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Twenty-First Century Cardiology Practice Can and Should Minimize Oxidative Stress and Optimize Heart Rate Variability

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ABSTRACT

This commentary is inspired by the 12 year study of 133 type II diabetics (DM) in whom sudden cardiac death(SCD) risk was identified with one autonomic screening and addressed , reducing SCD 43% (p = 0.0076) [1], as well as studies identifying/treating autonomic markers of major adverse cardiac events(MACE) in congestive heart failure(CHF), HTN, and coronary disease(CAD)[2-6] resulting in improved outcomes. Since oxidative stress, and secondary dysautonomia, is a common thread of all major cardiac disease, and there is preventative/corrective therapy, a new paradigm of screening/treating oxidative-stress cardiac dysautonomia as a major common final pathway to MACE should be considered.

Keywords

Oxidative stress, Heart rate variability, Ranolazine (r)Alpha Lipoic Acid, CoVid-19.

Introduction

Heart Rate Variability

1700 years ago, the Chinese physician Wang Shuhe wrote, "If the pattern of the heartbeat becomes as regular as the tapping of a woodpecker or the dripping sound of the rain on the roof, the patient will be dead in four days"-the 1st recorded recognition of the poor prognosis of reduced heart rate variability(HRV).In 1925, the critical role of the Autonomic Nervous System(ANS) in health and disease was prophesized: "The wise use of the autonomic nervous system will someday represent the core skill in the set of healing."-Heinrich Hering. In 1990, Heart Rate Variability (HRV = Sympathetic-tone [S] + Parasympathetic-tone [P]) was 1st used in clinical cardiology, emphasizing reduction in HRV was associated with poor prognosis in ***all*** major cardiovascular illness. In 2000, HRV was included in Sudden SCD risk stratification. However, all non-invasive ANS measurements only measured total autonomic activity, resulting in assumptions and approximations of the independent contributions of S and P to total HRV. Since HRV = S + P, both S and P must be identified. A technologic breakthrough accomplished this, developed, validated and verified by the 1st joint Bio-Medical Engineering program group from the Massachusetts Institute of Technology and Harvard [7-11] and is now available for user-friendly routine use. It is P&S Monitoring, quantifying the independent contribution of S and P to total HRV through two simultaneous measurements: (1) ECG recording establishing 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 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(LFa) = HRV – P(RFa); where P is no longer assumed to be the area under the HRV curve between a wide, noise-containing 0.15 - 0.40 Hz band, but is measured as the Respiratory Frequency area (RFa). 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.

Oxidative Stress

Many chronic and serious pathologies cause an over-production of oxidants, including reactive oxygen and nitrogen species (ROS, NOS), e.g. oxidative stress. While some level of oxidants is required by the immune system as defense against pathogens, excess oxidants cause damage, most significantly to mitochondria. The heart and the nervous system have the most mitochondria per cell and are more vulnerable to oxidative- stress damage. P&S dysfunction accelerates cardiovascular disease into a downward spiral, often before symptoms manifest.

The Oxidative Stress -Cardiovascular Disease Connection

Presently, although we are aware of the paradigm depicted in Figure 1, we still treat primarily the symptoms resulting from oxidative stress with stents, coronary artery bypass (or peripheral vascular interventions), defibrillators, ablations, and certain medications, rather than treating the oxidative stress *per se* or the autonomic dysfunction it causes. The exception is we address the neurohumoral paradigm of systolic CHF partially (see below).

SCD IN DM II

There is no better model of the oxidative stress-cardiovascular autonomic dysfunction-cardiovascular disease axis than Type 2 diabetes (DM II) [1].

Diabetics have a two-fold increased risk of SCD, the most common cause of death in adult diabetics. Subgroup analyses have not explained this adequately.

Diabetic Autonomic Neuropathy (DAN) [12], carries a 53% 5yr. mortality, half of the deaths sudden. DAN can progress to Cardiovascular Autonomic Neuropathy (CAN) in approximately 65% of patients with aging and diabetes duration; CAN, critically low Parasympathetic tone (P), increased SCD in the Framingham Study.

Hyperglycemic- oxidative stress causes dysautonomia (Figure 1). We hypothesized (r) Alpha Lipoic Acid (ALA), a natural, potent antioxidant, might reduce SCD in Type 2 Diabetics (DMII) with dysautonomias. We have shown previously (r) ALA improves autonomics in HTN [5] as well as Neurogenic Orthostatic Hypotension (NOH) [13].

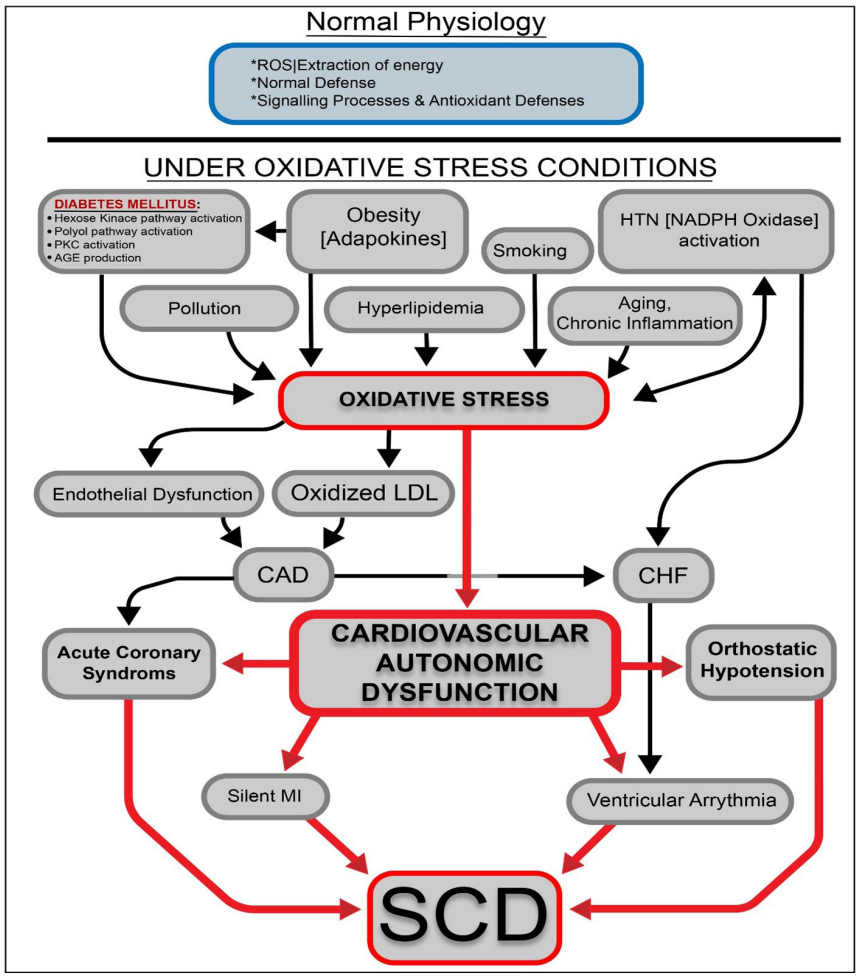

Figure 1: Oxidative Stress and Major Cardiovascular Diseases.

In 2006, 133 consecutive DMII referrals for cardiovascular evaluation underwent P and S testing via ANX 3.0 Autonomic Monitoring (P&S Monitoring, Physio PS, Inc., Atlanta, GA). P & S are normally: sitting LFa(S) and RFa(P) = 0.5 to 10.0 bpm^2; sympathovagal balance (SB) is age dependent = 0.4 to 1.0 for geriatrics; stand LFa is ≥ 10% increase with respect to(wrt) sit; stand RFa is a decrease wrt sit. High SB is defined as >2.5, as established in our 483-patient study [4]. High SB and CAN define a high risk of mortality, acute coronary syndromes (ACS), CHF, and ventricular tachycardia/fibrillation (VT/VF) alone or as a composite endpoint [4].

In the 83 (r) ALA patients (Group 1), P&S were recorded 2-3 mo. afterwards until maintenance dosage, then yearly. Non-(r) ALA patients (Group 2, refused (r)ALA) were tested yearly.

There was a 43% RRR in SCD in the (r)ALA-treated cohort (Figure 2).

Demographics, and P & S measures initially actually favored the non-(r)ALA Group. The difference in SCD was due to the autonomics (Table 1).

Only (r)ALA survivors demonstrated an increase in final, resting P(and HRV); P reduces VT/VF and silent ischemia [14-19], increasing 36.2% vs. a 7.6% decrease for non-(r)ALA survivors, a 10.5% decrease for (r)ALA SCDs, and a 67.5% decrease for non-(r)ALA patients with SCD. The progressive increase in the decline of resting P indicated mortality, from the lowest decline in resting P in non-(r)ALA survivors, to the next greater decline in (r)ALA SCDs, to those with the greatest decline, non-(r)ALA SCDs ($p < 0.001$). Changes in P were proportional to (r)ALA dose. High SB(>2.5) had a lesser influence on DM II SCD.

Fifteen-20% of deaths worldwide are sudden (w/i 1 hr. of symptoms), and the majority are cardiovascular. Eighty-five % of SCDs occur in patients not previously diagnosed with heart disease or who have a history of stable heart disease with LVEF >40%; our ability to predict these SCDs using current paradigms is limited to poor. Does the "DM II oxidative stress-cardiac dysautonomia model" of SCD apply to the general population? This is under study, but my guess is probably so. Cardiologists should have the capacity to screen and treat patients for cardiac dysautonomia. Low P correlates with coronary disease (CAD) as well as SCD, especially P<0.10bpm^2, and usually is responsive to (r)ALA. What about high SB?

We do this fairly well using beta blockers to counter the harmful effects of high S in CHF (the neurohumoral paradigm) (Figure 3).

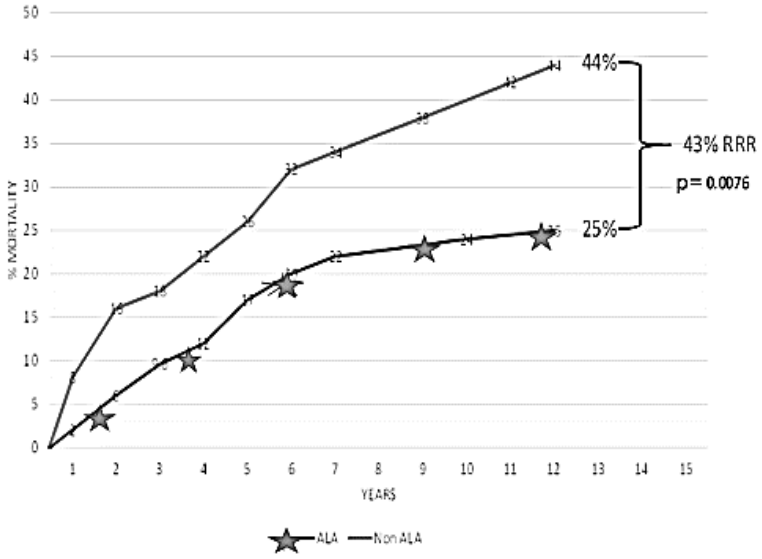

Figure 2: Sudden Cardiac Deaths in DM II Treated With and Without (r)ALA.

	Survivors ± (r)ALA				**Sudden Cardiac Death ± (r)ALA**			
N	90				43			
	Initial	**Final**	**Δ%**	**p**	**Initial**	**Final**	**Δ%**	**p**
Sitting (Rest)								
LFa (bmp^2)	1.25 ± 2.19	1.10 ± 1.55	-12	p = 0.045	0.89 ± 1.60	0.93 ± 1.09	+4.5	p = 0.039
RFa (bmp^2)	1.20 ± 2.33	1.35 ± 1.50	**+12.5**	p = 0.079	1.11 ± 1.93	0.45 ± 0.47	**-59.5**	p = 0.054
SB 1.23 ± 1.50	1.76 ± 1.47	**2.07 ± 1.49**	**+17.6**	p = 0.064	2.03 ± 1.92	**2.63 ± 2.60**	**+29.5**	p = 0.064
Standing								
LFa (bmp^2)	1.16 ± 2.05	1.00 ± 1.22	-13.8	p = 0.056	0.90 ± 1.28	0.68 ± 0.91	-24.4	p = 0.005
RFa (bmp^2)	0.97 ± 1.70	1.75 ± 1.95	+80.4	p = 0.051	0.82 ± 1.21	0.58 ± 0.66	-29.3	p < 0.001

Table 1: Comparison between Survivors and Sudden Cardiac Death patients, Mean P&S Measures. (Abbreviations as in text).

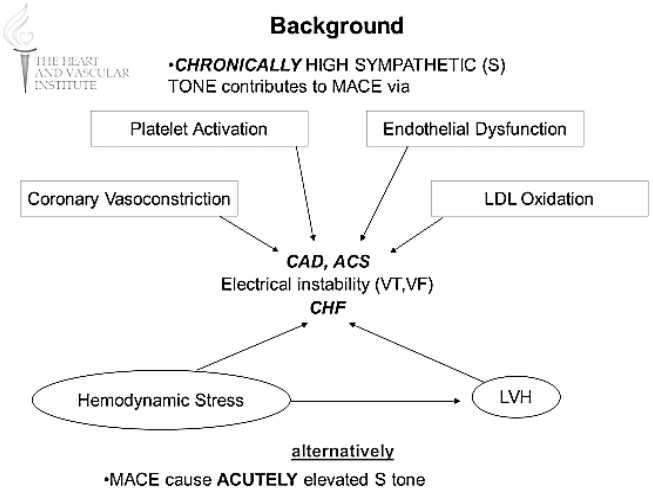

Figure 3: High S adverse effects.

CHF

Over 50% of ACC/AHA Guideline-treated chronic CHF patients have a persistently high SB{2,3] Fifty-four CHF patients were randomized to open-label RAN(RANCHF)added to usual therapy vs usual therapy(NORANCHF).P&S measurements were taken at baseline and at12mo. Sixteen/27(59%) patients in both groups had initially abnormal P&S measures, including high SB, CAN, or both. High SB normalized in 10/12(83%) RANCHF patients vs 2/11(18%) NORANCHF patients. SB increased in 5/11(45%) NORANCHF patients with initially normal P&S vs 1/11 (9%) RANCHF patients, and improved in 4/6(67%) RANCHF patients vs 5/7(45%) NORANCHF patients. CAN developed in 1/11(9%) RANCHF patients with initially normal P&S vs 4/11(36%) NORANCHF patients. Since improved P&S in RANCHF patients was independent of improved brain natriuretic peptide (BNP) and impedance cardiography (BioZ®) measurements, 5 days RAN was given to 30 subjects without CHF but with high SB and/or CAN. P&S improved in 90%, returning to baseline upon RAN discontinuation.

Neuronal $Na_{v1.7}$ is blocked in its open state in a strongly use-dependent manner by RAN via the local anesthetic receptor [2], so RAN can directly alter the function of the P&S branches of the ANS.

Ranolazine (RAN) also reduces the late sodium current (I_{Na}) in congestive heart failure (CHF), reducing myocardial calcium overload, thereby potentially improving LV function [3]. NYHA class 2-4 CHF patients were given open-label RAN (RANCHF, 41 systolic, 13 diastolic) added to guideline-driven therapy or no RAN (NORANCHF, 43 systolic, 12 diastolic). LVEF increased from 0.30 to 0.36(p=0.001); diastolic RANCHF patients' LVEF increased from 0.43 to 0.52(p=0.002). NORANCHF patients' LVEF remained unchanged. P & S measures every 6 mo. demonstrated improved SB in RANCHF subjects; SB worsened during control therapy (Tables 2,3). MACE tended to be lower in RANCHF vs. NORANCHF patients: cardiac death 5.6% vs. 12.7%, ventricular tachycardia/ventricular fibrillation events 11.1% vs. 23.6%, and CHF hospitalizations 22.2% vs. 27.3%.

	RANCHF (N = 46)			NORANCHF (N = 49)		
	Initial	Final	p	Initial	Final	p
Rest						
LFa	4.91	2.49	0.034	1.74	3.42	0.015
RFa	1.64	1.56	0.047	0.70	0.93	0.012
SB	2.42	1.98	0.019	2.61	4.28	0.039
Deep breathing						
RFa	15.8	13.7	0.065	7.66	11.8	0.267
E/I ratio	1.11	1.09	0.552	1.11	1.11	0.156
Valsalva challenge						
LFa	35.6	29.0	0.050	17.8	11.8	0.187
VR	1.20	1.24	0.359	1.17	1.19	0.753
Head-up postural change challenge (Stand)						
LFa	2.63	2.13	0.006	2.83	1.28	0.011
RFa	2.20	0.76	0.002	0.82	0.90	0.011
30:15 ratio	1.16	1.09	0.075	1.16	1.17	0.068
LVEF	0.34	0.41	0.0002	0.38	0.34	0.125

bpm^2 = beats per min^2; EFU = ejection fraction unit; E/I ratio = exhalation to inhalation ratio (unitless); LFa = low-frequency area (bpm^2), a measure of sympathetic activity (see Methods); LVEF = left ventricular ejection fraction; RAN = Ranolazine: RANCHF = congestive heart failure patients treated with RAN; RFa = respiratory frequency area (bpm^2), a measure of parasympathetic activity (see Methods); SB = sympathovagal balance (unitless, see Methods); VR = Valsalva ratio (unitless, see Methods); 30:15 ratio = ratio of 30° to the 15° R-R interval immediately after standing (unitless, see Methods).

Table 2: S & P, LVEF Results.

(Time domain measures E/I, VR, and 30:15 is displayed, but not discussed, in Tables 2,3,6.)

Pts w/Events+		pre & post RAN	p value	Pts w/o Events	p value
(N=15)				(N=31)	(Bx)
Rest				pre & post RAN	
LFa*		11.2 & 5.36	<0.001	1.90 & 1.10	0.011
RFa*		2.06 & 3.67	<0.001	1.44 & 0.70	0.006
SB‡		3.69 & 2.87	<0.001	1.80 & 1.54	0.025
Deep Breathing	RFa*	16.7 & 14.2	<0.001	15.3 & 12.7	0.011
	E/I Ratio	1.12 & 1.09	0.696	1.20 & 1.06	0.321
Valsalva	LFa*	32.6 & 29.9	<0.001	37.0 & 31.3	0.065
	VR	1.21 & 1.25	0.693	1.22 & 1.22	0.48
Stand	LFa*	19.2 & 4.79	<0.001	20.5 & 6.6	0.012
	RFa*	0.57 & 1.0	<0.001	7.36 & 0.64	0.045
	30:15:00	1.15& 1.10	<0.001	1.16 & 1.20	0.329
	LVEF	Δ = +6 EFUs	Δ = +9 EFUs	0.018	
Change: (pre & post RAN)					
0.30 to 0.36			0.35.5 to 0.44		

Table 3: Baseline and follow-up (pre- & post-RAN) P & S measures and LVEF in 46† RANCHF patients.
†no P & S 8 in patients with arrhythmia; abbreviations as in Table 2.

The (r)ALA study confirmed lower P increases MACE, and the (r) ALA and RAN studies suggested SB>2.5 increases MACE, and lowering SB should decrease MACE. We followed 483 patients

for a mean of 4.92 yr. (127 with CAD risk factors, 224 with CAD, 132 with chronic CHF) (Table 4) [4]. 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. There were 3 patterns of high SB (measured every 6 mo.): acute, chronic, and intermittent. An acutely high SB (20%) is the most ominous.

Table 4. SB best predicts MACE

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

HTN

Approximately 1.5 billion people are hypertensive. We are suboptimally dealing with this pandemic. Less than 50% of patients are controlled, and both mortality and morbidity are increasing (5), 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 [20]. None recommend utilizing an assessment of the S and 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. 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 can be, with a few comorbid/cost exceptions or physician preferences, treated the same in every patient. Do we treat all pneumonias, DM, or CAD 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.***

Several causative mechanisms of HTN have been proposed. Of these, we believe the neuro-adrenergic hypothesis [5] deserves the most attention, since our autonomic testing of hypertensives has revealed ANS abnormalities prevalent in over 90% of patients. Increased S tone and Cardiac Output (CO) accompanied by low Systemic Vascular Resistance (R_s) typifies young hypertensives. Over years, high S and CO decrease. R_s increases, likely due to end organ damage (Arterial Hypertrophy and Endothelial dysfunction), uncoupling R_s from S (although S still influences it, as does P), that causes decreased Baroreceptor Reflex (BR) and Cardiopulmonary Receptor sensitivity, accompanied by lowering of P activity. If P<<S, SB is too high, increasing MACE 7-fold (Table 4). Obesity, alternatively, is associated with high S and HTN.

Mean Arterial Blood Pressure (mBP)-mean right Atrial BP = R_s x CO.

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.

By focusing on the BP *per se* without obtaining S & P measures initially, we assume the HTN to be primary, e.g. essential HTN**,** in at least 90% of hypertensives, with patients rarely having secondary HTN, such as pheochromocytoma, Cushing's, etc.. This is a false assumption**,** as HTN may be secondary, due to primary autonomic dysfunction such as Parasympathetic Excess (PE), Sympathetic Excess (SE) (although common early in young essential hypertensives, SE is not confined to them), and Sympathetic Withdrawal (SW) upon standing, Treating these types of HTN as primary, rather than secondary, results in poor outcomes. A full discussion of these is beyond the scope of this article, so I'll focus on PE.

PE can present as anxiety, chronic regional pain syndrome, addictions (since P is associated with brain stem pleasure/comfort centers), chronic fatigue, sleep disorders, and cognitive disorder ("brain fog"). The PE causes a secondary SE to preserve cerebral perfusion, resulting in secondary HTN. The treatment of PE is $1/10^{th}$ the traditional dose of antidepressants or very low dose carvedilol, not the current guidelines' recommended ACEI/ARB, CCB, or diuretic (refer to Clinical Autonomic Dysfunction, by Colombo, et al.; Springer).

We performed a feasibility study comparing S & P assisted HTN therapy to JNC 8 therapy [5]. Forty-six patients were randomized. Of the S & P assisted Group 74% achieved JNC goals vs. 30.4% of the JNC 8 treated Group (p<0.001, home and office systolic and diastolic BP). The office P & S mean measures are listed in Table 5. Final S was lower sitting and P was higher sitting and standing (p<0.001) in the S & P Group. These results required 2.3 prescription drugs in the S & P Group vs. 3 in the JNC 8 Group.

Table 5: P&S Mean Measures.

	P&S Guided Therapy		JNC8-Guided Therapy		
	Initial	Final	Initial	Final	p
Resting pulse	82	61	76	72	<0.001
LFa (bpm2)	2.11	0.9	0.57	1.19	<0.001
RFa (bpm2)	2.15	0.71	0.47	0.62	<0.001
sBP (mmHg)	151	138	155	146	<0.001
dBP (mmHg)	74	71	73	65	<0.001
SB* (unitless)	3.26	1.86	1.83	1.84	0.004
Standing					
LFa (bpm2)	3.19	2.35	0.67	2.31	ns
RFa (bpm2)	1.67	1.56	0.5	0.875	0.005
sBP (mmHg)	153	138	155	145	<0.001
dBP (mmHg)	79	71	73	65	<0.001

dBP: Diastolic Blood Pressure; LFa: Low Frequency Area (S); P: Parasympathetic; RFa: Respiratory Frequency Area (P); SB: Sympathovagal Balance; sBP: Systolic BP.

In order to use S & P measures to guide therapy, one must know the S & P effects of anti-hypertensives. For example, Amlodipine increases SB, while beta- blockers decrease it; only Carvedilol among beta-blockers and ACEI/ARBs improve BR sensitivity (BRS), while non-Dihydropyridine CCBs decrease it. Sympatholytics worsen standing SW (except for Clonidine due to its central mechanisms of action and increased BRS. The central alpha action of Carvedilol, low dose SSRIs and Tricyclics (TC) lower PE.

We utilized S & P measures to choose anti-hypertensive therapy as follows: 1) If S & P balance (resting SB) was normal, any therapy was chosen; 2) if SB was high due to a relative or absolute excess S, a sympatholytic was given; 3) If SB was high due to low P, an ACEI/ARB and/or Diltiazem was given; (r)Alpha lipoic acid (rALA) can raise low P (33-6), so rALA was used as well. Upon standing, if no SW, any anti-hypertensive was chosen. If SW was noted, sympatholytics were avoided (excepting Clonidine or Carvedilol) as were Diltiazem and diuretics; Amlodipine, Hydralazine and/or rALA (which can raise S) were used. If PE occurred upon standing, diuretics and sympatholytics were avoided, except low dose Carvedilol. For PE upon standing, low dose SSRI or very low-dose TC were preferentially prescribed.

Diuretics were used for dependent edema only, since they don't improve endothelial dysfunction; unlike rALA, ACEI/ARB, CCB, and 3rd generation beta blockers.

CAD

Until recently, no pharmacologic chronic antianginal demonstrated MACE reduction. RAN was introduced to 51 successive anginal CD patients (RANCD) [6]. A control group of 54 successive non-anginal CD patients (NORANCD) continued baseline therapy. Mean study duration was 6.1 years, which included semi-annual P & S and yearly myocardial perfusion SPECT studies (MPI). MACE was experienced by 29% RANCD patients vs. 46% NORANCD patients (p=0.0105). The patients from both groups with abnormal P&S measures and MACE totaled 52% vs. 17% of those patients without MACE (p=0.0274). Abnormal MPI was demonstrated in 35% of those with abnormal P&S measures and MACE vs. 12% without MACE. Sympathovagal balance (SB) was lower, indicating higher, relative parasympathetic tone (known to be cardio-protective) in the RANCD group. ACS occurred 4.5 times as often in NORANCD patients. High SB occurred more frequently than abnormal MPI in CD patients experiencing MACE (Table 6).

Table 6: Final P&S measures (mean values).

	RANCD (N=51)	NORANCD (N=54)	p-value	EVENT (N=40)	NO EVENT (N=65)	p-value
SB	1.99	2.34	0.0346	**2.91**	**1.73**	**0.0105**
RFa	0.85	0.73	0.0262	**0.64**	**0.88**	**0.0268**
E/I	1.11	1.09	0.1370	1.12	1.08	0.0102
VR	1.22	1.09	0.0414	1.20	1.18	0.1516
30:15	1.16	1.12	0.5520	1.11	1.16	0.0635
Hi SB	**10/51 (19.6%)**	**14/54 (25.9%)**	**0.0439**	**17/40 (42.5%)**	**7/65 (10.8%)**	**0.0237**
CAN	3/51 (5.9%)	5/54 (9.3%)	0.0791	**4/40 (10%)**	**4/65 (6.2%)**	**0.0245**

CAN: Cardiac Autonomic Neuropathy; E/I: Exhalation to Inhalation Ratio (unitless); NORANCD: Coronary Disease Patients not treated with Ranolazine; RANCD: Coronary Disease Patients treated with Ranolazine; RFa: Respiratory Frequency Area in beats per minute squared (bpm^2); SB: Sympathovagal Balance; VR: Valsalva ratio (unitless); 30:15 = 30 to 15 ratio (unitless).

Testing for Oxidative Stress or Dysautomia Associated with Cardiovascular Disease/Mace in Daily Practice

Practically, hsCRP and Lp-PLA2 are routinely available for detecting oxidative stress-related inflammation. CV ANS testing Is inexpensive(about $250), and useful for reducing MACE, since low P(especially <0.10bpm^2) and/or SB>2.5, are treatable with therapeutic life-style changes and, if necessary, (r)ALA or ALA(a 50%-50% racemic mixture of (r)ALA and inactive (s)ALA) for low P and sympatholytic for high SB. ANS testing is indicated at least in:

- CAD
- CHF
- DM I 5 yr. post onset (ADA Guideline)
- DM II @ diagnosis (ADA Guideline)
- New or uncontrolled HTN
- Hyperlipidemia
- FHx SCD, CAD
- Males ≥ 40 yr. old
- Postmenopausal females
- Chronic inflammatory disorders
- Obesity
- Smokers

Conclusion

Oxidative-stress dysautonomias, major adult cardiac diseases, and autonomic SCD are major common enemies of survival (Figure 1). When we consider SCD, we focus on acute coronary thrombosis

or electrophysiologic studies, not dysautonomias. Perhaps a new screening paradigm, including emphasizing an autonomic profile, should be employed in most adults.

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 $\leq$ 2.5 and P>0.10 bpm2 , 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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