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(r)Alpha Lipoic Assists With Control of Neurogenic Orthostatic Hypotension, Hypertension, and Reduces Sudden Cardiac Death in Geriatric Diabetics

Gary L Murray[1*]

Director of research, The Heart and Vascular Institute, Germantown, TN, USA.

Corresponding author: Gary L Murray, Director of research, The Heart and Vascular Institute, Germantown, TN, USA. Email:drglmurray@hotmail.com.

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Abstract

Background: 10-30% of people have Orthostatic Hypotension (OH), 1/3rd of the world's population has Hypertension (HTN), and Sudden Cardiac Death (SCD) is twice as common and the most frequent manner of death in Type 2 diabetes (DM II), all of which can involve oxidative stress.

Objective: To study the effect of the potent, natural antioxidant (r)Alpha Lipoic Acid in (1) neurogenic OH (NOH), (2) HTN, and (3) DMII SCD.

Methods:(1) A cohort of 109 patients with low sympathetic tone(S) upon standing was detected using the ANX-3.0, Autonomic Monitor Physio PS, Inc., Atlanta GA USA. From the cohort, 29 patients demonstrated neurogenic orthostatic hypotension (NOH) (change in (Δ) standing BP –20/–10 mmHg) and 60 patients demonstrated orthostatic intolerance (OI, Δ standing systolic BP between –6 and–19 mm Hg). These 89 were given ALA orally: either 590 to 788 mg (r) ALA or 867 to 1500 mg of the less expensive 50 to 50% mixture (r) ALA and inactive (s)ALA. Changes in their S and parasympathetic tone (P), and BPs, were compared with 20 control patients during mean follow-up of 2.28 years.

(2) 46 uncontrolled HTN patients were randomized to P&S-assisted management, vs. JNC 8 therapy using the ANX 3.0 Autonomic Monitor and adding (r) Alpha Lipoic Acid (Group 1) vs. JNC 8 (Group 2).

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

Results:

(1) Nineteen of 29 (66%) NOH patients responded with a Δ standing BP from –28/–6 mm Hg to 0/+2 mm Hg. Forty of 60 (67%) of patients with OI responded with a Δ standing BP of –9/+1 mm Hg to 6/+2 mm Hg. Although all patients treated with ALA increased S tone, the Δ BP depended upon the pretreatment of S tone. Those with the lowest S tone responded the least well.

(2) The two Groups were similar in: (1) age (mean 66 vs. 70 y/o for Groups 1 and 2, respectively; (2) initial resting home Blood Pressure (BP, Group 1 mean=162/90 mmHg vs. Group 2 mean=166/87 mmHg), (3) initial resting office BP(BP, Group 1 mean=151/75 mmHg vs. Group 2 mean=155/73 mmHg), and (4) ethnicity. Upon follow-up (mean=8.35 mo.): (1) mean resting home BPs were 145/77 mmHg (Group 1, 74% of patients at JNC 8 goal) vs. 155/83.5 mmHg (Group 2, 30.4% at JNC 8 goal), and (2) mean resting office BPs were 138/71 mmHg (Group 1) vs. 146/65 mmHg (Group 2). At the study's conclusion, Group 1 S tone was lower than Group 2 at rest, and Group 1 P tone higher than that for Group 2 both at rest and upon standing .

(3) A 43% Relative Risk Reduction (RRR) in SCD occurred with (r) ALA (25% SCD Group 1 vs. 44% SCD Group 2, p=0.0076).

Conclusions: ALA is useful in NOH, HTN, and reduces DMII SCD.

Key words: Oxidative stress; Alpha Lipoic acid; Orthostatic hypotension; Hypertension; Sudden death;

Introduction

Oxidative-stress, and its role in the development and progression of NOH, and HTN, have long been recognized but likely under-appreciated as risk factors for SCD except in DMII [1,2] which has high oxidative stress. We all know heart rate variability (HRV) and cardio-protective P-tone are decreased, while S- tone is harmfully increased (resulting in platelet activation, hemodynamic stress, oxidation of LDL, ventricular arrhythmias) by oxidative stress. But none of this is addressed except in CHF when beta blockers are prescribed.

(1) Chronic OH, defined as fall of systolic blood pressure(BP) or diastolic BP 20/10 mm Hg within 3 minutes of standing still, is prevalent at any age, but mostly in the elderly [3] in whom NOH (such as low [S] tone with standing) is by far more common than venous stasis or iatrogenic causes, with OH prevalence rates up to 30% [4]. 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. OH is associated with increased mortality in the elderly: hazard ratios of systolic BP OH= 1.69 to 2.04; diastolic BP OH=2.2.5 [5,6]. Oxidative stress, regardless of the source (hyperglycemia, low antioxidant levels, psychosocial stress, lack of exercise, smoking, pollution, etc.), causes autonomic injury resulting in NOH. α-Lipoic acid (ALA), through its multiple antioxidant properties, has long been found to slow or stay the progression of autonomic injury [7-9]. The autonomic nervous system plays a critical role in BP regulation [10]. Since (r) ALA has been used in treating diabetic orthostatic dysfunction [8,9], 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 [11].

(2) Hypertension (HTN) is the most common disorder seen in family practice, affecting over 25% of primary care patients. Less than 50% of hypertensives are controlled, and mortality as well as morbidity is increasing [12]. While several causative mechanisms of HTN have been elucidated, much investigation remains. A neuroadrenergic cause is prominent: Increased Sympathetic (S) tone and Cardiac Output (CO) with low systemic vascular resistance (Rs) occur in young hypertensives; eventually, the high CO and S-tone usually come down [13]; Rs increases, uncoupling it from S-tone; and decreased Baroreceptor Reflex (BR), cardiopulmonary receptor sensitivity and Parasympathetic (P) tone are present, likely resulting from end-organ damage [13-19]. If P<<S, high sympathovagal balance (SB=resting S/resting P) results, which we and others have shown is associated with a 7-fold increase in adverse cardiovascular events [20,21]. Alternatively, obesity is associated with high S and HTN [22].

Despite the involvement of Parasympathetic and Sympathetic function in HTN, routine pharmacologic management of HTN is not tailored for it, potentially contributing to reduced time in therapeutic range that is inversely associated with all-cause mortality, resistant HTN, a 24% HTN recidivism rate, as well as undesirable orthostasis and fatigue [23,24]. Additionally, the increased oxidative stress that can contribute to the development of HTN and ANS dysfunction is also not specifically addressed therapeutically. We, as have others, have found the potent, natural antioxidant (r) Alpha Lipoic Acid ([r] ALA) can reduce sitting systolic and diastolic BP [25-27]. Therefore, our hypothesis is that pharmacologic HTN treatment, adjusted for P&S dysfunction when present treated with adjunctive (r)-ALA, could result in improved P&S function and HTN control using fewer prescription medications. The cost and side effects of treatment might be reduced. This is a prospective, controlled, hypothesis-generating, feasibility study.

(3) Diabetics have a two-fold increased risk of Sudden Cardiac Death (SCD), the most common cause of death in adult diabetics. Subgroup analyses have not explained this adequately [28]. Diabetic Autonomic Neuropathy (DAN) carries a 53% 5yr. mortality, half of the deaths sudden [29,30]. DAN can progress to Cardiovascular Autonomic Neuropathy (CAN, P<0.10bpm2) in approximately 65% of patients with aging and diabetes duration [31]; low P increased SCD in the Framingham Study [32]. Hyperglycemic- oxidative stress causes dysautonomia [28-30]. We hypothesized (r) ALA, a natural, potent antioxidant, might reduce SCD in Type 2 Diabetics (DMII) with dysautonomias.

ALA is a naturally occurring substance, a powerful thiol antioxidant that restores and recycles vitamins A, C, E, and glutathione, enhancing their efficacy. ALA also improves hyperglycemia, endothelial dysfunction, nitric oxide levels; reduces nuclear factor kappa B activity, is essential for the function of certain oxidative enzymatic activities; and has been mainly used to treat diabetic dysautonomia [9]. It exists as two enantiomers, with (r)ALA much more active than (s)ALA, and does not require a prescription.

Methods and Statistics

(1) NOH

Using the ANX-3.0 Autonomic Monitor, sympathetic- (S) and parasympathetic (P)-activity were computed simultaneously and independently based on concurrent, continuous, time frequency analysis of respiratory activity, and heart rate variability [33-38]. P activity measured as the respiratory frequency area (RFa) is defined as the spectral power within a 0.12 Hz-wide window centered on the fundamental respiratory frequency in the heart rate variability spectrum. Fundamental respiratory frequency is identified as the

peak spectral mode from time-frequency analysis of respiratory activity. RFa is a measure of vagal outflow as it affects the heart. S activity (low frequency area [LFa]) is defined as the remaining spectral power in the low-frequency window (0.04–0.15 Hz) of the heart rate variability spectrum, after computation of RFa. P- and S activity was recorded from a standard autonomic test, including (1) 5 minutes rest (seated), (2) 1 minute of breathing at 6 breaths/minute, (3) a series of 5 Valsalva maneuvers, including a 15 second Valsalva maneuver, and (4) a quick stand to 5 minutes of quiet standing. The average ratio of resting S to P activity (sympathovagal balance) reported was the average of the ratios recorded during the sampling period, not the ratio of the averages.

A cohort of 109 patients with low S tone upon standing was detected. From the cohort, 29 patients demonstrated NOH (change in [Δ] standing BP –20/–10 mmHg) and 60 patients demonstrated orthostatic intolerance (OI, Δ standing systolic BP between –6 and –19 mm Hg). These 89 were given ALA orally: either 590 to 788 mg (r) ALA or 867 to 1500 mg of the less expensive 50 to 50% mixture (r) ALA and inactive (s) ALA. Changes in their S- and P tone, and BPs, were compared with 20 control patients during mean follow-up of 2.28 years. All 109 study patients had low S sitting or standing. The only change in patients' therapy was the addition of (r) ALA or ALA (a racemic mixture of (r)- and (s)ALA). Syncopal responders had no recurrence of syncope, otherwise response was defined as Δ standing systolic BP < –6 mmHg. This study was approved by our Institutional Review Board, and all patients signed informed consent. Continuous data were assessed for normality with normally distributed data analyzed 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 was considered significant. Student t-tests were performed as two-tailed with equal variance. Sig-nificance values were determined on the null hypothesis that the pre- and post-treatment values are equal.

(2) HTN

In a suburban, mid-west cardiology clinic 46 consecutive patients (70% Female, average age 66 years, age range 33 to 88 years, 92% Caucasian) were recruited for this feasibility study. At baseline, all patients were under standard care based on the Eighth Joint National Committee (JNC-8) guidelines. At baseline, all patients recruited: 1) Were treated but uncontrolled HTN (unmet JNC goals) patients with any abnormality in P-and/or S-tone regardless of all other vital characteristics, 2) Signed informed consent, and 3) Were randomly, prospectively assigned to P&S-assisted therapy (Group 1) or JNC 8- guided only therapy (Group 2).

All patients were on a 2 gm. sodium diet and asked to perform at least 2.5 hr. aerobic activity/wk. and to stop smoking. All patients with obstructive sleep apnea were appropriately treated. P&S-assisted therapy consisted of adjusting JNC 8 therapy as well as adding (r)-ALA per our usual treatment for dysautonomia in patients without HTN. The groups' ages were: Group 1 averaged 66 y/o and Group 2 averaged 70 y/o ($p<0.001$). The groups' follow-up times were: Group 1 averaged 8.7 months and Group 2 averaged 8.0 ($p<0.001$). Five days of home morning and evening BP monitoring were collected.

Each monitoring event recorded BP after 5 minutes of quiet sitting and the data were averaged upon entry. Three days of b.i.d BPs were averaged 2 months after adding (r)-ALA in Group 1, in order to allow it to take full effect and monthly thereafter, whereas BPs were repeated 2 weeks after entry in Group 2 and monthly afterwards. Physician measured BPs were never used in this unblinded trial and doses of antihypertensive medications, along with changes, were per JNC 8 guidelines in both groups; only the choice of medication, the use of alpha lipoic acid, and the frequency of medication change (less frequent in Group 1 since alpha lipoic acid requires at least 2 months for full effect, thereby excluding bias in favor of Group 1) differed. Blood pressure goals were identical: patient recorded home BPs that would meet JNC goals. Office P&S testing measurements were taken with the ANX 3.0 autonomic monitor. Follow-up BPs and P&S measures were recorded 2 months after therapy adjustment in Group 1, whereas BPs were rechecked 2-4 weeks after adjustments in Group 2. Statistical analyses were performed in SPSS v22.0. Dichotomous data were analyzed using the chi-square test. A p-value of 0.05 or less was significant. Student t-tests as two-tailed with equal variance.

(3) DMII SCD

In 2006, 133 consecutive DMII referrals for cardiovascular evaluation underwent P and S testing via ANX 3.0 Autonomic Monitoring. P&S were computed simultaneously and independently by concurrent, continuous time-frequency analysis of Respiratory Activity (RA) and Heart Rate Variability (HRV), as we detailed previously. P & S are normally: sitting LFa and RFa = 0.5 to 10.0 bpm2; 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 [20]. 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 [20]. 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.

Exclusion criteria were (1) arrhythmia precluding HRV measurement, and (2) cancer within 5 yrs. The inclusion criterion was DM II with any abnormality of P or S. Informed consent was obtained for this open-label, un-blinded study. The cause of SD was determined from hospital records or death certificates. Out of hospital SCD was defined as pulseless SD(w/i 1hr of symptoms) of cardiac origin. Group 1 patients were subcategorized: survivors, Group AA; non-survivors Group AD. Group 2 (Controls): survivors,

Group NA; non-survivors, Group ND. All patients took aspirin. All patients had a Cardiovascular Autonomic Reflex Test (CART) w/o isometric grip (grip has only 25% sensitivity for CAN [19]). DAN was defined as any abnormality of S or P, or high SB. CAN was defined as P < 0.10 bpm2, or 2 abnormalities of CARTs. Median follow-up was 5 yrs. Mean age was 66 y/o. There were 83 males, 50 females. Upon referral, rhythm assessment (Holters ± event monitors) were performed if clinically indicated: Groups AA 60%, AD 57.1%, NA 60.7%, ND 31.8%. The abbreviations are: Δ, change from initial to final; A1C, glucose form hemoglobin;(r) ALA, (r)alpha-lipoic acid (the r-isomer functional in humans); BMI, body mass index; Bx, Baseline; CAN, cardiovascular autonomic neuropathy; DAN, diabetic autonomic neuropathy; dBP, diastolic blood pressure; HL, hyperlipidemia; HR , heart rate; Init, initial; L, low; LFa, low frequency area(=S); LVEF, left ventricular ejection fraction; mg, milligrams; N, number; Nml, normal; ns, not significant; p, significance; P, parasympathetic tone; PE, parasympathetic excess; QTc, corrected QT; RFa, respiratory frequency area(=P); S, Sympathetic tone; SB, sympathovagal balance; sBP, systolic BP; SW, sympathetic withdrawal. Given the size of the cohort, statistical significance is p < 0.100. Statistical significance was determined with either a two-tailed, student T-test or a Pearson correlation.

RESULTS

(1) NOH

Patient demographics are listed in Table-1. In the OH Group (n =29), there were no females in the 10 non-responders; there were more diabetics; 80% were prescribed midodrine, fludrocortisone, or desmopressin; and 20% were on beta blockers. There were fewer patients with hypertension or congestive heart failure, but more with syncope. In the OI group (n = 60), there were fewer congestive heart failure patients, but more with syncope, fatigue, and headache.

Patient autonomics and BPs are listed in Tables-2 and Table-3. In the OH group, pre-and post-treatment Δ standing BP was –32/–9 mmHg versus –29/–11 mm Hg in non-responders, and –28/–6 mm Hg versus 0/+2 mm Hg in responders. In the OI group, pre- and post-treatment Δ standing BP was -13/-19 mm Hg versus -12/+2 mm Hg in non-responders, and -9/+1 mm Hg versus +6/+2 mm Hg in responders. Responders had higher S tone (Table-3). Regardless of the Δ standing BP, (r)ALA reduced sitting BP in most patients. In the controls, there was no significant difference in Δ standing BP (from a baseline of-13/-1 to a follow-up of-13/+3), and there was a decrease in S activity with follow-up.

Table- 1: Patient demographics

	OH(n = 29)		p	OI (n = 60)		p	Control(n = 20)	p
	R–(10)	R +(19)		R–(20)	R + (40)			
Age (yrs)	72 ± 13.8	70 ± 9.6	ns	69 ± 7.5	64 ± 9.5	ns	66 ±9.0	ns
Gender (M%)	**9**	68	0.010	60	58	ns	40	ns
Symptoms (% of population)								
Fatigue	40	37	ns	65	30	0.030	30	n/a
Dizziness	70	47	0.010	55	37.5	ns	30	n/a
Syncope	40	26	0.049	50	22.5	0.049	10	n/a
Headache	0	0	ns	10	0	0.0163	10	n/a
Medications (% of population)								
	OH (n = 29)		p	OI (n = 60)		p	**Control(n = 20)**	P
Midodrine	50	0	<0.001	0	0	ns	0	n/a
Fludrocortisone	30	0	<0.001	0	0	ns	0	n/a
Desmopressin	20	0	0.001	0	0	ns	0	n/a
(r)ALA (%)	80	68	ns	85	72.5	ns	0	n/a
(r)ALA mean dose (mg)	610 ± 510	754 ±570	0.080	788 ±510	590±500	0.030	0	n/a
ALA%	20	32	ns	15	27.5	0.060	0	n/a
ALA mean dose (mg)	1500 ± 760	867 ±440	0.035	1000 ±460	993 ±450	ns	0	n/a
Follow-up (mean yrs)	2.28 ±1.6	1.74 ±2.0	ns	1.94 ±1.5	1.29 ± 1.2	ns	2.16 ±1.7	ns

Abbreviations:

ALA- α lipoic acid;

n/a- not applicable;

n- number;

ns- not significant;

OH- orthostatic hypotension;

OI- orthostatic intolerance;

R +-responders;

R– -non-responders;

Yrs- years.

Table- 2: Autonomic and BP measures

	OH						OI						Controls =20)		
	R+ (*n* = 19)			*R*– (*n* = 9)			*R*+ (*n* = 40)			*R*– (*n* = 20)			Initial	Final	*p*
	Pre	Post	*p*	Pre	Post	*p*	Pre	Post	*p*	Pre	Post	*p*			
Rest (sitting)															
BP, systolic (mm Hg)	145	126	0.002	136	136	ns	130	124	0.006	138	130	0.016	140	138	ns
BP, diastolic (mm Hg)	73	66	0.003	77	76	ns	70	69	ns	71	69	ns	76	72	ns
LFa (bpm^2)	0.78	1.20	0.0172	0.20	0.25	ns	0.77	0.72	ns	0.41	0.56	0.0362	1.14	0.90	0.0301
RFa (bpm^2)	0.97	1.83	0.0199	0.34	0.27	ns	0.71	0.67	ns	0.49	0.59	ns	0.51	0.70	0.0517
SB (unitless)	1.35	1.59	ns	1.25	1.12	ns	1.55	1.61	ns	1.43	1.37	Ns	2.28	2.20	ns
Valsalva															
SB (unitless)	9.59	8.90	ns	12.5	13.6	ns	9.09	11.1	ns	6.10	20.0	0.0652	14.0	12.6	ns
Stand															
BP, systolic (mm Hg)	117	126	0.0210	104	107	ns	121	130	ns	125	118	0.0433	127	125	ns
BP, diastolic (mm Hg)	67	68	ns	68	65	ns	71	73	ns	52	71	0.0338	75	75	ns
LFa (bpm^2)	0.53	0.88	0.0361	0.11	0.29	0.0362	0.92	0.98	ns	0.48	0.62	ns	1.69	0.55	0.0221
RFa (bpm^2)	0.69	1.03	0.0300	0.14	0.11	ns	0.47	0.47	ns	0.40	0.55	ns	1.69	0.55	0.0056
SB (unitless)	2.24	1.69	0.0083	1.70	2.46	0.0654	2.94	4.20	0.0271	2.37	1.99	ns	4.08	1.91	0.0164
ΔBP, systolic (mm Hg)	−28	0	0.0129	−32	−29	ns	−9	6	<0.001	−13	−12	ns	−13	−13	ns
ΔBP, diastolic (mm Hg)	−6	2	0.0456	−9	−11	ns	1	2	ns	−19	2	0.0068	−1	3	ns

Abbreviations:

Δ- change;

BP- blood pressure (mm Hg);

LFa, low frequency area (beats/min2);

n- number;

ns- not significant;

OH-orthostatic hypotension;

R +- (R)α lipoic acid responders;

R–- (R)α lipoic acid non-responders;

RFa- respiratory frequency area (beats/min2);

SB-sympathovagal balance.

Table- 3: Sympathetic activity as measured by LFa (bpm2)

Sympathetic activity (LFa, bpm^2)	*R*–			*R*+		
	OH	OI	*p*	OH	OI	*p*
Pre-Rx						
Sit	0.20	0.41	0.0230	0.78	0.77	na
Stand	0.11	0.48	0.0107	0.53	0.92	0.0220
Post-Rx						
Sit	0.25	0.56	0.0258	1.20	0.92	0.0345
Stand	0.29	0.12	0.0253	0.88	0.98	na

Abbreviations:
Δ-change;
LFa- low frequency area (beats/min2);
OH- orthostatic hypotension;
OI- orthostatic intolerance;
R +- (R)α lipoic acid responders;
R–-(R)α lipoic acid non-responders;
Rx- treatment with ALA.

(2) **HTN**

Demographics

Table 4 Lists patient demographics which will be detailed below.

	P&S-Guided Therapy (N-23)		JNC-8-Guided Therapy-(N-23)	
Age (yrs); BMI; RR	66; 30.9; 18/min		70; 31.2; 19/min	
Gender (F/M)	30%/70%		37%/63%	
Ethnicity(Caucasian)	92%		88%	
Smokers	13%		8.70%	
Medications				
CCB	39%		61%	
ARB/ACEI	56.50%		78%	
DIURETIC	48%		52%	
Sympatholytics				
BB	39%		70%	
Clonidine	22%		9%	
Hydralazine	13%		17%	
Comorbidi-ties				
CAD	30%		42%	
HL	65%		70%	
Diastolic CHF	0%		17%	
LVEDD	5.4 cm		5.5 cm	
LVEF	0.65		0.63	
LVH	96%		100%	
PAD	17%		9%	
AODM	26%		39%	
CRI	13%		13%	
F/U (mo.)	8.7		8	
Resting BP	**Group 1**		**Group 2**	
	Initial	**Final**	**Initial**	**Final**
(mean mmHg)	162/90	145/77	166/87	157/83.5

Abbreviations:
F/M-Female/Male;
CAD-Coronary Artery Disease;
HL-Hyperlipidemia;
CHF- Congestive Heart Failure;
PAD-Peripheral Artery Disease;
AODM-Adult Onset Diabetes Mellitus;
CRI-Chronic Renal Insufficiency;
F/U-Follow-Up;
RR-Respiratory rate;

Although the two groups had similar initial BPs, home BP control was more normalized in the P&S-assisted patients. After a mean f/u of 8.35 mo., mean resting, home BPs were lower in Group 1 (145/77 mmHg, 74% 0f patients at JNC 8 goal, mean pulse 61 bpm) vs. Group 2 (155/83.5 mmHg, 30.4% of patients meeting JNC 8 goal, mean pulse 73 bpm; p<0.001 systolic, p= <0.001 diastolic, p<0.001 pulse). Similarly, Group 1 mean sitting office BPs were 138/71 mmHg vs. Group 2's 146/65 mmHg; p<0.001 systolic, p<0.001 diastolic.

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 (bpm^2)	2.11	0.9	0.57	1.19	<0.001
RFa (bpm^2)	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(unit-less)	3.26	1.86	1.83	1.84	0.004
Standing					
LFa (bpm^2)	3.19	2.35	0.67	2.31	ns
RFa (bpm2)	1.67	1.56	0.5	0.87	0.005
sBP (mmHg)	153	138	155	145	<0.001
dBP (mmHg)	79	71	73	65	<0.001

Abbreviations: SB=[resting S-activity]/[resting P-activity], an average of the ratios, not the ratio of the averages,
LFa-The measure of S-activity;
RFa-The measure of P-activity;
sBP-systolic Blood Pressure;
dBP-diastolic Blood Pressure.

All Group 1 patients demonstrated at least 1 abnormal autonomic measure initially, managed exactly as in normotensives, and improved final office P&S measures (Table-5), including: lower resting (sitting) S-tone (LFa=0.90, p<0.001), higher final P-tone (RFa=0.71, p<0.001), and higher standing P-tone (RFa=1.56, p=0.005) as compared with final Group 2 values were present. All of these differences are consistent with improved HTN control. Prescribed sympatholytic influenced the results. Initially, 6 of 23 (23%) Group 1 patients had low sitting S-tone (LFa<0.5 bpm2) vs. 17 of 23 (74%) in Group 2, p<0.001. Group 2 had a higher percentage of patients prescribed a sympatholytic.

As a result, with P&S-Assisted therapy, all but one (5 of 6 or 83%) of the Group 1 patients with low resting S-tone improved vs. 9 of 17 (53%) of similar Group 2 patients, p<0.001. These improvements also reduced the symptoms of fatigue and orthostatic hypotension in these low resting S-tone patients. P-tone directly and indirectly affects S-tone and thereby may affect BP. Low-resting P-tone may result in high resting S-tone, since P-and S-tone typically variate reciprocally. High S-tone increases BR activity, attempting to lower BP; low P-tone does the opposite. These opposing actions may increase difficulty in controlling BP in hypertensives. Initially, 7 of 23 (30%) Group 1 patients had low resting P-tone (<0.5 bpm2), vs. 15 of 23 (65%) Group 2 patients (p<0.001). Group 1 final P-tone increased in 4 of 7 (57%) patients with low P-tone vs. Group 2 in which only 3 of 15 (20%) patients increased P-tone (p<0.001). CAN is extremely low P-tone (<0.01 bpm2). CAN is often associated with high SB. CAN with high SB is associated with increase MACE risk [9]. Initially, no Group 1 patient presented with CAN, vs. 7 of 23 (30%) Group 2 patients (p<0.001). At the end of the study, 3 of 23 (13%) Group 1 patients had CAN vs.5 of 23 (22%) with CAN in Group 2 (p=ns). A lower S-tone in Group 1 is associated with a smaller, increased MACE risk of CAN [9]. High SB was demonstrated by 8 of 23 (35%) of the Group 1 patients vs.4 of 23 (17%) patients in Group 2 (p<0.001). SB was corrected (normalized SB) in 5 of the 8 (62.5%) high SB patients of Group 1 vs. no (0%) high SB patients of Group 2 demonstrated normalized SB (p<0.001). High SB is a measure of (relatively) high resting S-tone. Combining the resting S-tone results and CAN (very low P-tone) results, these findings support the hypothesis that lower S-tone lowers the risk of CAN [9]. At the end of the study, Group 1 patients had more patients with lower S-tone and patients with lower CAN risk. Upon standing, 8 of 23 (35%) of Group 1 patients initially had Sympathetic Withdrawal (SW, consistent with BR and cardiopulmonary receptor dysfunction) vs. 12 of 23 (52%) of Group 2 patients (p=0.01). SW was corrected in 5 of the 8 (62.5%) Group 1 SW patient vs. 4 of the 12 (33.3%) Group 2 SW patients (p<0.003). Corrected SW indicates improved BR function. Inappropriately increased P-tone (P excess, PE) upon standing (the normal change is to decrease) initially occurred in 9 of 23 (39%) of Group 1 vs. 5 of 23 (21%) of Group 2 patients (p=0.004). PE was corrected in 6 of 9 (67%) of Group 1 PE patients and in 1 (20%) of the patients in Group 2 PE patients (p<0.001). However, PE developed in 3 (21%) of the other Group 1

patients and in 2 (11%) of the other Group 2 patients. Therefore, final PE was equally present (26%) in both Groups. Probably PE indicates a compensatory mechanism (vasodilatation) to increase blood volume thus attempting to maintain HTN.

While increased standing P-tone lowers BP, a pronounced increase can result in orthostasis, as can extreme SW. SB improved dramatically in Group 1 patients from 3.26 to 1.86 (p=0.004, Table 5), despite fewer patients using beta blockers, contrasted with essentially no change of SB in Group 2. This is consistent with the difference in HTN control. Despite nearly equal mean lower final S-and P-tone in Group 1, SB fell substantially, because SB is reported as the average of ratios, rather than the ratio of averages. Since the final SB in both Groups was virtually equal, SB cannot be inferred solely by the BPs which was significantly different. With adjunctive P&S-guided therapy, home BP control was more normalized in Group 1 than in Group 2: 134/77 mmHg vs. 155/83.5 mmHg, respectively (p<0.001 for systolic BP and p<0.001 for diastolic BP). The two patient groups were prescribed a mean of 2.3 vs. 3.0 prescription anti-hypertensive, respectively. More Group 2 patients were prescribed Calcium Channel Blockers (CCB) and at a higher daily mean dose (7.1 mg vs. 12.1 mg of Amlodipine for Groups 1 and 2 respectively). Both groups were prescribed Beta Blockers (BB) at similar mean doses, except for Carvedilol (40 mg for Group 1 vs. 32.5 mg for Group 2). Both groups were prescribed Angiotensin Receptor Blockers (ARB) or Angiotensin Converting Enzyme Inhibitors (ACEI) at similar mean doses, except for Losartan (100 mg for Group 1 vs. 50 mg for Group 2) and Lisinopril (40 mg for Group 1 vs. 22 mg for Group 2). More Group 1 patients took Clonidine at a lower mean dose (0.24 mg vs. 0.6 mg) and Hydralazine was used similarly in both Groups (Table 4). Changes in medications were as follows: 5 of 23 (22%) of Group 1 vs. 7 of 23 (30%) of Group 2 patients were prescribed higher doses of medication; 14 of 23 (61%) of Group 1 vs. 100% of Group 2 had a new drug introduced; 3 of 23 (13%) of Group 1 vs. 2 of 23 (9%) of Group 2 were prescribed lower doses of medications and 17% of Group 1 vs. 9% of Group 2 had a change of medication drug class. Group 1 took a mean dose of 761 mg (r)-ALA.

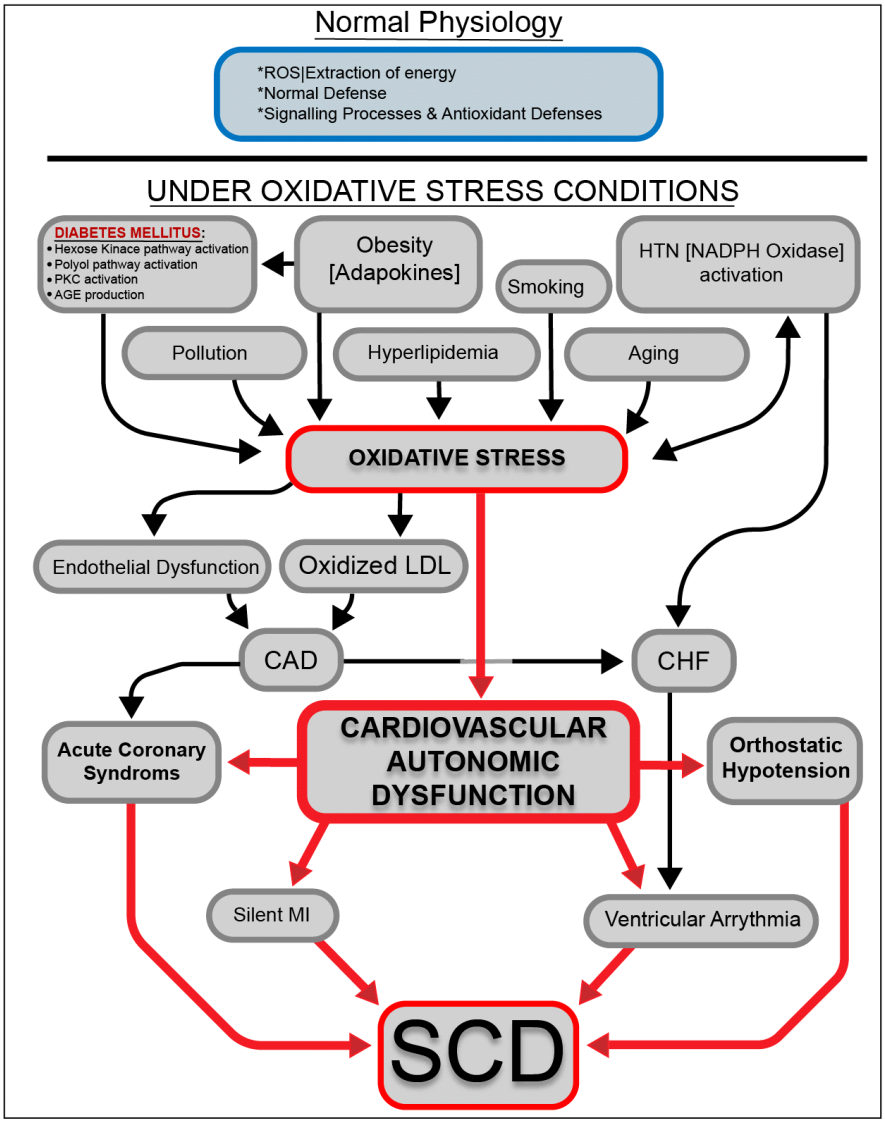

FIGURE- 1: DIABETES MELLITUS AS A CAUSE OF OXIDATIVE STRESS, CARDIOVASCULAR AUTONOMIC DYSFUNCTION AND SUDDEN CARDIAC DEATH

(3) **DMII SCD**

Twenty-five % of (r) ALA patients experienced SCD vs.44% non-(r) ALA patients, a 43% Relative Risk Reduction (RRR, p = 0.0076 (Figure-2)), altering the natural history of DAN [3].

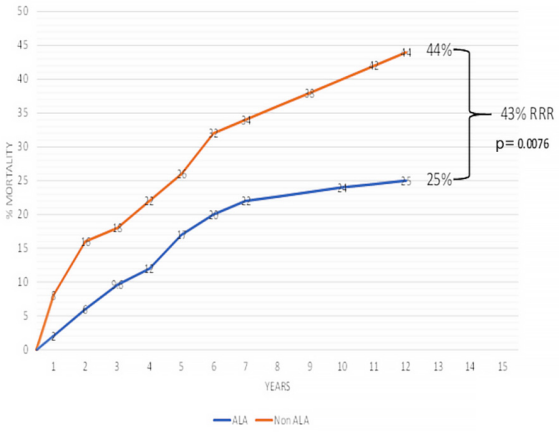

FIGURE 2. SUDDEN DEATH RISK DMII PATIENTS WITH VS. WITH-OUT (r)ALA

FIGURE LEGEND

Sudden Death Mortality risk of a Diabetic type 2 cohort from a south-central USA cardiology practice. (r)ALA (blue curve) reduced this cohort's relative risk ratio (RRR) by 43% (p=0.0076 as compared to controls (brown curve).

DEMOGRAPHICS

Group AA had significantly more males and higher final A1C; their initial LVEF was insignificantly lower, factors not favoring survival [40,4]; tending to favor survival were insignificantly fewer with CAD (although all AA and NA patients were vascularized with normal stress tests), less Chronic Kidney Disease (CKD); and significantly more Angiotensin blocker therapy (ACEI or ARB, p< 0.100) [40,45]. Eleven % more (r) ALA patents required insulin. Control Group NA had significantly more females and lower final A1C; there were insignificantly higher initial LVEFs and insignificantly more patients on Empagliflozin, Liraglutid, and Metformin, tending to favor survival [46-49] (Table- 6).

Table-6: Survivor Patient Demographics

	Group AA	**Group NA**	**p**
N	62	28	
Male	61%	39%	p < 0.100
Age (mean yrs)	67	64	p > 0.100
Ethnicity			
Caucasian	74%	73%	ns
African Am	23%	24%	ns
Other	3%	2%	ns
2° Dx			
HTN	95.0%	86.0%	ns
HL	80.0%	82.0%	ns
CAD	24.0%	37.0%	ns
CHF	21.0%	20.0%	ns
CKD	25.0%	35.0%	ns
Smoker	5.0%	4.0%	ns
AODM Rx			
Insulin	25.0%	14.0%	ns
Metformin	14.5%	36.0%	ns
Sulfonylurea	9.7%	11.0%	ns
Sitagliptin	5.0%	7.0%	ns
Empagliflozin	1.5%	11.0%	ns
Liraglutid	5.0%	36.0%	ns
Pioglitazone	5.0%	0%	ns

Anti-HTN Rx					
ACEI/ARB	64%		41%		p < 0.100
CCB	39%		30%		p < 0.100
BB	36%		35%		p > 0.100
Clonidine	9%		3%		p < 0.100
(r)ALA (mean mg)	634±458.5		0		
	Initial	**Final**	**Initial**	**Final**	
BMI (mean kg/m^2)	31.6±5.6	32.1±6.6	32.7±9.3	32.1±6.5	p > 0.100
A1c (mean mmol/mol)	6.22±0.9	6.61±0.6	6.7±0.9	6.25±0.5	p = 0.047
LVEF (mean %)	60±11.1	60±11.	68±11.8	60±8.1	p < 0.100
QTc (mean msec)	373±47.5	380±50.3	370±39.7	379±44.5	p > 0.100

Abbreviations:
2° Dx- Secondary Diagnosis;
ACEI- angiotensin converting enzyme inhibitor;
ARB- angiotensin renin blocker;
BB- beta-blocker;
CCB- calcium channel blocker;
HL-hyperlipidemia ;
Rx- therapy;

Group AD had significantly more males and higher A1C; there were insignificantly higher final BMI [44], lower LVEFs, more CHF, and less Metformin use, all tending unfavorably regarding survival. But 9% more took ACEI/ARBs (p<0.100). Control Group ND was 4 years older (p>0.100); QTc had no significance on SD, as SD increases when QTc is >450ms in males or >470ms in females [50]. Insignificantly more Group ND African Americans tends to favor SD [51].

(Table- 7). CAD causes most adult SDs [44]. Although more SD patients had CAD vs. survivors, CAD prevalence was insignificantly different in Groups AD, ND.

GROUP AA vs. GROUP ND

Improved Group AA survival occurred despite Group ND having a normal final BMI (p=0.067), less HTN (p=0.021), greater use of Empagliflozin (p<0.100), Metformin (p<0.100), lower final A1C (p=0.034), and fewer males (p<0.100), all favoring less SCD in Group ND. DMII attenuates gender differences in SD [42]. Group ND was 3 yrs. older (p=0.067) with more CAD (p < 0.100); all were revascularized (normal myocardial perfusion stress tests). Fewer in Group AA took insulin (p<0.100).Initially, Group AA had 18.4% VT (1 sustained) vs. 14.3% non-sustained in Group ND, p= 0.3559.

Table-7: Non-Survivor Patient Demographics (Sudden Death Patients)

	Group AD	**Group ND**	**p**
N	21	22	
Male	91%	41%	p < 0.100
Age (mean yrs)	66±12.3	70±11.5	p > 0.100
Ethnicity			
Caucasian	81%	73%	ns
African Am	11%	28%	ns
2° Dx			

HTN	68.0%		59.0%		ns
HL	96.0%		86.0%		ns
CAD	67.0%		73.0%		ns
CHF	38.0%		23.0%		ns
CKD	27.0%		30.0%		ns
Smoker	5.0%		4.5%		ns
AODM Rx					
Insulin	42.0%		45.0%		ns
Metformin	10.0%		45.0%		ns
Sulfonylurea	19.0%		13.6%		ns
Sitagliptin	11.0%		9.0%		ns
Empagliflozin	5.0%		13.6%		ns
Pioglitazone	5.0%		0%		ns
Anti-HTN Rx					
ACEI/ARB	73%		64%		p < 0.100
CCB	27%		11%		p < 0.100
BB	50%		64%		p > 0.100
HCTZ	25%		25%		p > 0.100
(r)ALA (mean mg)	548±306.8		0		
	Initial	**Final**	**Initial**	**Final**	
BMI (mean kg/m^2)	30.7±10.3	32.±11.2	30.3±10.2	28.8±11.0	p <0.100
A1c (mean mmol/mol)	7.74±1.0	6.30±0.6	6.59±0.9	6.00±0.6	p <0.100
LVEF (mean %)	57±10.5	48±9.1	59±10.4	61±8.4	p < 0.100
QTc (mean msec)	390±51.2	430±54.6	386±41.0	454±43.3	p > 0.100

Abbreviations:
HCTZ- hydrochlorothiazide.
*See Table-1 or Methods for other abbreviations

GROUP NA vs. GROUP AD

NA patients were 2 yrs. younger (p = 0.081); more hypertensive (p = 0.086); had greater use of Empagliflozin (p <0.100), Metformin (p<0.100), Liruglutid (p<0.100), higher final LVEFs (60% vs. 48%, p<0.100), fewer males (p<0.100), and less CAD (p<0.100; revascularized with normal stress tests), mostly favoring survival. Fewer in Group NA took insulin (p<0.100). Initially, Group NA had 0% non-sustained VT vs. 16.7% in Group AD, p= 0.1661.

Autonomic Measures

Mean Bx LFa, decreased in survivors (p=0.045), increasing in SCD (p=0.039). Bx RFa, increased in 55/90 patients (60%), by a mean 12.5% in survivors and severely decreased in 29/43(67%) non-survivors, mean --59.5%, (p<0.0001). SB increased 17.6% in survivors, but had a greater increase in SCD to > 2.5:+29.5% (p=0.064) (Table- 8).

Table-8: Comparison between Survivors and Sudden Cardiac Death patients, Mean P&S Measures. See Methods for parameters' normal ranges.

	Survivors (AA,NA)				Sudden Cardiac Death (AD,ND)			
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±2.3	1.35±1.5	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	1.0±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

Abbreviations:

Standing represents positive head-up posture, equivalent to head-up tilt.

*See Table 1 or Methods for other abbreviations

Non-Survivors demonstrated a more abnormal final alpha-S-response standing, SW (-24.4% vs. – 13.8% [p=0.066]), indicating greater Baroreceptor Reflex dysfunction, which increases SCD risk. PE upon standing developed more significantly in survivors (+65%) vs. SCD (+29%) because initial to final standing RFa increased in survivors vs. decreasing in SCD (p=0.022). In parallel, SCD patients experienced a dramatic 59.5% decrease in resting P in addition to SW. All P- and S- final values were lower in SCD, the lowest being resting P. Since HRV = S + P, HRV was lower in SCD (p<0.0001) mainly due to lower P.

Survivors

Group-AA, Survivors with (r) ALA (Table- 9)

Table- 9: Mean P&S measures for DM II Survivors on (r)ALA (Group AA).

DMII (r)ALA Survivors (Group AA)				**N=62**	
Age	66.5	**Range**:	48 to 89		
(r)ALA (mg)	637.1±458.5				
Population	**Initial**	**Final**	**Δ**	**p:Δ**	**p:ALA**
SB>2.5	13	4	-9	ns	ns
CAN	8	5	-3	0.08	0.004
BMI	32.2±5.6	32.1±6.6	-0.1	ns	ns
LVEF	63.2±11.1	60.7±11.0	-2.5	ns	ns
QTc	375.2±47.5	380.7±50.3	2.5	ns	ns
A1C	6.2±0.9	6.6±0.6	0.3	0.047	0.071
Bx LFa	1.03±2.0	1.08±1.7	0.06	0.095	ns
Bx RFa	**0.80**±1.3	**1.09**±0.6	**0.29**	**0.07**	**0.014**
Bx SB	1.80±1.4	2.10±1.8	0.31	ns	ns
Bx HR	70.2±13.2	68.9±12.0	-1.3	ns	0.089
Bx sBP	134.2±17.7	135.8±17.9	1.5	ns	ns
Bx dBP	73.8±12.2	68.5±10.1	5.3	0.019	0.009
Stand LFa	1.01±1.55	0.90±1.16	-0.11	0.073	ns
Stand RFa	0.58±1.85	0.91±0.77	0.34	0.053	ns
SW	37	33	-4	ns	0.097
PE	26	27	1	ns	0.098

Individuals		N=	No Δ	(+)	(-)
ΔSB			16	6	40
ΔHR			4	53	5
ΔsBP			10	15	37
ΔdBP			14	43	5
ΔBP			21	37	4
SW			24	21	17
PE			33	14	15

Abbreviations

(+)- improved;

(-)- declined;

Δ, change demonstrated;

Ns- not significant (p > 0.100);

*See Table 1or Methods for other abbreviations

A1C increased (increasing oxidative stress, p=0.047), inversely proportional to (r) ALA dosage (p=0.071); but resting RFa increased proportionally (p=0.014). Average resting Bx LFa increased (p=0.095) as did resting Bx RFa (p = 0.070). HRV increased.

The mean initial standing response was SW. At final testing, 4 patients' SW were relieved (p=0.097); consequently, BRS improved. One more patient demonstrated PE (p = 0.098) (standing RFa increased) proportional to (r)ALA dosage.

Group-NA, Survivors without (r) ALA (Table 10)

Table-10: Mean P&S measures for DM II Survivors not on (r) ALA (Group NA), the control group

DMII No (r)ALA Survivors (Group NA)				N=28
Age	63.2	Range:	45 to 88	
(r)ALA (mg)	0			
Population	Initial	Final	Δ	p:Δ
SB>2.5	5	6	1	ns
CAN	0	1	1	ns
BMI	34.2±9.3	32.1±6.5	-2.1	ns
LVEF	68.±11.0	62.8±8.1	-5.2	ns
QTc	372.3±.39.7	379.2±44.5	6.9	ns
A1C	6.7±0.9	6.3±0.5	-0.4	ns
Bx LFa	1.74±2.6	1.14±1.1	-0.60	0.075
Bx RFa	2.10±3.6	1.94±3.7	-0.16	ns
Bx SB	1.67±1.6	1.73±1.5	0.06	0.088
Bx sBP	135.3±21.1	138.1±20.8	2.8	ns
Bx dBP	72.8±12.4	70.8±8.9.	-2.0	0.049
Stand LFa	1.86±2.82	1.16±1.35	-0.70	0.092
Stand RFa	1.66±2.71	1.06±2.19	-0.60	ns
SW	16	14	-2	ns
PE	13	8	-5	ns

Individuals	N=	No Δ	(+)	(-)
ΔSB		9	6	13
ΔsBP		5	10	13
ΔdBP		4	22	2
ΔBP		8	19	1
SW		14	8	6
PE		19	7	2

Abbrevations

(+)- improved;

(-)- declined;

Δ- change demonstrated;

ns- not significant (p > 0.100);

*See Table 1 or Methods for other abbreviations

Similar to Group-AA, the average initial P&S levels are normal, and given their age, SB is high (but lower than Group AA and not > 2.5).Contrary to Group AA, final Bx LFa decreased (p = 0.075), as did Bx RFa (and HRV). SB increased (p = 0.088).

Standing, Group-NA initially demonstrated normal P- and slightly low S-responses. Individually, 57.1% demonstrated SW. Of these, 81.3% demonstrated PE. At final testing, 2 patients' SW were relieved; 5 relieved PE, different from the Group AA patients (p < 0.027).

Survivors' Mortality Risk

Thirteen % Group AA patients demonstrated CAN initially, improving to 8.1%, proportional to (r)ALA dose(p=0.004).Group AA was the only Group that increased resting Bx RFa, (Table 9). Group-AA's final RFa increased 36.2%, correlating with the dose of (r)ALA (p=0.014). Group AA's increase in resting Bx LFa (Table 9). So the SB change was insignificant. Group NA had no CAN initially; increasing to 3.6%. This group's average resting Bx LFa decreased (34.5%); Bx RFa fell 7.6%. SB (the average of 4 sec. ratios, not the ratio of these reported averages) significantly increased 3.6% (p=0.088), increasing MACE risk.

In Table-9 and Table-10, Group AA's Bx LFa and Bx RFa were initially lower than Group NA's (p < 0.100), indicating lower HRV. Group AA increased both, decreasing mortality risk (Table-4). Group NA decreased both Bx LFa (Table -10) (p = 0.075) and Bx RFa (p = ns), indicating an accelerated progression towards increased mortality risk (decreased HRV).

Non-Survivors

Group AD, Non-Survivors with (r) ALA (Table-11)

Initial P&S levels are below normal and lowest of all Groups

Table-11: Mean P&S measures for DM II Non-Survivors on (r)ALA (Group AD).

DMII (r)ALA Non-Survivors (Group AD)					N=21
Age	65.7	Range:	47 to 89		
(r)ALA (mg)	528.6±306.8				
Population	Initial	Final	Δ	p:Δ	p:ALA
SB>2.5	5	6	1	ns	ns
CAN	1	8	7	0.080	0.014
BMI	32.1±10.3	31.4±11.2	-0.8	ns	ns
Bx LFa	0.44±0.9	0.92±1.1	0.48	0.047	ns
Bx RFa	0.38±0.4	0.34±0.4	-0.04	0.098	0.033
Bx SB	2.13±2.3	2.72±2.4	0.59	ns	0.028
Bx sBP	133.9±22.7	139.0±24.4	5.1	ns	ns
Bx dBP	71.1±14.8	68.2±7.9	-2.9	ns	ns
Stand LFa	0.71±1.2	0.68±0.9	-0.03	ns	0.092

Stand RFa	0.58±1.1	0.24±0.2	-0.34	ns	ns
SW	16	12	-4	0.037	0.060
PE	12	7	-5	0.061	ns
Individuals		N=	No Δ	(+)	(-)
ΔSB			4	6	11
ΔsBP			6	2	13
ΔdBP			7	11	3
ΔBP			11	9	1
SW			11	3	7
PE			10	3	8

Abbreviations:

(+)-improved;

(-)-declined;

Δ-change demonstrated;

ns- not significant (p > 0.100);

*See Table 1or Methods for other abbreviations

(lowest HRV). Given their age, SB is high (but not > 2.5). Final LFa increased (p=0.047); RFa decreased (p = 0.098); and SB increased to 2.72. Resting P protects against VT/VF and silent ischemia [21, 32-36]; seven progressed to CAN (p =0.080), not surprising since initial BxRFa was so severely depressed. Group AD was beyond help.

Standing, 57% of Group AD initially demonstrated PE; 33 % ended with PE (p = 0.061) and 57 % ended with SW (p = 0.037) indicative of BRS dysfunction (increases SCD). Finally, Group AD's, average stand LFa was SW. These Sympathetic results are significantly similar to Group AA (p = 0.061). However, the P-responses, are different (p = 0.185).

Group ND, Non-Survivors without (r)ALA (Table-12)

Table-12: Mean P&S measures for DM II Non-Survivors not on (r) ALA (Group ND)

DMII No (r)ALA Non- Survivors (Group ND)				**N=22**
Age	70.2	Range:	47 to 90	
(r)ALA (mg)	0			
Population	Initial	Final	Δ	p:Δ
SB>2.5	7	5	-2	ns
CAN	3	5	2	0.020
BMI	30.6±7.5	28.8±7.3	-1.8	ns
Bx LFa	1.40±2.0	0.86±1.1	-0.54	0.100
Bx RFa	1.69±2.5	0.55±0.5	-1.14	0.020
Bx SB	1.93±1.5	2.55±2.8.	0.62	ns
Bx sBP	136.6±15.7	135.8±19.4	-0.9	0.059
Bx dBP	71.9±19.2	66.8±11.0	-5.1	0.034
Stand LFa	1.05±1.3	0.69±0.9	-0.36	ns
Stand RFa	1.05±1.3	0.54±0.9	-0.51	ns
SW	13	15	2	ns
PE	10	10	0	ns

Individuals	N=	No Δ	(+)	(-)
ΔSB		7	3	12
ΔsBP		17	5	0
ΔdBP		1	16	5
ΔBP		11	9	2
SW		10	5	7
PE		16	3	3

Abbreviations:

(+)- improved;

(-)- declined;

Δ-change demonstrated;

ns- not significant (p > 0.100);

*See Table 1or Methods for other abbreviations

Initial resting Bx LFa, resting Bx RFa, were normal; SB high for age (but not > 2.5 Final Bx LFa decreased, p = 0.100; Bx RFa severely decreased, p = 0.020. Two more patients (67%) developed CAN (p =0.020) in spite of initially good BxRFa .Group ND's initial standing P was normal, but S showed SW. Final average S-stand remained SW; P barely normalized. The P-responses as compared with the Group-AA are different (p = 0.106).

Mortality Risk

Resting Bx RFa decreased in both Groups (Table-11 and Table-12): 10.5%, Group AD and 67.5%, Group ND (p = 0.033); a higher risk of developing CAN. Final SB was > 2.5 in both, which we have shown increases MACE 700% [20].SB greater than 2.5 with CAN is particularly deadly in both Groups, and final average standing response was SW (impaired BRS), increasing SCD as well. Bx LFa increased in Group AD (Table-11) by 109.1% vs decreasing 38.6% in Group ND (Table-12. p = 0.100), causing increased SB in Group AD. In Group ND, despite the decrease in S, the severe decrease in resting Bx RFa increased SB anyway. Two more patients had CAN. Non-survivors' (r) ALA preserved their severely lowest P and S (LOWEST HRV) even in death. Group ND's final Bx LFa and Bx RFa fell severely to the 2nd lowest among all Groups. CAN and high SB were most frequent in Groups AD and ND.

Traditional Standards Comparison

Comparing the gold standard of CARTs, without isometric hand-grip, to any abnormality of P&S Monitoring for diagnosing DAN or CAN, CARTs' sensitivity was 48.2% of Group 1 and 30.0% of Group 2 patients; an overall unsatisfactory sensitivity of 41.4%.

Discussion

(1) NOH

NOH is caused by failure of the baroreceptor reflex and/or too low S tone. As an antioxidant, ALA can improve the baroreceptor reflex and S tone, in contrast to the commonly used medications, so it should affect healing of the disorder, rather than simply treating its symptoms. Furthermore, it uniquely reduces resting hypertension and endothelial dysfunction (52-56). Although only 28% of the patients were diabetic (Table 1), 59 of 89 (66% of all) patients responded to ALA. Sixteen of the 25 diabetics (64%) responded and 43 of 64(67%) non-diabetics (p = ns), suggesting that ALA may be equally effective for all patients with orthostatic dysfunction. Nineteen of 29 (66%) NOH and 40 of 60 (67%) OI patients responded to ALA (p = ns), furthering the above suggestion.

(r)ALA raised LFa (S activity) in all patients except in OI non-responders (Table 2). Treatment Δ BP was related to pretreatment S activity. Those with the lowest sitting to standing change in S activity were the non-responders (Table 3); perhaps droxidopa would be useful in these patients. Responders had both a decrease in mean sitting BP (145/72–125/68 mm Hg, pre- to post-(r) ALA treatment, mean dose 643 mg/d or ALA 949 mg/d), and an increase in Mean standing BP (120/70–129/71 mm Hg, pre- to post treatment). This Δ sitting BP indicates an improvement in resting hypertension and the Δ standing BP indicates an improvement in orthostatic dysfunction. OI non-responders demonstrated a +19 mm Hg (increase) in standing diastolic BP, which is vital in preserving coronary perfusion (Table-1 and Table- 2). In patients with coronary artery disease, a J-curve relationship has been reported between BP and major adverse events [57]. Given this J-curve of coronary flow and since major adverse cardiac events increase at diastolic BPs < 60 to 70 mmHg [57] the increase in diastolic BP in the OI non-responder group could have been considered a positive

OI response, but we defined a positive response as a standing decrease in only systolic BP less than -6 mm Hg, and the absence of syncope. Even though the OI non-responders' standing systolic BP fell 6 mm Hg or more (an average fall of 12 mmHg, Table 2), their diastolic BPs increased significantly (from a fall of 19 mm Hg to an increase of 2 mm Hg;p = 0.0068, Table 2). This improved outcome would raise the positive response rate to (r)ALA to 88% had we considered the J-curve of coronary perfusion.

Although previous human studies of the effect of ALA upon high BP have been mixed [58] it can reduce high BP, increase baroreceptor reflex afferent limb sensitivity, improve endothelial dysfunction, increase nitric oxide, and improve diabetic dysautonomia. In our 19 OH responders, mean ΔBP to standing from pre- to post-treatment was –28/–6 mm Hg (sitting to standing, pretreatment) to 0/+2 mm Hg (sitting to standing, post-treatment). To date, we know of no other pharmacologic treatment that both decreases resting hypertension and OH. Such treatment has the potential to reduce substantially major cardiovascular events such as stroke, congestive heart failure, myocardial infarction, and cardiovascular death (major adverse cardiac events), as well as therapeutic costs and side effects. Nausea, rare flushing, and biotin depletion are the only known side effects of (r)ALA or ALA, and are harmless or easily treatable. In the 20 control patients, S activity decreased, although ΔBP did not, possibly because their initial S activity was the highest of all groups. Regardless, the decrease in S activity may be the prelude to further decreases in BP, if therapy is not prescribed. Since S activity controls BP and BP changes with stand (and other activities), the persistent decrease in S activity with stand indicates that there is a continued drive to further decrease BP upon standing, exacerbating orthostatic dysfunction and the associated morbidity and mortality risks. Because these untreated patients' S activity might continue to fall, perhaps they should be started on (r) ALA or ALA.

(2) HTN

This study demonstrates improved HTN BP control on fewer prescriptions using adjunctive (r)-ALA in Group 1 (74% of patients at JNC 8 goal vs. 30.4% of Group 2 patients, p<0.001). We and others have shown (r)-ALA can reduce resting BP and in this study concomitantly may assist lowering standing BP [27,59]. Superficially, the medication administration profiles do not explain the improvement in BP control, as more Group 2 patients took beta blockers, CCBs, and ARB/ACEIs. It may be that (r)-ALA's favorable P&S effects significantly contributed to better HTN control via S-and P-dependent as well as its ANS-independent endothelial effects. Two Group 1 patients normalized BP solely by taking (r)-ALA. Based upon P&S measures, 17% of Group 1 patients had a change of drug class vs. 9% in Group 2. This likely was also beneficial. High SB corrected in 71% of Group 1 patients vs. none in Group 2, contributing to lowering HTN [59]. Amlodipine increases SB, while beta blockers and clonidine decrease SB; beta-blockers and ARB/ACEIs improve BRS; and non-dihydropyridine CCBs decrease BRS [59-64]. (r)-ALA is a powerful natural antioxidant that improves P&S function including BRS, nitric oxide levels, and endothelial dysfunction [26-27 and 59,61]. Sympathetic Withdrawal upon standing results in compensatory mechanisms to preserve perfusion of vital organs that include increasing S-tone, both supine and sitting. This exacerbates HTN, thereby causing its control to be more difficult. Sympatholytics, therefore, can worsen SW (only clonidine has a minimal adverse effect as it increases BRS [61-62 and 66] Group 1 patients significantly improved SW. This is consistent with improved BRS, probably by (r)-ALA and higher doses of Lisnopril and Losartan. P-excess (PE) upon standing is indicative of ANS dysfunction, and 9 of 23 (39%) of Group 1 vs. 5 of 23 (22%) of Group 2 patients initially displayed PE. PE may also trigger compensatory measures, including secondary S-excesses that increase BP.

The central alpha action of Carvedilol, Low Dose Serotonin Reuptake Inhibitors (SSRI), as well as Tricyclics (TC) may help to reduce PE. One Group 1 patient normalized PE and HTN with addition of (r)-ALA alone. Resting P&S measures were utilized in choosing medications as follows. If P&S balance (as measured by SB) was normal, then any anti-hypertensive was prescribed. If SB was high due to a relative, resting S-excess), then sympatholytics were chosen or adjusted. If SB was high due to low P, then sympatholytics were avoided and an ARB/ACEI and/or Diltiazem were chosen or adjusted. High dose (r)-ALA may increase resting P-activity and thereby lower SB. Upon standing, if SW was absent, then any antihypertensive was prescribed. If SW was demonstrated, then sympatholytics were avoided (excepting Clonidine) as was Diltiazem and Amlodipine, Hydralazine and/or high dose (r)-ALA prescribed. Diuretics were utilized only for dependent edema, since intravascular volume needed to be maintained. Low dose ARB/ACEI also might be prescribed. If PE presented, again intravascular volume should be preserved, so diuretics were avoided. Since an increase in S-activity is a compensatory mechanism to combat orthostasis, sympatholytics were avoided (except low dose carvedilol whose central alpha action reduces P-tone and possibly clonidine). Amlodipine is a good choice only if S-tone isn't high, since it increases S-activity.

Adjunctive low dose TC or SSRI would have useful to reduce P-activity, but we confined our therapy to traditional anti-hypertensives. The uncoupling of P&S function to Rs in HTN results in variable P&S profiles. Anti-hypertensives have variable P&S effects. Consequently, knowledge of S-and P-tone is essential for choosing the best anti-hypertensive drugs and (r)-ALA enhances their effectiveness, given (r)-ALA's ANS antioxidant effect which reduces ANS dysfunction secondary to the increased oxidative stress associated with HTN, chronic diseases and the aging process (Tables 13, 14 and 15 are illustrative).

Table 13: (Recidivism) 80 y/o Group 2 patient with recidivism due to PE standing. Medications: (A) 100 mg. Metoprolol and 100 mg Losartan/d; (B), (C): Metoprolol and Losartan were changed to Telmisartan 40/5/12.5 mg and Bystolic 20 mg/d. Bystolic increases standing P-tone (RFa) (long-term administration of Metoprolol would have lowered it) (C) resulting in a compensatory increase in S-tone (LFa) to maintain BP; Amlodipine also increases S-tone. Bystolic should be switched back to Metoprolol or to Clonidine, low dose TC or SSRI could be added, Amlodipine discontinued and (r)-ALA added.

LFa (bpm^2)	0.18	0.2	0.38
RFa (bpm^2)	0.14	0.18	0.07
SB	1.3	1.12	5.41
BP (mmHg)	175/68	149/59	193/79
Standing			
LFa (bpm^2)	0.46	0.82	4.1
RFa (bpm^2)	0.69	0.28	5.96
BP (mmHg)	176/76	139/66	179/68

Abbreviations

BP-Blood Pressure;

bpm2-beats per minute2;

mmHg-millimeters Mercury;

LFa-Low Frequency area (a measure of sympathetic activity);

RFa-Respiratory Frequency area (a measure of parasympathetic activity);

SB-Sympathovagal Balance.

Table 14: 76 y/o Group 1 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 theses abnormalities (Same as Table 13).

Sit	**(A)**	**(B)**
LFa bpm^2	0.30	0.40
RFa bpm^2	1.22	0.36
SB	2.7	1.08
BP mmHg	166/65	136/65
Standing		
LFa bpm^2	22.32	0.15
RFa bpm^2	3.50	0.41
BP mmHg	172/67	147/65

Table 15: 76 y/o Group 1 patients with SW on Losartan 100 mg/d and Amlodipine 10 mg/d (A). Medications were changed to Clonidine 0.1 mg bid and (r)-ALA, correcting SW (B) (Same as Table 13).

Sit	**(A)**	**(B)**
LFa bpm^2	0.09	0.01
RFa bpm^2	0.18	0.03
SB	0.5	0.25
BP mmHg	190/86	151/65
Standing		
LFa bpm^2	0.02	0.02
RFa bpm^2	0.04	0.02
BP mmHg	165/86	150/60

(3) DMII SCD

Administration of (r)ALA resulted in a 43% RRR of SCD, rather than the demographics that may have favored survival in Controls. Rapid separation of the SCD curves (Figure-1) strongly implies treatment effect. Lower initial HRV, Group 1 vs. Group 2, $p<0.0001$, predicted SCD: AA 1.83 vs. AD 0.82, p= 0.0171; NA 4.14 vs. ND 3.09, p=0.0051. More initial CAN ((rALA 10.8% vs. Controls 6%, p= 0.0013) and initial BRS dysfunction ((r)ALA 63.9% vs. Controls 58%, p= 0.0044) predicted SCD better than recorded VT. (r)ALA preserved P and S vs. Controls. Those with the lowest P&S (HRV) died. Reduced HRV is a common thread in SCD. Only Group AA demonstrated an increase in final, resting P(and HRV); P reduces VT/VF and silent ischemia [9,41 and 68-70], increasing 36.2% vs. a 7.6% decrease for Group NA, a 10.5% decrease for Group AD, and a 67.5% decrease for Group ND. The progressive increase in the decline of resting P indicated mortality, from the lowest decline in resting P in Group NA, to the next greater decline in Group AD, to those with the greatest decline, Group ND ($p < 0.001$). Changes in P were proportional to (r)ALA dose. These trends are not found in the other physiologic measures: BMI, LVEF, and QTc; and only different between the survivors' A1Cs (Group AA vs. Group NA, p = 0.034). Since SW and PE can cause both NOH and systemic HTN [71-72], DMII patients not on (r)ALA might experience orthostasis, or labile HTN. HTN could be secondary (neurogenic), and is over twice as well controlled treating the primary SW± PE [71] than treating the BP per se.

(r)ALA preserved P and S, especially P, in survivors and non-survivors. (r)ALA is a natural, powerful thiol antioxidant. (r)ALA restores and recycles vitamins A, C, E and glutathione [9 and 71-72]. It improves hyperglycemia, endothelial dysfunction, nitric oxide levels (protective against VT/VF, silent ischemia [73-76]), reduces nuclear kappa B, and is essential for certain mitochondrial oxidative enzymes. (r)ALA prevents diabetic-induced reduction of the afferent limb function of the baroreceptor reflex (BR) [77], reducing MACE. SW, found in 50% to 74% of patients, failed to correct in 88% of Group NA and all SCD patients. SW disappeared substantially only in Group AA, 59.7% reduced to 53.2%, p = 0.097, decreasing SCD risk.

The other most common, and most important, P&S finding was low resting P in 56% to 81% of patients, improving only in Group AA (initial 56%, final 9%; p = 0.070), vs. Group NA (initial 29%, final 43%; p= 0.098), and worsening most severely in Group ND patients, a 67% reduction in RFa vs.10.5% reduction in Group AD (p = 0.020). CAN decreased 37.5% in Group AA vs.an increase of 67% in Group ND. Twenty-nine% of Group AD had high SB vs.50% in Group ND (p = 0.037). More CAN in Group 2 increased mortality; high SB increased mortality risk in Group 1.Group 1's autonomic profiles generally stabilized or improved(HRV); Group 2's deteriorated, especially a 59.5% decrease in resting P, reducing Group 2's ability to combat VT/VF, silent ischemia, and life stresses. Standard deviations decreased over time, with the most decreases correlating with the (r)ALA dosage.

The pleotropic effects of (r)ALA likely contributed to SCD reduction. Increased nitric oxide improves P&S, endothelial dysfunction, protects against VT/VF and silent ischemia [73-76]. Decreased nitric oxide levels prolong QTc [73]. Improved mitochondrial function should reduce SCD also [78]. Asymptomatic SW (BR dysfunction) was the most common presentation of DAN. Approximately 90% of patients had HTN, presumed to be essential (primary), not possibly secondary to DAN. Ultimately, CAN with, or without, dangerously high SB can develop while under our care. How simple it is to diagnose and treat dysautonomia early; how tragic it may be not to.

Limitations

These are all single center studies with relatively small numbers of patients. More studies need to be done.

Conclusions

(1) NOH

(r)ALA or ALA appears to safely improve NOH and OI by increasing standing S activity, as measured by LFa, and thereby standing BP responses to stand.

(2) HTN

P&S-assisted treatment of HTN, with adjunctive (r)-ALA for dysautonomia is feasible and results in more normalized BP control within one year. Our hope is that reduced long-term medication costs, mortality, and morbidity will follow if BP control is sustained. A randomized, prospective clinical outcome study should be done.

(3) DMII SCD

(r)ALA given to geriatric DMII patients with even minimal dysautonomia reduced SCD 43%, p=0.0076, due to improved P & S, increasing HRV, probably assisted by its pleotropic effects, altering DAN's natural history. Since CARTs detected only 41% of dysautonomia, non-CARTs screening of DMII is recommended. The ANX 3.0 Autonomic Monitor provides the only independent measures of P&S. It is our preferred assessment, allowing (r)ALA titration. If CARTs is done and normal, non-diagnostic, or not done, we recommend empiric (r)ALA 600mg/d.

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