assumed to be the area under the curve between 0.15-0.40 Hz, but now is quantitatively measured as the Respiratory Frequency area. The curves are analyzed using continuous wavelet transforms rather than the frequency-only fast Fourier transforms. The latter, although accurate for stationary signals, compromises time and frequency resolution due to the fixed length windows used in analysis.

This unscrambles S & P tone
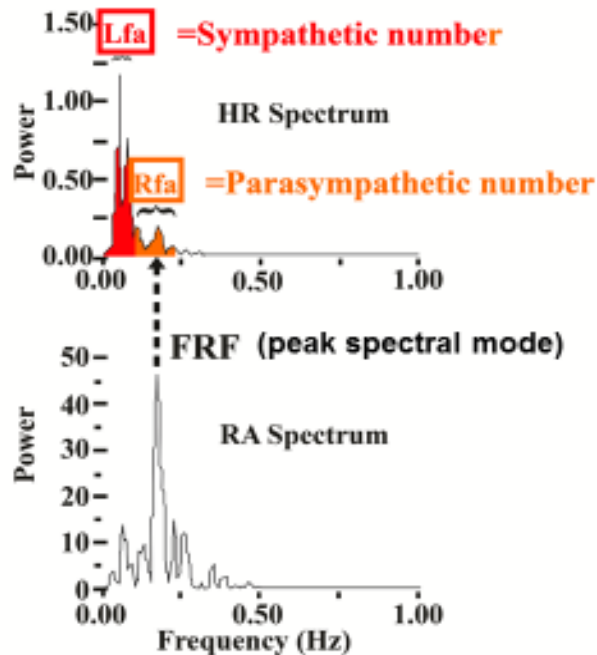
$$S(LFa) = HRV − P(RFa)$$

BENEFITS OF THIS NEW TECHNIQUE TO OUR PATIENTS

 OFF-LABLE RANOLAZINE FOR CHF

Ranolazine(RAN) is probably the best pharmacologic agent for CHF there is, based upon our 2 studies [6,7]. In CHF there is an increase in the myocardial late sodium (Na^+) current (I_{Na}) leading to an intracellular $Na^=$ and calcium(Ca^{++}) overload, via the Na^+/Ca^{++} exchanger (NCX) causing diastolic/systolic

dysfunction, microvascular ischemia, and early/delayed after depolarizations increasing the risk of sudden death. In therapeutic concentrations, ranolazine(RAN) decreases I_{Na} by 50%, thereby improving this Ca^{++} related mechanical and electrical dysfunction[8].Additionally, RAN is an inactivated-state atrial Na channel(Na_v) blocker, causing a selective atrial 1B-type Na_v blockade, and is effective treating atrial fibrillation, with or without another antiarrhythmic[9]. Neuronal $Na_{v1.7}$ is blocked in its open state in a strongly use-dependent manner by RAN at therapeutic concentrations(2-6 micromolar) via the local anesthetic receptor [10], so it is possible that RAN can directly alter the function of the Parasympathetic and Sympathetic(P&S) branches of the autonomic nervous system (ANS). These were the first studies reporting changes in P&S measures and LVEF in CHF patients treated with RAN added to guideline-driven therapy.

Seventy % of HF_r EF patients increased LVEF on average 11 EFUs (non-ischemic cardiomyopathies responded better than ischemic); remarkable, considering all patients were already fully treated. Despite treatment meeting ACC/AHA Guidelines, 59% of patients had dangerously abnormal S and P. Independent of hemodynamic changes: RAN favorably directly reduced high sympathovagal balance(SB = S/P) in 83% by reducing harmful high S-tone, the job that beta blockers failed to accomplish;Cardiac Autonomic Neuropathy=Advanced Autonomic Dysfunction(CAN/AAD) (P[=RFa] <0.10bpm^2) corrected in 50%, associated with a 40% reduction in MACE .All of this would have been unknown to the treating cardiologist**.**

Changes in abnormal P&S measures in RANCHF vs. NORANCHF patients, 1st study

	RANCHF (N=16)			NORANCHF (N=16)		
	preRAN	12 months	p	Initial	12 months	p
Rest						
LFa	7.80±15.6	0.88±1.18	0.034	3.65±4.64	2.35±2.55	0.056
SB	15.9±40.71	1.90±0.98	0.033	7.02±5.89	8.27±6.33	0.132
Head-Up Postural Change (Stand)						
LFa	4.12±13.7	0.67±0.97	0.071	1.90±2.68	1.16±1.20	0.485

RFa	1.85±5.83	0.17±0.15	0.208	0.88±0.82	1.03±0.87	0.049

(bpm)^2=beats per minute squared:NORANCHF =congestive heart failure group not on ranolazine;Paramod(RFa)=parasympathetic modulation in the rapid frequency area; pre - RAN=prior to ranolazine therapy;Sympmod(LFa)=sympathetic modulation in the low frequency area;SB=average of the ratios of sympathetic/parasympathetic modulation recorded during sampling period

In the 2nd CHF study, regarding MACE (SCD,VT/VF,CHF admission):

- SB was ≤ 2.5 in 51/63 (81%) CHF pts.who were MACE-free
- LVEF was ≥ 0.32 in 50/63 (79%) CHF pts.who were MACE free

- SB was > 2.5 in 19/32 (59%) CHF pts. who suffered MACE
- LVEF was < 0.32 in 16/32 (50%) CHF pts. who suffered MACE

HYPERTENSION

Approximately 1.5 billion people are hypertensive. We are sub-optimally dealing with this pandemic. Less than 50% of these patients are controlled, and both mortality and morbidity are increasing [11], despite our wide variety of pharmacologic therapies and multitude of guidelines. A recent comparison of the AHA/AHACDC, ESH/ESC, ASH/ISH, and NICE guidelines all recommend 4 main drug classes (Angiotensin Converting Enzyme Inhibitors[ACEI], Angiotensin Receptor Blockers (ARB), Calcium Channel Blockers (CCB), and Diuretics with no need to emphasize differences between drugs within each class [12]. None recommend utilizing an assessment of the Sympathetic (S) and Parasympathetic (P) abnormalities we've identified over the past 14 years (frequently present),or using the results to identify which drug(s) to choose if S and P malfunction(s) are identified. Hypertension (HTN), by definition, is a hemodynamic disease, and there are major inter- and intra-class differences in the hemodynamic effects, which can be autonomically mediated, among the drugs we administer. One possible explanation for our difficulty controlling HTN is that we do not tailor therapy to each patient's pathophysiology. A blood pressure of 160/95 is, with a few comorbid/cost exceptions or physician preferences, treated the same in every patient. Do we treat all pneumonias, diabetes, or coronary disease the same? In our defense, until recently, we couldn't do otherwise for HTN. But now we can more scientifically choose and adjust therapy; we have a tool that could assist in meeting this goal. A tool that's not being employed. So we continue treating the blood pressure *per se.*

Mean Arterial Blood Pressure (mBP)]-=mean Right Atrial BP = R_s x CO. Therefore, HTN is expressed mathematically. Logically, HTN treatment can (and should) be rendered with this in our minds.

We only measure mBP (e.g. BP) while treating HTN. S & P profoundly affect both of the unmeasured variables in this equation, yet S & P are unmeasured as well. Incredibly, we don't measure major factors that alter the 2 unmeasured variables in the equation! So there are actually 4 values (S, P, R_s, CO), each of which differ in every patient, yielding a multitude of combinations affecting the BP we're attempting to control. No wonder we struggle.

In order to improve HTN control, we must mathematically quantitate as many of these 4 factors as possible. Impedance plethysmography had potential for yielding BP, R_s, and CO, but it failed to provide us reliable information for HTN management. So we turned toward at least measuring S & P[13], achieving 74 % control vs. 30.4% control in JNC 8-managed patients (p <0.001) w/I 9 months on fewer prescriptions. For example:

76 y/o ANS-managed patient with uncontrolled HTN taking Coreg 12.5 mg bid, 10 mg Ramipril 10 mg/d (A) Standing high RFa (PE) with secondary high LFa are present, as is high SB. (r)-ALA was added (B), associated with improvement of these abnormalities

Sitting	(A)	(B)
LFa (bpm2)	0.30	0.40
RFa (bpm2)	1.22	0.36
SB	2.7	1.08
BP (mmHg)	166/65	136/56
Standing		
LFa (bpm2)	22.32	0.15
RFa (bpm2)	3.50	0.41
BP (mmHg)	172/67	147/65

NEUROGENIC HYPOTENSION

Chronic Orthostatic Hypotension (OH, defined as a fall of systolic blood pressure [BP] or diastolic BP $\geq 20/10$ mmHg within 3 minutes of standing still) is prevalent at any age, but mostly in the elderly [14] in whom Neurogenic Orthostatic Hypotension (NOH [such as low Sympathetic tone with head-up postural change (*i.e.*, standing)]) is by far more common than venostasis or iatrogenic causes, with OH prevalence rates up to 30% [14]. OH is a common cause of lightheadedness in elderly or chronic disease patients and is one of the earliest, and arguably the most debilitating, symptom of autonomic dysfunction [15,16].

OH is associated with increased mortality in the elderly: hazard ratios of systolic BP OH: 1.69-2.04; diastolic BP OH: 2.2 [17]. Oxidative stress, regardless of the source (sugar acidosis, low antioxidant levels, psychosocial stress, lack of exercise, smoking, pollution, etc.), causes autonomic injury.

The Autonomic Nervous System plays a critical role in BP regulation [18]. Since (r)alpha-lipoic acid (ALA) has been used in treating diabetic Cardiac Autonomic Neuropathy, including orthostatic dysfunction and hypertension 19-22], we postulated it might improve NOH as well as

Orthostatic Intolerance (OI) in non-diabetics, without causing or worsening hypertension or volume overload; as do most frequently used pharmacologic agents.

LOW SYMPATHETIC TONE ORTHOSTASIS AND (R)ALA

| | OH | | | | Orthostasis | | | | Control (n=20) | |
| | Responders(N=19) | | Non-Responders(N=9) | | Responders(N=40) | | Non-Responders(N=20) | | Initial | Final |
	Pre	Post	Pre	Post	Pre	Post	Pre	Post		
BP	145/73	126/66	136/77	136/76	130/70	124/69	138/71	130/69	140/76	138/72
Sit										
LFa	0.78	1.20	0.20	0.25	0.77	0.72	0.41	0.56	1.14	0.90
RFa	0.97	1.83	0.34	0.27	0.71	0.67	0.49	0.59	0.51	0.70
SB	1.35	1.59	1.25	1.12	1.55	1.61	1.43	1.37	2.28	2.20
Valsalva										
SB	9.59	8.90	12.5	13.6	9.09	11.1	6.1	20.0	14.0	12.6
Stand										
LFa	0.53	0.88	0.11	0.29	0.92	0.98	0.48	0.62	1.69	0.55
RFa	0.69	1.03	0.14	0.11	0.47	0.47	0.40	0.55	0.43	0.36
SB	2.24	1.69	1.7	2.46	2.94	4.20	2.37	1.99	4.08	1.91
BP	117/67	126/68	104/68	107/65	121/71	130/73	125/52	118/71	127/75	125/75
Change in BP (mmHg)	-28/-6	0/+2	-32/-9	-29/-11	-9/+1	+6/+2	-13/-19	-12/+2	-13/-1	-13/+3

66% responded by increasing SBP; the response depended upon the initial S.

LFa(bpm²)

| | NON-RESPONDERS | | RESPONDERS | |
	OH	ORTHOSTASIS	OH	ORTHOSTASIS
Pre Rx				
Sit	0.20	0.41	0.78	0.77
Stand	0.11	0.48	0.53	0.92
Post Rx				
Sit	0.25	0.56	1.20	0.92
Stand	0.29	0.12	0.88	0.98

Since corornary perfusion falls below 60mmHg, if this is considered, >80% responded.

CAD(and CHF)

Chronically elevated S tone contributes to MACE through hemodynamic stress, increased shear stress, and left ventricular hypertrophy, all risk factors for CHF; coronary vasoconstriction, platelet activation, endothelial dysfunction, and LDL oxidation occur, all pathophysiologically involved in CAD and acute coronary syndromes[23,24]. Acute myocardial ischemia also causes high S activity, and even early left ventricular dysfunction activates S drive [25-28]. Therefore increased S tone can both precede as well as follow MACE. Low P activity also has been associated with CHF as well as development of CAD[29], VT/VF,SCD[30-32]). In a study of 483 patients(127 with risk factors,224 CAD,132 CHF) over a mean 4.92 years, SB>2.5 was the best prognostic indicator of MACE(SCD,ACS,VT/VF,acute CHF)[33].

For predicting MACE, SB > 2.5(p<0.001) *outperformed* +MPI(reversible defect[s]) in all 3 groups, *outperforming* Framingham in Group 1, & 2DE LVEF ≤ 0.33 in Group 3.

Events

	Sensitivity	OR	Specificity	PPV	NPV
SB > 2.5(all)	0.59	7.03(CI 4.59-10.78)	0.83	0.64	0.80
+MPI (CD)	0.31	1.93(CI 0.90-4.16)	0.88	0.67	0.62
LVEF≤0.33(CHF)	0.67	3.46(CI 1.49-8.05)	0.67	0.50	0.81

In CDR patients, Framingham Risk Score (14.5% vs 12.15%) was not useful

PREVENTING SCD IN THE GENERAL POPULATION

Eighty-five % of SCDs occur in patients not previously diagnosed with heart disease or a history of heart disease with left ventricular ejection fraction(LVEF) >40%; our ability to predict these SCDs using current paradigms is limited to poor{34]. Although many mention dysautonomia as one of many risk factors, it's never heavily emphasized.

Oxidative-stress, and its role in the development and progression, of the major adult cardiac diseases (coronary artery[CAD],hypertension [HTN], and congestive heart failure[CHF] has long been recognized but likely underappreciated as risk factors for SCD except in DMII[2,3] which has high oxidative stress.

We all know with oxidative stress, heart rate variability (HRV) and cardio-protective parasympathetic tone (P) are decreased, while sympathetic tone (S) is harmfully increased (resulting in platelet activation, hemodynamic stress, oxidation of LDL, ventricular arrhythmias). But none of this is addressed except in DMII with its up to 3.25x increased SCD and CHF (beta blockers).

So we studied geriatric DMI patients to ascertain if SB>2.5 and or CAN(AAD) P<0.10bpm^2,risk factors for SCD could be prevented by (r)ALA, since these patients should have a high risk for SCD.

133 patients (mean age 66y/o) with DAN(any S or P abnormality)or CAN were offered (r) ALA: 83 agreed (Group 1), and 50 refused (Group 2). P and S were re-measured up to 3 times/yr. (mean f/u 6.31 yrs.); SCDs were recorded.

A 43% Relative Risk Reduction (RRR) in SCD occurred with (r) ALA (25% SCD Group 1 vs. 44% SCD Group 2, p=0.0076). Initial to final patients with high SB or CAN were 21.7%- 12%(p=0.010), 10.8%-15.7%(p=0.045), Group 1 vs. 24%-22%(p=ns), 6%-12%(p=0.083), Group 2. Only Group 1 survivors increased mean resting P. The progressive increase in P's decline, increasing CAN risk, in the other patients correlated with mortality (p<0.001) and (r)ALA dose. Initially, Group 1 had insignificantly less high SB (p=0.449) and significantly more CAN (p=0.013) vs. Group 2. Finally, Group 1 had significantly less high SB vs Group 2, also improving to insignificantly more CAN.

SUDDEN CARDIAC DEATH
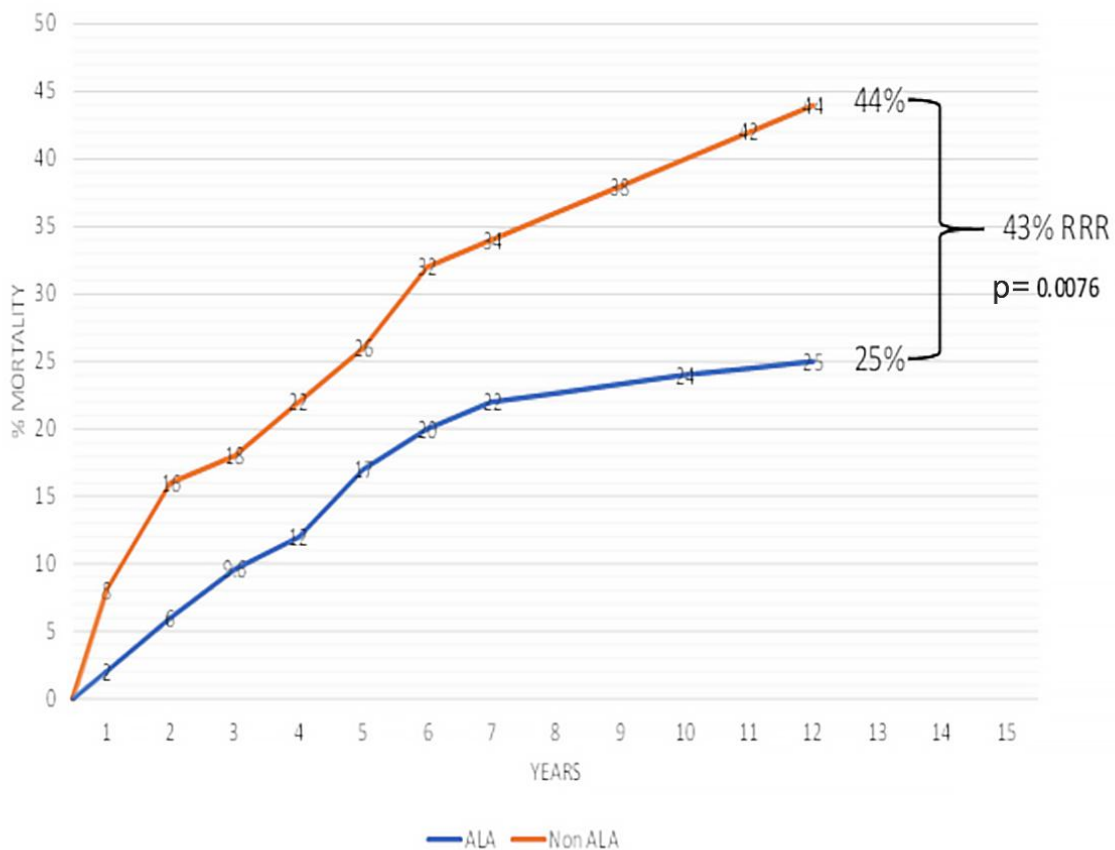
Since oxidative stress is a common thread among adults with most acquired heart diseases, perhaps (r)ALA will prevent SCD in non-DMII as well. We are currently investigating this.

CONCLUSIONS

The ANS has a major influence on MACE in patients with risk factors for CAD, CAD, CHF, HTN, NOH, and DMII. Now that we have accurate S and P measures, and targets to reach, such as SB<2.51 and P>0.10 bpm^2 , perhaps we can improve mortality and morbidity of our patients by routinely evaluating their ANS status(at least yearly), adjusting therapy accordingly.

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