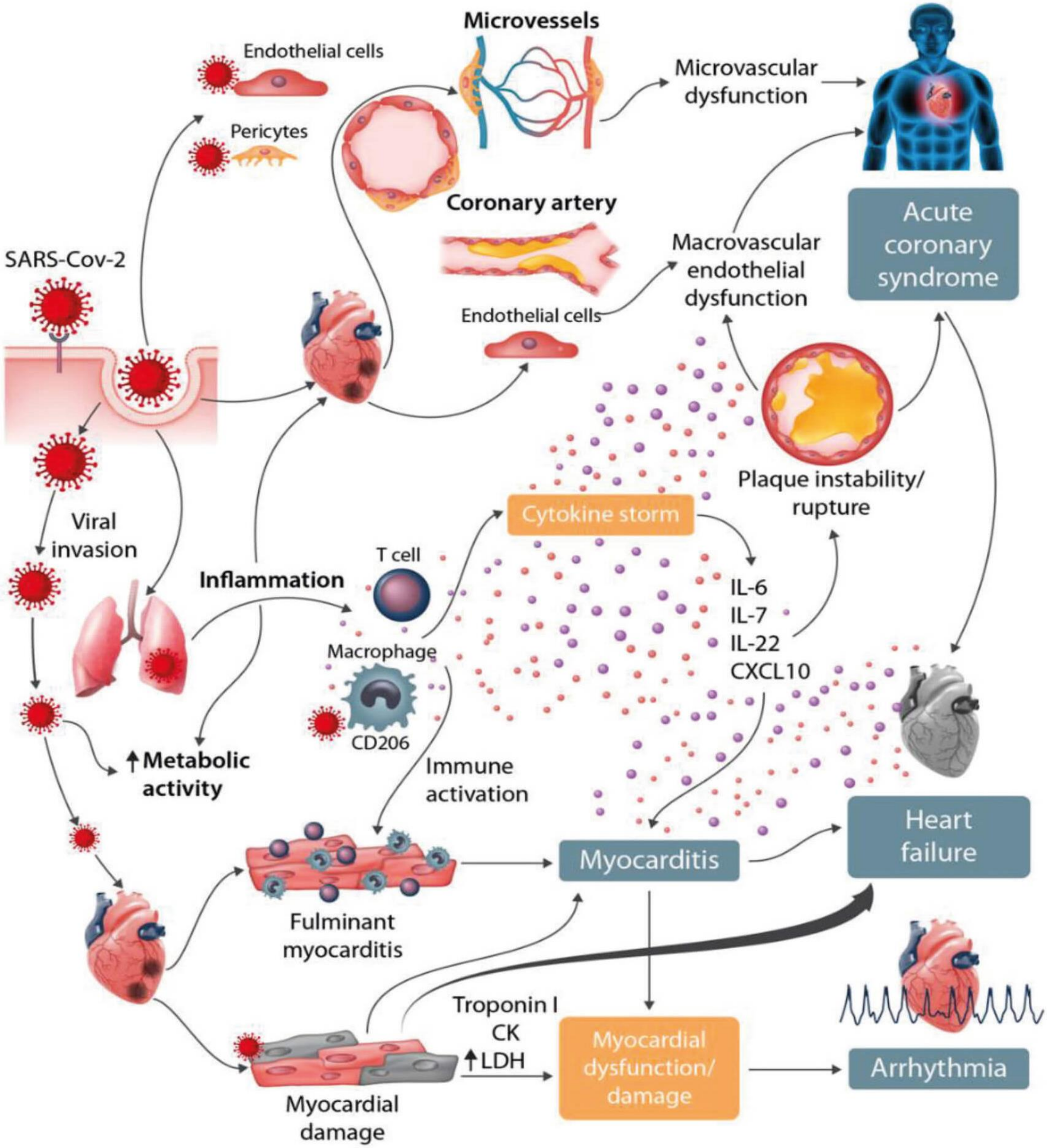

Re-Print- COVID-19 Cardiac Complications: Is an Easy, Safe treatment Strategy Right under Our Noses?

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Authored by

Gary L Murray*

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

Published Date

December 11, 2020

Published in the Journal of

Clinical Cardiology and Cardiovascular Interventions

Auctores Publishing, LLC

16192 Coastal Highway

Lewes, DE 19958,

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Journal of Clinical Cardiology and Cardiovascular Interventions
Gary L Murray*

Open Access

Research Article

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Gary L Murray
Director of research, The Heart and Vascular Institute, Germantown, TN USA.
Corresponding author: Gary L Murray, The Heart and Vascular Institute, 7205 Wolf River Blvd, Germantown,

Received date: November 19, 2020; **Accepted date:** December 01, 2020; **Published date:** December 11, 2020

Citation: Gary L Murray (2020) Re-Print- COVID-19 Cardiac Complications: Is an Easy, Safe treatment Strategy Right under Our Noses?. *J, Clinical Cardiology and Cardiovascular Interventions*, 3(13); **Doi**:10.31579/2641-0419/111

Abstract

Background: Many chronic conditions, as Diabetes Mellitus (DM) and cardiovascular Diseases, suffer Major Adverse Cardiac Events (MACE): congestive heart failure (CHF), Ventricular Tachycardia (VT), Ventricular Fibrillation (VF), Acute Coronary Syndromes [ACSs], and Sudden Cardiac Death (SCD). Acute infections, like COVID-19, also involve oxidative stress, leading to increased Sympathetic tone (S) and decreased Parasympathetic tone (P), increasing Sympathovagal Balance (SB) and MACE. The antioxidant (r) Alpha Lipoic Acid (ALA) improves SB. The antianginal Ranolazine (RAN), also an antioxidant, is an antiarrhythmic. Our studies of their effects on MACE, in DM, and non-DM patients with CHF, ventricular arrhythmias and SCD are reviewed herein, as our findings may apply to acute diseases, such as COVID-19.

Methods: (1) In a case-control study, 109 CHF patients, 54 were given adjunctive off-label RAN added to ACC/AHA Guideline therapy (RANCHF). MACE and SB were compared with 55 NORANCHF patients; mean f/u 23.7 mo. (2) 59 adults with triggered premature ventricular contractions (PVCs), bigeminy, and VT were given off-label RAN. Pre- and post-RAN Holters were compared; mean f/u 3.1 mo. (3) 133 DM II with cardiac diabetic autonomic neuropathy were offered (r) ALA; 83 accepted; 50 refused. P&S were followed a mean of 6.31 years, and SCDs recorded.

Results: (1) 70% of RANCHF patients increased LVEF 11.3 EFUs ($p \leq 0.003$), SCD reduced 56%; VT/VF therapies decreased 53%. (2) 95% of patients responded: VT decreased 91% ($p<0.001$). (3) SCD was reduced 43% in DM II patients taking (r) ALA ($p=0.0076$).

Conclusion: RAN, (r) ALA treat CHF, VT, and prevent SCD. Trials in COVID-19 are needed.

Keywords: ranolazine; (r) alpha lipoic acid; sudden cardiac death; congestive heart failure; COVID-19

Abbreviations:

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;

ACE2R: Angiotensin Conversion Enzyme 2 Receptor;

ACS: Acute Coronary Syndrome;

ANG II: Angiotensin II;

CaMK: Ca++/Calmodulin Kinase II;

CHF: Congestive Heart Failure;

bpm2: Beats Per Minute Squared;

rALA: (r)Alpha Lipoic Acid;

RAN: Ranolazine;

SB: Sympathovagal Balance;

VF: Ventricular Tachycardia;

VT: Ventricular Tachycardia;

2° Dx: Secondary Diagnosis;

ACEI: Angiotensin Converting Enzyme Inhibitor;

ARB: Angiotensin Renin Blocker;

BB: Beta-Blocker;

CCB: Calcium Channel Blocker;

HL: Hyperlipidemia;

Rx: Therapy.

Introduction

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, perhaps most significantly to mitochondria. The heart and the nervous system have the highest number of 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.

COVID-19 is an example of a serious acute condition causing oxidative stress (cytokine storm), with hypertension or hypotension in approximately 50% of patients, acute cardiac injury in >8%, CHF in 23%, VT/VF in 5.9%, and fatal cardiac arrest in 8.2% [1]. S-activity increases and P-activity decreases, increasing Sympathovagal Balance (SB=S/P at rest) [2]. Very low P (<0.1 bpm2), is associated with Cardiovascular Autonomic Neuropathy (CAN), which with high SB (>2.5) increases MACE (CHF, VT, VF, ACSs, and SCD) [3] (Table1).

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
Positive 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	0.5	0.81

Note: *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 5 0.33 in Group 3.*

Table 1: High SB best predicts cardiac events

Antioxidants decline during chronic illness or aging. Fortunately, antioxidants may be supplemented, including (r) ALA and Ranolazine (RAN).

(r) ALA is a natural thiol antioxidant with 2 enantiomers, the (r) enantiomer much more active. (r) ALA restores and recycles vitamins A, C, E, and glutathione, improves hyperglycemia, endothelial dysfunction, nitric oxide levels, reduces nuclear kappa B activity, and is essential for certain mitochondrial oxidative enzymes [4]. (r) ALA prevents diabetic-induced reduction of the afferent limb function of the baroreceptor reflex (BR), reducing SCD [5]. (r) ALA reduced SCD in DM II patients by 43% via improving S, P, and SB [6] (Figure 1).

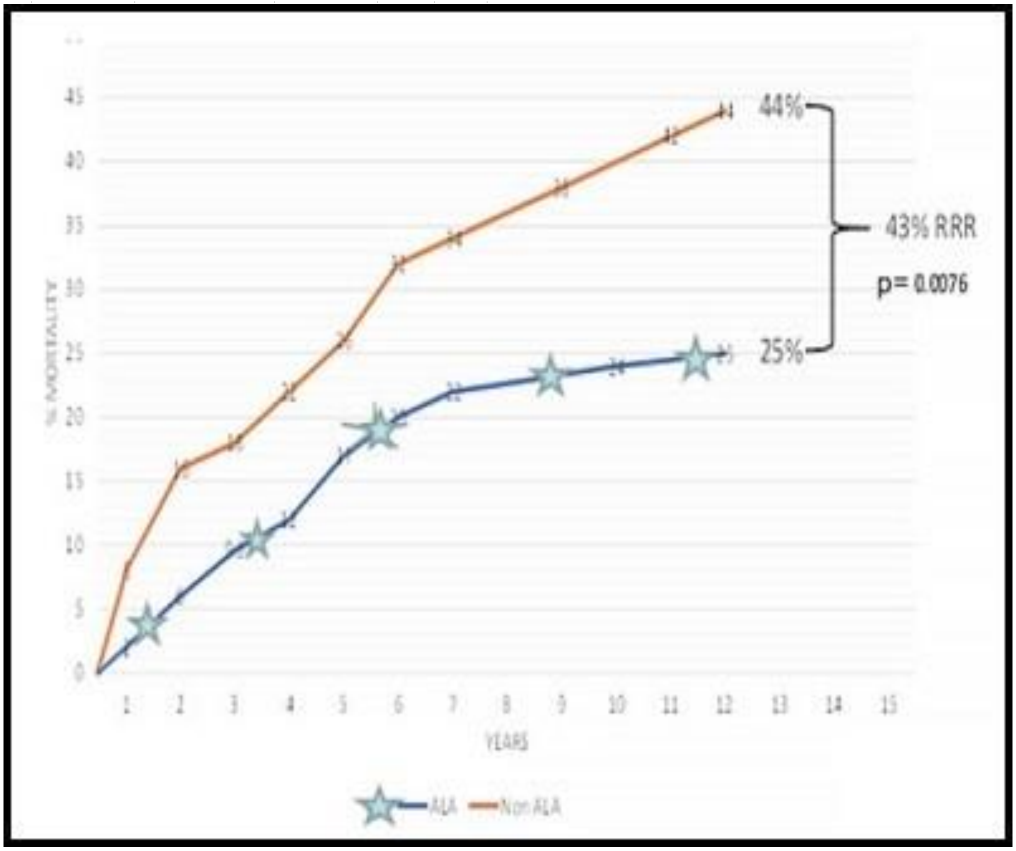

Figure 1: SCD in DM II with/without (r) ALA.

Despite advances in pharmacologic management [7-11], including Entresto, and device therapy [12], improvement in left ventricular (LV) function in CHF is usually mild. The late sodium current (INa) from faulty gating of cardiac sodium channel 1.5 (Nav1.5) due to oxidative stress-related Ca++ / Calmodulin Kinase II (CaMK II) phosphorylation causes a calcium (Ca++) overload via the Na+ /Ca++ exchanger (NCX), resulting in diastolic dysfunction and microvascular compression; worsening LV function [13]. RAN binds to amino acid F1760 of Nav1.5, reducing the late INa, reducing Ca++ overload by 50%. RAN' s antioxidant effect reduces C- Reactive Protein (CRP), Interleukins 1 and 6 (IL-1, IL-6), and Tumor Necrosis Factor-alpha (TNFα), while increasing anti-inflammatory Peroxisome Proliferator-Activated Receptor ɣ (PPAR-ɣ) [14-16]. RAN blocks neuronal sodium channel 1.7 (Nav1.7) in a strongly use-dependent manner [17,18], directly altering ANS function. These actions of RAN improved LV function and P&S measures in CHF [19].

RAN has electrophysiological effects with no known proarrhythmia [13]. Inhibition of the late sodium current (INa) suppresses early and delayed afterdepolarizations (EAD/DADs), reducing triggered ventricular ectopy [14]. DADs are due to spontaneous release of Ca++ from the sarcoplasmic reticulum, and EADs are directly due to Ca++ entry through the Ca++ window current, except in Purkinje fibers where EADs are due to the late INa window current. The diastolic transient inward current in the long QT syndrome 3 is caused by Ca++ overload and is inhibited by RAN [20]. RAN is an effective and safe treatment of adults with symptomatic PVCs [21]. RAN prolongs the QT interval by approximately 6 msec due to IKr inhibition, EADs/DADs are suppressed and there is no transmural dispersion of repolarization, so RAN is protective against torsades. RAN selectively inhibits the atrial Nav1.8 channel in its inactivated state, so can be used to treat or prevent Atrial Fibrillation [22,23].

Research Methodology

(1)CHF study

Matched CHF patients were given RAN (1000 mg p.o., b.i.d.) added to guideline-driven therapy (RANCHF, 41 systolic, 13 diastolic) or no adjuvant therapy (control, NORANCHF, 43 systolic, 12 diastolic) [19]. Echocardiographic LVEF and P&S measures were obtained at baseline and follow-up (mean 23.7 months). P & S function was assessed noninvasively using the ANX 3.0 autonomic function monitor (P&S Monitoring, Physio PS, Inc., Atlanta, GA).which computes simultaneous, independent measures of P & S activity based on continuous, time-frequency analysis of heart rate variability (HRV) with concurrent, continuous, time-frequency analysis of respiratory activity (RA) [24-29]. The following variables were recorded: seated resting (5 min.) P was computed from spectral power in the Respiratory Frequency area (RFa) defined as the spectral power within a 0.12 Hz-wide window centered on the fundamental respiratory frequency (FRF=modal peak of the time-frequency RA curve in the HRV spectrum). FRF is a measure of vagal outflow. S (LFa) was defined as the remaining spectral power, after computation of RFa, in the low frequency window (0.04-0.15 Hz) of the HRV spectrum. Normal ranges for P&S are: sitting LFa and RFa=0.5 to 10.0 bpm2; sitting SB (LFa/RFa) is age dependent =0.4 to 1.0 for geriatrics, otherwise 0.4-2.5; stand LFa is ≥ 10% increase with respect to (wrt) sitting; stand RFa is a decrease wrt sitting. Exhalation/ inhalation (E/I) ratio and RFa response were computed from 1 min. of deep breathing (paced breathing at 6 breaths/min); Valsalva ratio (VR) and LFa during a series of short Valsalva maneuvers (≤ 15 seconds); postural BP, LFa, RFA and 30:15 ratio in response to 5 min. of head-up postural change (quick stand followed by 5 min. of quiet standing).

Cardiac autonomic neuropathy (CAN) was defined as $P<0.10$ bpm2, reflecting very low P. A high Sympathovagal Balance (SB=LFa/RFa) was defined as a resting LFa/RFa ratio >2.5 High SB and CAN define a high risk of SCD and ACS [19,30-35]. The average SB reported is the average of the ratios recorded during the sampling period, not a ratio of averages. The 30:15 ratio is the ratio of the 30th R-R interval after a quick head-up postural change (standing) to the 15th R-R interval after standing. The 30:15 ratio reflects the reflex bradycardia upon standing dependent upon sympathetic vasoconstriction. The Valsalva ratio is the ratio of the longest R-R interval to the shortest R-R interval during a 15 sec. Valsalva maneuver. The E/I ratio is the ratio of the heartbeat interval during peak exhalation over that during peak inhalation during paced breathing. The E/I ratio is a measure of vagal tone, as are the 30:15 and Valsalva ratios. P&S measures were recorded every 6 mo.

(2) PVC study

59 patients with symptomatic PVCs were identified from full-disclosure Holters. Doses of 500 - 1,000 mg RAN b.i.d. were given to 34% and 66% of patients, respectively, and Holters were repeated (mean 3.1 months) [21].

(3)DM II study

One hundred thirty-three consecutive DM II patients underwent P & S testing via ANX 3.0 Autonomic Monitoring [6]. 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, those who 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. 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. Diabetic autonomic neuropathy (DAN) was defined as any abnormality of S or P, or high SB. CAN was defined as $P<0.10$ bpm2. Median follow-up was 5 yrs. Mean age was 66 y/o. There were 83 males, 50 females. Holters ± event monitors were performed if clinically indicated: Groups AA 60%, AD 57.1%, NA 60.7%, ND 31.8%.

Statistical analysis

(1)CHF study

We determined that we needed 50 patients per group to have a sufficient sample size using an alpha of 0.05, difference of means of 6 units and expected standard deviation of 15 units with a power of 80%.All statistics are performed under SPSS v 14.1. Student t-tests are performed as two-tailed with equal variance. Significance values are determined on the null hypothesis that pre- and post-treatment values are equal.

(2) PVC study

All statistics, including means, standard deviations, and Student's t-tests, were performed under SPSS v 14.1 (IBM). Student's t-tests were performed as two-tailed tests with equal variance. Significant values were determined on the null hypothesis that the pre- and post-treatment values were equal.

(3) DM II study

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. For all 3 of these previously reported studies, all patients signed informed consent.

Results (1) CHF study

LVEF increased in 70% of RANCHF patients, an average of 11.3 units

Mean LVEF remained unchanged in NORANCHF patients (Table 2). P&S measures indicated CAN in 20% of NORANCHF patients at baseline and 29% at follow-up (increasing in both groups). Initially, 29% of patients had SB>2.5. RAN normalized SB in over 50%; the NORANCHF group had a 20%increase in patients with high SB (Table 3 - Arrhythmia prevented analysis in 8 RANCHF and 6 NORANCHF patients). Independent of hemodynamics (BioZ®), P and S measures determined MACE. SB ≤ 2.5 was the strongest predictor (Table 4).

Healthcare outcomes

Although underpowered for this, the study showed RAN reduced MACE 40%: SCD 56%, PCD or amiodarone therapy for VT/VF 53%, and CHF admissions by 23%.

	ΔEFU ≤ -7	-6 ≤ EFU ≤ +6	ΔEFU ≥ +7	p value
RANCHF (N=54)	1 (2%)	27 (50%)	26 (48%)	<0.001
NORANCHf (N=55)	8 (15%)	43 (78%)	4 (7%)	<0.001S

Table 2: Change (Δ) in LVEF.

Variables	RANCHF (N=46)			NORANCHF (N=49)		
	Initial	Final	p	Initial	Final	p-value
Rest						
SB	2.42	1.98	0.019	2.61	4.28	0.039
LFa (sympathetic)	4.91	2.49	0.034	1.74	3.42	0.015
RFa pwasyncoliteci	1.64.	1.56	0.047	0.70	0.93	0.012
Deep Breathing						
LFa	15.8	13.7	0.065	7.66	11.8	0.267
VR	1.11	1.09	0552	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	1.26	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

Table 3: Autonomic measures in patients without arrhythmias precluding analysis.

Variables	Pts w/Events		No event	
	Pre/Post-RAN	P (LVEF)	Pre/Post-RAN	P (Bx)
Rest				
LFa	2.26 & 0.74	<0.001	1.87 & 1.05	0.011
RFa	1.04 & 0.19	<0.001	0.88 & 1.06	0.006
SB	6.18 & 3.04	<0.001	1.26 & 1.08	0.025
ΔLVEF	0.30 to 0.36	0.018	0.35 to 0.44	0.005
Stand				
LFa	0.83 & 1.81	<0.001	1.08 & 2.57	0.012
RFa	0.53 & 0.82	<0.001	0.86 & 3.01	0.045

Table 4: P&S measures and LVEF in 46 RANCHF patients with (N=15) and without (N=31) events without arrhythmias precluding analysis.

(2) PVC study. Patient demographics

Mean age was 63 years; 58% were males; mean LVEF was 0.60, 8% having a history of CHF (2 systolic, 3 diastolic); 73% were hypertensive; 34%had CAD; all revascularized; 34% were taking a beta blocker; the mean RAN dose was 866 mg/d. Holter results of the responders (95% of patients) to RAN are in Table 5. All patients experienced palpitations, 65% dizziness, and 33% fatigue. These symptoms improved in proportion to PVC reduction: 100% of responders reported fewer palpitations, 90% less fatigue, and dizziness improved in 73%.

Variables	Pre-RAN	Post-RAN	p-value
Total QRS	1,02,667	99,826	p=NS
Isolated PVCs	13,329	3,837 (-71%)	p<0.001
Ventricular bigeminy	4,168	851 (-80%)	p<0.001
Ventricular couplets	374	81 (-78%)	p<0.001
Runs VT	56	5 (-91%)	p<0.001

Table 5: Holter results of patients responding to ranolazine.

Over 40% of patients had ≥ 10,000 PVCs/d, >25% had >20,000 PVCs/d.RAN reduced PVCs by 71% (mean: 13,329 to 3,837; p<0.001). 24% (14/59) of patients had >90% decrease in PVCs, 34% (20/59) had 71 to 90% decrease, and 17% (10/59) had 50 to 70% decrease. Ventricular bigeminy was reduced by 80% (4,168 to 851; p<0.001), couplets were reduced by 78% (374 to 81; p<0.001), and VT reduced by 91% (56 to 5; p<0.001). The maximum reduction in PVCs was from 47,211 with 29,573 ventricular bigeminy to 13 PVCs per 24 hours, and no bigeminy. No proarrhythmia, and no significant side effects occurred. Approximately 6% of patient's reported constipation, dizziness, nausea, or headache. One of the initial three non-responders had response 1.5 years later with 16,890 PVCs and 10, 114 ventricular bigeminy reduced to 3 PVCs/d.

(3)DMII. Patient demographics. Table 6 represents the survivor demographics. Group AA had significantly more males and higher final A1C; initial LVEF was insignificantly lower, factors not favoring survival [31-33]; tending to favor survival: insignificantly fewer with CAD (all CAD patients in the study were revascularized with normal stress tests), less Chronic Kidney Disease (CKD); and significantly more Angiotensin blocker therapy (ACEI or ARB) [34,36], 11% more (r) ALA patents required insulin. Group NA had significantly more females and lower final A1C; insignificantly higher initial LVEFs and insignificantly more patients on Empagliflozin, Liraglutid, and Metformin, tending to favor survival [37-41].

Variables	Group AA	Group NA	p value
N	62	28	
Male	61%	39%	p<0.100
Age (mean years)	67	64	p>0.100
Ethnicity			
Caucasian	74%	73%	ns
African Am	23%	24%	ns
Other	3%	2%	ns
2° Dx			
HTN	95.00%	86.00%	ns
HL	80.00%	82.00%	ns
CAD	24.00%	37.00%	ns
CHF	21.00%	20.00%	ns
CKD	25.00%	35.00%	ns
Smoker	5.00%	4.00%	ns
AODM Rx			
Insulin	25.00%	14.00%	ns
Metformin	14.50%	36.00%	ns
Sulfonylurea	9.70%	11.00%	
Sitagliptin	5.00%	7.00%	
Empagliflozin	1.50%	11.00%	
Liraglutid	5.00%	36.00%	
Pioglitazone	5.00%	0%	

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	0	
	± 458.5		

	Initial	**Final**	**Initial**	**Final**	
BMI (meankg/m2)	31.6 ± 5.6	32.1 ± 6.6	32.7 ±	9.332.1 ±	6.5p>0.10
A1c (meanmg/dl) %	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 ± 11.0	68 ± 11.8	60 ± 8.1	p<0.100
QTc (meanmsec	373 ± 47.5	380 ± 50.3	370 ± 39.7	379 ± 44.5	p>0.100

Table 6: Survivor patient demographics.

Table 7 shows Non-Survivors. Group AD had significantly more males and higher A1C; there was insignificantly higher final BMI [36], 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 >450 ms in males or >470 ms in females [42]. Insignificantly more Group ND African Americans tends to favor SD [43]. CAD causes most adult SDs [36]. Although more SD patients had CAD vs. survivors, CAD prevalence was insignificantly different in Groups AD and ND

Variables	**Group AD**	**Group ND**	**p value**
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	68.00%	59.00%	ns
HL	96.00%	86.00%	ns
CAD	67.00%	73.00%	ns
CHF	38.00%	23.00%	ns
CKD	27.00%	30.00%	ns
Smoker	5.00%	4.50%	ns
AODM Rx			
Insulin	42.00%	45.00%	ns
Metformin	10.00%	45.00%	ns
Sulfonylurea	19.00%	13.60%	ns
Sitagliptin	11.00%	9.00%	ns
Empagliflozi	5.00%	13.60%	ns
Pioglitazone	5.00%	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 (meankg/m2)	30.7 ±10.3	32.4 ± 11.2	30.3 ± 10.2	28.8 ± 11.0	p<0.100
A1C (mranmmol/mol)	7.74 ± 1.0	6.3 ± 0.6	6.59 ± 0.9	6 ± 0.6	p<0.100
LVEF (mean%)	57 ± 10.5	48 ± 9.1	59 ± 10.4	61 ± 8.4	p<0.100
QTc (meanmsec)	390 ± 51.2	430 ± 54.6	386 ± 41.0	454 ± 43.3	p>0.100

Table 7: Sudden death patient demographics.

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), favoring less SCD. Group ND was 3 yrs. older (p=0.067) with more CAD (p<0.100). 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.

Group NA vs. Group AD

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), mostly favoring survival. Fewer in Group NA took insulin (p<0.100). Group NA had 0% non-sustained VT vs. 16.7% in Group AD, p=0.1661.

Autonomic measures

Table 8 shows 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).Non-survivors demonstrated a more abnormal final alpha-S-response standing, sympathetic withdrawal (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 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

(Table 9) shows 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). Resting Bx LFa increased (p=0.095) as did resting Bx RFa (p=0.070). HRV increased.

Variables	Survivors (AA, na)				Sudden Cardiac Death (AD, ND)			
N	90				43			
	Initial	Final	Δ%	p	Initial	Final	Δ%	p-value
Sitting (Rest)								
LFa (bmp2)	1.25 ± 2.19	1.1 ± 1.55	-12	p=0.045	0.89 ± 1.60	0.93 ± 1.09	4.5	p=0.039
RFa (bmp2)	1.2 ± 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 (bmp2)	1.16 ± 2.05	1 ± 1.22	-13.8	p=0.056	0.9 ± 1.28	0.68 ± 0.91	-24.4	p=0.005
RFa (bmp2)	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 8: Survivors and SCD patients, Mean P&S Measures. See Methods for parameters' normal ranges.

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

DMII (r) ALA Survivors (Group AA)				**N=62**	
Range: 48 to 89					
Age	66.5				
(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	0.8 ± 1.3	1.09 ± 0.6	0.29	0.07	0.014
Bx SB	1.8 ± 1.4	2.1 ± 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	0.9 ± 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			No Δ	(+)	(-)
Δ SB			16	6	40
Δ HR			4	53	5
Δ sBP			10	15	37
Δ dBP			14	43	5
Δ BP			21	37	4
SW			24	21	17
PE			33	14	15

Note: (+) =improved; (-) =declined; Δ=change demonstrated; ns=not significant (p>0.100)

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

Group-NA (Table 10) shows that similar to Group-AA, the 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).

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	-0.6	0.075
Bx RFa	2.1 ± 3.6	1.94 ± 3.7	-0.2	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	0.049
Stand LFa	1.86 ± 2.82	1.16 ± 1.35	-0.7	0.092
Stand RFa	1.66 ± 2.71	1.06 ± 2.19	-0.6	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

Note: (+) =Improved; (-) =Declined; Δ=Change demonstrated; ns=Not significant (p>0.100)

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

Survivors' mortality risk

A total of 13% 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) was mitigated by the increase in resting Bx RFa, so the SB change was insignificant. Group NA had no CAN initially, increasing to 3.6%. This group' resting Bx LFa decreased (34.5%); Bx RFa fell 7.6%. SB significantly increased 3.6% (p=0.088), increasing MACE risk. In Tables 9 and 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 9). Group NA decreased Bx LFa (Table 10) (p=0.075), Bx RFa (p=ns), and HRV, indicating an accelerated progression towards increased mortality risk.

Non-survivors

Group AD. (Table 11) shows that Initial P&S levels are below normal and lowest of all Groups (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 [44,45]; seven progressed to CAN (p=0.080), not surprising since initial Bx RFa was so severely depressed. Group AD was beyond help. Standing, 57% of Group AD initially demonstrated PE; 33% ended with PE (p=0.061); 57% ended with SW (p=0.037) (BRS dysfunction increases SCD). Finally, Group AD's stand LFa was SW. These Sympathetic results are significantly similar to Group AA (p=0.061). The P-responses are different (p=0.185)

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	0.08	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	0.05	ns
Bx RFa	0.38 ± 0.4	0.34 ± 0.4	-0.04	0.1	0.033
Bx SB	2.13 ± 2.3	2.72 ± 2.4	0.59	ns	0.028
Bx sBP	133.9 ± 22.7	139 ± 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	0.04	0.06
PE	12	7	-5	0.06	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

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

Group ND. (Table 12) shows Initial resting Bx LFa and Bx RFa, were normal; SB is 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 Bx RFa.

Group ND's initial standing P was normal, but S showed SW. Final S stand remained SW; P barely normalized. The P-responses as compared with the Group-AA are different (p=0.106).

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	0.02
BMI	30.6 ± 7.5	28.8 ± 7.3	-1.8	ns
Bx LFa	1.4 ± 2.0	0.86 ± 1.1	-0.5	0.1
Bx RFa	1.69 ± 2.5	0.55 ± 0.5	-1.1	0.02
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	-0.4	ns
Stand RFa	1.05 ± 1.3	0.54 ± 0.9	-0.5	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

Note: (+) =Improved; (-) =Declined; Δ=Change demonstrated; ns=Not significant (p>0.100)

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

Non-Survivors' Mortality risk

Resting Bx RFa decreased in both Groups (Tables 11 and 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.SB greater than 2.5 with CAN is particularly deadly in both Groups, and final standing response was SW, increasing SCD as well. Bx LFa increased in Group AD (Table 6) by 109.1% vs decreasing 38.6% in Group ND (Table 12) p=0.100), increasing 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 HRV among all Groups. CAN and high SB were most frequent in Groups AD and ND.

Discussion

COVID-19 binds to the angiotensin 2 receptor (ACE2R), increasing angiotensin 2 (Ang II), resulting in cardiovascular inflammation, fibrosis, and oxidative-stress myocardial injury. [1] Cytokines and other immune factors (oxidative stress) typically result in increased S and decreased P, increasing SB. [2] The same myocardial and autonomic changes occur in non-COVID CHF (the neurohumoral paradigm).

Congestive heart failure

Improvements in LV function and outcomes in systolic CHF have been attributed to pharmacologic therapy addressing the neurohumoral paradigm, and device therapy [7-12]. However, even more improvement is needed. This has triggered stem cell trials [46, 47] and a search for new pharmacologic agents such as Entresto, which when added after RAN, has not improved LVEF or P & S further in my patients. To date, no therapy in diastolic CHF (LVEF ≥ 50%) has shown improved survival. We have yet studied RAN in these patients. RAN is a first in class drug. It reduces Ina, reducing the Ca++overload caused by the late INa via the Na+/Ca++ exchanger 50% [13]. Since LVEF is accepted as one of the most important prognostic indicators in CHF (50), we focused on its change. Certainly, RAN's antioxidant action could have contributed to the increases in LVEF. RAN also inhibits neuronal Nav1.7 via the local anesthetic receptor in a use-dependent fashion [17,18]. Consequently, RAN alters ANS function directly, improving P&S measures. High SB with critically low P (CAN) indicate high mortality risk, and have been associated with SCD, CHF and ACS [3,4,44,48]. This study is the first to correlate CHF outcomes with changes in both LVEF and P&S measures. RAN increased LVEF by 6.4 EFUs in systolic CHF patients and 9.5 EFUs in LVEF ≥ 40% CHF (Table 3). In the NORANCHF group, final LVEF fell 1 EFU and 0.5 EFU in these groups. In systolic RANCHF patients, the increase in LVEF was solely due to a decrease in LVIDs [19]. In LVEF ≥ 40% RANCHF patients, the increase in LVEF was due to a slight increase in LVIDd (suggesting increased filling) coupled with a slight decrease in LVIDs (suggesting improved emptying). Only 1/54 (2%) RANCHF patients decreased LVEF by ≤ -7 EFUs, and 26/54 (48%) RANCHF patients increased LVEF by ≥ +7 EFUs, with the remaining 50% of patients showing little LVEF change (p<0.001, Table 2). In the control group, 8/55 (15%) decreased LVEF by ≤ −7EFUs, and only 4/55 (7%) patients increased LVEF by ≥+7EFUs, with the remaining 43/55 (78%) demonstrating little change. LVEF is more than 6 times as likely to increase and 1/8th as likely to decrease following RAN therapy. RAN increased LVEF by ≥ +7 EFUs in 17/41 (41.5%) systolic CHF patients vs. 9/13 (69%) of LVEF ≥ 40% CHF patients (p<0.001). Furthermore, when RAN increased LVEF by ≥ +7 EFUs, 9/26 (35%) patients had a history of CAD, whereas 17/26 (65%) did not (p<0.001). Since almost 80% of the CAD patients were revascularized, and only 14% had a positive stress test, we feel the smaller increases in LVEF in CAD patients were due to LV scarring secondary to remote myocardial infarctions. Finally, whether LVEF increased by ≥ +7 EFUs did not depend upon the maximum tolerated dose of beta-blocker (94% took carvedilol), as the mean daily dose differed by only 0.5 mg. Table 3 presents the P&S and LVEF data without regard to clinical outcomes. RANCHF patients demonstrated a decrease in SB from 2.42 to 1.98 (p=0.019), resulting from a reduction in LFa, a sympatholytic effect. Sympatholytics, such as beta-blockers, are cardioprotective. This decrease in SB is associated with reduced CAN risk. NORANCHF patients almost doubled their initially high-normal SB because of a marked increase in LFa, increasing the risk for MACE. The ANS responses to standing were more normal after RAN, indicating improved ANS function and reduced risk of orthostasis. Orthostasis not uncommonly limits the tolerability of beta-blockers and ACE-Is/ARBs in CHF patients. Conversely, NORANCHF patients displayed a more abnormal standing response during follow-up, resulting from a decrease in LFa (SW) consistent with worsening of BR function, increasing the risk for orthostasis. In contrast to the dramatic LFa changes noted in both groups, RFa changes were very small, consistent with the lack of significant changes in the Time Domain Ratios, and CAN was not improved. The lack of a significant impact upon CAN means RAN's reduction of SB might be an important mitigating factor reducing the CV risk of CAN. Differences in ANS measures in patients with or without events are presented in Table 4. S and SB were higher and initial LVEF lower in patients with events, although both groups increased LVEF: + 6 EFUs and + 9 EFUs in patients with and without MACE, respectively, consistent with our study regarding SB as the best predictor of MACE. While this study was a nonrandomized trial and underpowered to make final health outcome assessments, we found a qualitative reduction in the composite endpoint of cardiac death, CHF admissions and therapies for VT/VF in the RANCHF group. There was a 40% event reduction, with 57% fewer SCDs, 60% fewer VT/VF therapies and 20% fewer CHF hospitalizations. The initial LVEF was lower in MACE patients than in non-MACE patients with or without RAN. Only the RANCHF group increased LVEF during follow-up, and the increase was more in patients without events. The increase in MACE patients' LVEF was the same as the LVEF increase of the entire systolic RANCHF group (+ 6 EFUs), yet RANCHF patients had 40% fewer events. When SB was ≤ 2.5 or LVEF was≥ 0.32, 81% or 79% of subjects, respectively, were MACE free; when SB was>2.5, 59% of patients suffered MACE vs. 50% of patients when LVEF was<0.32. Recently, it was proposed that diastolic CHF be defined as CHF with LVEF ≥ 0.50 [49]. Had we used this definition, only one of our diastolic RANCHF patients would have remained, increasing the systolic RANCHF group to 50 patients. With a new definition, RAN would have increased LVEF≥ +7 EFUs in 26/53 (49%) systolic CHF patients, an increase from the 17/41(41.5%) herein reported (p<0.001), with RAN being the last add-on therapy.

Triggered PVCS

RAN has several electrophysiological effects with no known proarrhythmia (detailed previously) [50-52]. EADs and DADs trigger PVCs. Some clinical scenarios of EAD/DAD-mediated ventricular arrhythmias include CHF, catecholaminergic polymorphic VT, hypokalemia, left ventricular hypertrophy (LVH), long QT syndrome, and cocaine use [52-57]. Our patients met criteria for ventricular parasystole (VP) [58]. This was the second study reporting effects of RAN on PVCs in humans, but the first focusing exclusively on triggered ventricular ectopy. VP (PVCs with variable coupling, fusion, interpolation, and a mathematical relationship with R-R intervals) occurs in 1of 1,300 patients and can be a highly symptomatic arrhythmia. Prognosis depends upon any coexisting cardiac disease. Rarely does VF or syncope occur, and VT is slower than reentrant VT. Several drugs have been tried as treatment for VP. Verapamil produced a satisfactory response in 18% of treated patients [59]. A report of two patients responding to adenosine has been published [60]. Dilantin was successful in one patient [61]. Cardiac pacing succeeded in two patients [62]. Amiodarone produced good results in nine patients [63]. Only 33% of patients with VP responded to the usual sodium channel blockers, but ablation is frequently successful. Activation of late INa (for example, by phosphorylation by Ca++/ calmodulin kinase ll activated by oxidative stress), may be a common myocardial response to stress. Therefore, RAN may have a therapeutic role in treating many cardiac conditions, including unstable ischemic patients with PVCs and patients with atrial fibrillation, since RAN selectively inhibits atrial Nav 1.8 in its inactivated state [22,23]. RAN was very well tolerated, with only 6% of patients experiencing headache, dizziness (a direct CNS effect), nausea, or constipation, with no known organ toxicity with an exception of possibly worsening pre-existing severe chronic renal disease, especially in DM. In canine ventricular wedge preparations, RAN did not induce torsades de pointes, reduced the action potential duration of M cells, and suppressed EADs induced by d-sotalol [64]. These are potential explanations of why RAN administration caused no proarrhythmia in this study. RAN is metabolized by CYP 3A so that inhibitors of this enzyme, such as ketoconazole, diltiazem, verapamil, macrolide antibiotics, HIV protease inhibitors, and grapefruit juice, increase RAN levels. Inhibitors of g-glycoprotein increase plasma levels two-to threefold. RAN increases digoxin concentrations 1.4- to 1.6-fold, and simvastatin C max is doubled other statin doses may need reduction as well. The patient population herein reported seems reasonably typical of adults who would be referred to a cardiology practice primarily for ventricular arrhythmia evaluation and therapy. Patients were essentially Medicare-age with multiple comorbidities (high risk COVID-19), but well-preserved LVEF and highly symptomatic with palpitations, dizziness, and fatigue. Syncope and cardiac arrest were not methods of presentation.

SCD in Diabetes mellitus II

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 ((r) ALA 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); produces VT/VF and silent ischemia [4,31,43,45], 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 resting in 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. (r) ALA preserved P and S, especially P, in survivors and non-survivors. (r) ALA increases nitric oxide levels (protective against VT/VF, silent ischemia [65,66]), reduces nuclear kappa B, and is essential for certain mitochondrial oxidative enzymes. Decreased nitric oxide levels prolong QTc [67,68]. SW, found in 50% to 74% of patients, failed to correct in 88% of Group NA and all SCD patients. SW decreased only in Group AA, 59.7% 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. a 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 a 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 oxidative stress. 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. Improved mitochondrial function should reduce SCD [69]. Asymptomatic SW was the most common presentation of DAN. Approximately 90% of patients had HTN, presumed to be essential (primary), not possibly secondary to DAN per se. Ultimately, CAN with, or without, 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 **(Figure 2).**

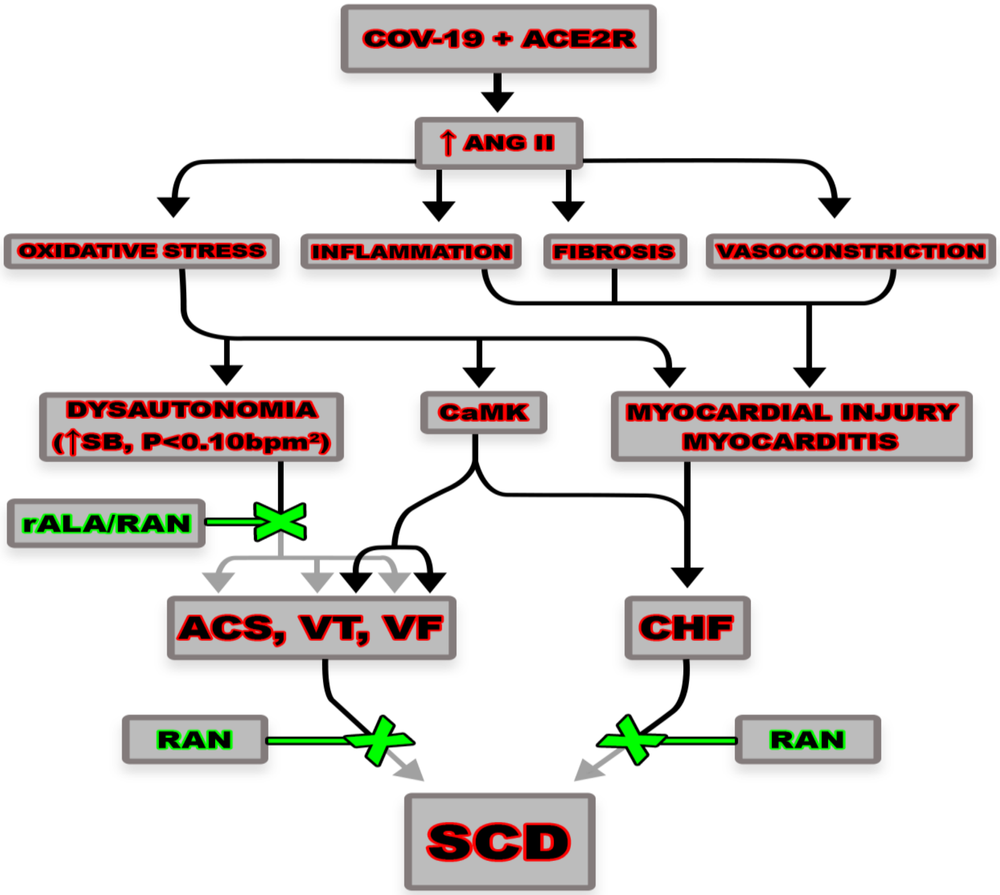

Figure 2: CoV-19 and SCD.

Limitations

Congestive heart failure

This is a single-center study. Recently, it was proposed that diastolic CHF be defined as CHF with LVEF ≥ 0.50. Had we used this definition, only one of our diastolic RANCHF patients would have remained, increasing the systolic RANCHF group to 50 patients. With a new definition of systolic CHF requiring an LVEF<0.50 (instead of ≤ 0.40), RAN would have increased LVEF ≥ +7 EFUs in 26/53 (49%) systolic CHF patients, an increase from the 14/41 (34%) herein reported (p<0.001), with RAN being the last add-on therapy. Using spectral analysis of HRV to estimate cardiac sympathetic activity in CHF has its limitations. The sinoatrial node becomes less responsive to norepinephrine and acetylcholine, so HRV decreases despite high norepinephrine levels [70]. Therefore, absolute cardiac LFa is inversely related to sympathetic outflow to muscle. Spectral analysis measures the modulation of autonomic neural outflow to the heart. SB reflects this modulation, and an SB>2.5 has a positive predictive value of 61% for MACE. In comparison to Metaiodobenzylguanidine(MIBG) imaging to assess cardiac sympathetic activity, only 29% of CHF patients with high MIBG washout suffered MACE within a mean follow-up of 31 months [71].

Triggered PVCS

This is a single-center open-label study. A larger, randomized prospective study might be useful in confirming these results. Furthermore, RAN can suppress the more common reentrant PVCs. Reentrant patients were not studied, but if RAN were successful therapy because of its safety, then RAN could be the first drug choice to treat the majority of patients with symptomatic PVCs.

SCD in Diabetes Mellitus II

This was not a double-blind, randomized, placebo-controlled study. Also, in autopsy studies, not all SDs are cardiac.

CONCLUSION:

Both RAN and (r) ALA share being antioxidants as one of their mechanisms of action. Thus, both could mitigate the life-threatening CHF, VT/VF, and SCD caused by oxidative stress due to chronic diseases or disorders, or severe acute diseases. To conclude our example of COVID-19, Figure 2 presents the progression from COVID-19 induced cytokine storms to SCD. Upon hospital admission, all patients could be started on (r) ALA 300mg bid if P & S testing is unavailable. If troponin, echocardiogram, or cardiac MRI indicate cardiac involvement, RAN 1000mg po bid, should be given. For ventilator-dependent patients, RAN has been safely administered I.V in animals (70), and (r) ALA given per feeding tube along with I.V. RAN.RAN probably can be safely crushed and given 250mg per feeding tube every 3 hours.

Acknowledgement

Joseph Colombo, PhD for his invaluable assistance and advice.

Conflicts of Interest

None.

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DOI:10.31579/2641-0419/111