Expert Review
Volume 9:7, 2021

Journal of Cardiovascular Diseases & Diagnosis

ISSN: 2329-9517 **Open Access**

Is an Easy, Safe Management Strategy for the Life-Threatening Cardiac Complications of COVID-19 Right Under our Noses?

Gary L. Murray*

Director of Clinical Research, The Heart and Vascular Institute, Germantown, USA

Abstract

Background: Many chronic conditions, as diabetes (DM) and cardiovascular Diseases, suffer Major Adverse Cardiac Events (MACE): i myocarditis, 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 anti-anginal Ranolazine (RAN), also an antioxidant, an anti-arrhythmic. 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: 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. 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. 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 yrs, and SCDs recorded.

Results: (1) 70% of RANCHF patients increased LVEF 11.3 EFUs (p≤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).

Conclusions: 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.

Introduction

Many chronic and serious pathologies cause an over-production of oxidants, including reactive oxygen and nitrogen species (ROS, NOS, respectively), e.g. oxidative stress. While some level of oxidants are required by the immune system as a first-line defense against pathogens and for u programmed cell death and general house-keeping, 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, therefore, more susceptible to oxidative stress. Then as the heart and the Parasympathetic and Sympathetic (P&S) nervous systems become disordered, the P&S disorder accelerates cardiovascular disease, resulting in a downward spiral, often long before disease become symptomatic. Further, in addition to collecting oxidants for beneficial use, the immune system is primarily responsible for applying antioxidants to neutralize excess oxidants.

COVID-19 is an example of a serious acute condition that may cause oxidative stress (cytokine storm). COVID-19 causes 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%. Survivors may be burdened with chronicity of these acute abnormalities [1]. The immune and autonomic nervous systems interact adversely via oxidative stress. This interaction increases S-activity and decreases P-activity, thereby increasing Sympathovagal Balance (SB = S/P at rest) [2]. Very low P (< 0.1 bpm^2), is associated with Cardiovascular Autonomic Neuropathy (CAN), which with high SB (> 2.5) increases the odds (OR) of MACE (CHF, VT, VF, ACSs, and SCD) over 700% [3] (Table 1).

Antioxidants production declines during chronic illness or aging. Fortunately, antioxidants may be supplemented, including (r) ALA and Co-Enzyme Q-10, for example. Some pharmacological agents have antioxidant properties too,such as the anti-anginal, Ranolazine (RAN), and the beta-blocker Carvedilol. Here we investigate (r) ALA and 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. It 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) , improving survival [5]. (r) ALA reduced SCD in DM II patients by 43% via improving S, P, and SB [6] (Figure 1).

Despite advances in pharmacologic management [7-11], including Entresto, and device therapy [12], improvement in left ventricular (LV) function

Table 1. High SB best predicts cardiac events.

	Events				
	Sensitivity	OR	Specificity	PPV	NPV
SB >2.5 (all)	0.59	7.03 (CI 4.59-1078)	0.83	0.64	0.80
+MPI (CD)	0.31	1.93 (CI 0.90-4.16	0.88	0.67	0.62
LVEF ≤0.33 (CHF)	0.67	3.46 (CI 1.49-8.05)	0.67	0.50	0.81

***Address for Correspondence:** Gary L. Murray, Director of Clinical Research, The Heart and Vascular Institute, Germantown, USA, Tel: +19015073100; Fax: 1905073101; E-mail: drglmurray@hotmail.com*

Received 02 August 2020; **Accepted** 23 July 2021; **Published** 30 July 2021

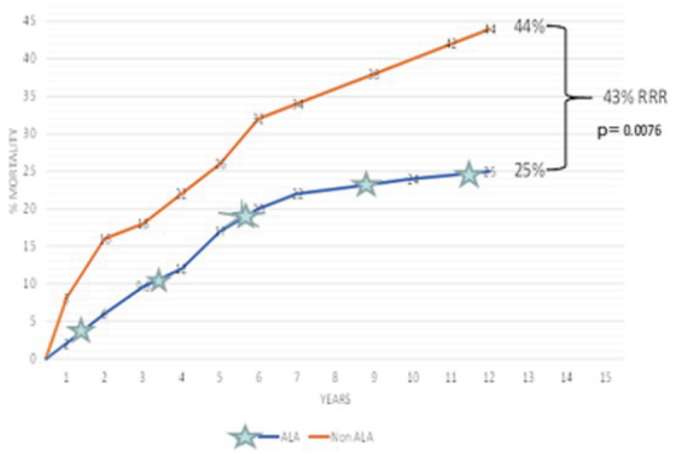


Figure 1. SCD in DM II with/without (r) ALA.

in CHF, is usually mild. The late sodium current (INa) from faulty gating of cardiac sodium channel 1.5 ($Na_{v1.5}$) due to oxidative stress-related Ca^{++} / Calmodulin Kinase II (CaMK II) phosphorylation in CHF causes a myocellular 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 $Na_{v1.5}$, reducing the late I_{Na}, reducing myocellular 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 γ (PPAR-γ) [14-16].

RAN blocks neuronal sodium channel 1.7 ($Na_{v1.7}$) in a strongly use-dependent manner via the local anesthetic receptor [17,18]. Therefore, RAN directly alters function of the P&S branches of the autonomic nervous system (ANS). These actions of RAN resulted in favorable changes in LV function and P&S measures in CHF [19].

RAN has several electrophysiological effects with no known proarrhythmia [13]. Inhibition of the late sodium current (I_{Na}) suppresses early and delayed afterdepolarizations (EAD/DAD), thereby reducing triggered ventricular ectopy [14-19]. DAD are due to spontaneous release of Ca^{++} from the sarcoplasmic reticulum, and EAD are directly due to Ca^{++} entry through the Ca^{++} window current, except in Purkinje fibers where EAD are due to late I_{Na} 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]. Although the QT interval is prolonged by approximately 6 msec due to I_{Kr} inhibition, there is no transmural dispersion of repolarization, so RAN is protective against Torsades De Pointes. RAN also selectively inhibits the atrial $Na_{v1.8}$ channel in its inactivated state, so can be used to treat or prevent Atrial Fibrillation [22,23].

Literature Review

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). 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); seated resting S was computed from spectral power in the Low-Frequency area (LFa, 0.04-0.15 Hz); exhalation/inhalation (E/I) ratio and P response (RFa) were computed from 1min. of deep breathing (paced breathing at a paced 6 breaths/min); Valsalva ratio (VR) and S (LFa) during a series of short Valsalva maneuvers (≤15 seconds); postural BP, LFa, RFA and 30:15 ratio in response to 5min. of head-up postural change (quick stand followed by 5 min. of quiet standing). Cardiac autonomic neuropathy (CAN) was defined as P<0.10 bpm^2, reflecting very low P. P (RFa) was 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 was identified from the time-frequency analysis of RA. Effectively, FRF is a measure of vagal outflow as it affects the heart. 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. 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 that is dependent upon sympathetic vasoconstriction. The Valsalva ratio is the ratio of the longest R-R interval to the shortest R-R interval during a 15sec. Valsalva maneuver. The E/I ratio is the ratio of the heart beat interval during peak exhalation over that during peak inhalation during paced breathing. The E/I ratio is a measure of, more or less, vagal tone, as are the 30:15 and Valsalva ratios. P&S measures were recorded every 6mo.

Fifty-nine (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).

One hundred thirty-three 133 consecutive DM II patients underwent P&S testing via ANX 3.0 Autonomic Monitoring. Normal ranges for P&S are: sitting LFa and RFa = 0.5 to 10.0 bpm^2; SB 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. 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 1 hr 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<0.10bpm^2. 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%.

The abbreviations are: △: 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.

Statistical analysis

Continuous data were assessed for normality with normally distributed data analyzed using Student *t*-tests and non-normally distributed data assessed using a Mann-Whitney test. Dichotomous data were analyzed using the Chi-square test or Fischer's Exact Test. A p-value of ≤0.05 was considered significant. 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 1.4. 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.

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. 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

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, 28% of patients had SB >2.5. RAN normalized SB in over 50% of these; whereas the NORANCHF Group had a 20% increase in patients with high SB (Table 3). Independent of hemodynamics (Bio Z®), P and S measures determined MACE. SB ≤2.5 was the strongest predictor. Table 4 is illustrative.

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%.

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. 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%.

Holter results of the responders (95% of patients) to RAN are in Table 5.

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 hour, and no bigeminy, accompanied by a robust resolution of the patient's incapacitating fatigue. No proarrhythmia, and no significant side effects occurred. Approximately 6% of patients reported one or more of the following: 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.

Demographics: Survivor demographics: Group AA had significantly more males and higher final A1C; their initial LVEF was insignificantly lower, factors not favoring survival [36-39]; tending to favor survival were insignificantly fewer with CAD (although all AA and NA patients were revascularized with normal stress tests), less Chronic Kidney Disease (CKD); and significantly more Angiotensin blocker therapy (ACEI or ARB, p<0.100) [36-40]. 11% 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 [41-44] (Table 6).

Non-survivors: Group AD had significantly more males and higher A1C; there were insignificantly higher final BMI [39], 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 [45]. Insignificantly more Group ND African Americans tends to favor SD [46]. CAD causes most adult SDs [39]. Although more SD patients had CAD vs. survivors, CAD prevalence was insignificantly different in Groups AD and ND (Table 7).

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. 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.

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.

Table 2. Change (Δ) in LVEF.

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

Table 3. Autonomic measures.

	RANCHF (N=46)			NORANCHF (N=49)		
	Initial	**Final**	**P**	**Initial**	**Final**	**P**
			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 (parasympathetic)	1.64	1.56	0.047	0.70	0.93	0.012
			Deep Breathing			
RFa	15.8	1.37	0.065	7.66	11.8	0.267
E/I Ratio	1.11	1.09	0.552	1.11	1.11	0.156
			Valsalva Challenge			
LFa	35.6	29.0	0.050	17.8	11.8	0.187
VR	1.20	1.24	0.359	1.17	1.19	0.753
			Head-Up Postural Change Challenge (Stand)			
LFa	2.63	2.13	0.006	2.83	1.28	0.011
RFa	2.20	0.76	0.002	0.82	0.90	0.011
30:15 Ratio	1.16	1.09	0.075	1.16	1.17	0.068
LVEF	0.34	0.41	0.0002	0.38	0.34	0.125

Table 4. Baseline and follow-up (pre- and post-RAN) P&S measures and LVEF in 46 RANCHF patients with (N-=15) and without (N=31) events.

	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 5. Holter results of patients responding to ranolazine.

	Pre-RAN	**Post-RAN**	***p*-Value**
Total QRS	102.667	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 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 mg/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 (mean msec)	373±47.5	380±50.3	370±39.7	379±44.5	p > 0.100

Autonomic measures: Survivors and SCD patients initial to final 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).

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

Table 7. Sudden death patient demographics.

	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	32.4±11.2	30.3±10.2	28.8±11.0	p < 0.100
A1C (mran 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

Table 8. Survivors and SCD 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±2.33	1.35±1.50	+12.5	p = 0.079	1.11±1.93	0.45±0.47	-59.5	p = 0.054
SB 1.23 ±1.50	1.76±1.47	2.07±1.49	+17.6	p = 0.064	2.03±1.92	2.63±2.60	+29.5	p = 0.064
Standing								
LFa (bmp^2)	1.16±2.05	1.00±1.22	-13.8	p = 0.056	0.90±1.28	0.68±0.91	-24.4	p = 0.005
RFa (bmp^2)	0.97±1.70	1.75±1.95	+80.4	p = 0.051	0.82±1.21	0.58±0.66	-29.3	p < 0.001

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). 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: 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) (Table 10).

Survivors' mortality risk: 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'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 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 both Bx LFa (Table 10) (p =0.075) and Bx RFa (p =ns), indicating an accelerated progression towards increased mortality risk (decreased HRV).

Group AD, Non-Survivors with (r) ALA: 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 [4,37,47,48]; seven progressed to CAN (p =0.080), not surprising since initial BxRFa was so severely depressed. Group AD was beyond help (Table 11).

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: Initial resting Bx LFa and resting 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 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) (Table 12).

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), resulting in a higher risk of developing CAN. Final SB was > 2.5 in both, which we have shown increases MACE 700% (3). 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.

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	0.080	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**	**0.070**	**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			**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

(+) , improved; (-) , declined; △, change demonstrated; ns, not significant (p > 0.100) ; See Methods for other abbreviations

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	68.0±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

(+) , improved; (-) , declined; △, change demonstrated; ns, not significant (p > 0.100) ; See Methods for other abbreviations

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

(+) , improved; (-) , declined; △, change demonstrated; ns, not significant (p > 0.100) ; See Methods for other abbreviations

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

(+) , Improved; (-) , Declined; △, Change demonstrated; ns, Not significant (p > 0.100) ; See Methods for other abbreviations

Bx LFa increased in Group AD (Table 6) 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 HRV among all Groups. CAN and high SB were most frequent in Groups AD and ND.

Discussion

Continuing our example of COVID-19, 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).

In the past 30 years, improvements in LV function and outcomes in systolic CHF have been attributed to pharmacologic therapy addressing the neurohumoral paradigm, together with the advent of device therapy [7-12]. However, even more improvement is needed. This has triggered stem cell trials [49] 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 so far. 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 intramyocellular Ca^{++} overload caused by the late INa via the Na^{+}/Ca^{++} exchanger 50% [13]. This improves diastolic, and microvascular dysfunction, and resulted in improved LV systolic function [19]. Since LVEF is widely 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 potentially alters ANS function directly, improving P&S measures. High sympathetic tone (high SB) with critically low parasympathetic activity (CAN) indicates high mortality risk, and have been associated with SCD, CHF and ACS [3,4,47,51]. 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 diastolic CHF (Table 3). In the NORANCHF group, final LVEF fell 1 EFU in systolic CHF patients and 0.5 EFU in diastolic CHF patients. These LVEF changes represent mean values of the cohort groups. In systolic RANCHF patients, the increase in LVEF was solely due to a decrease in LVIDs [19]. In diastolic RANCHF patients, the increase in LVEF was due to a slight increase in LVIDd (suggesting increased diastolic filling) coupled with a slight decrease in LVIDs (suggesting improved systolic 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). Increases in the RANCHF patients' LVEF were sufficient to avoid defibrillator implantation in 10 subjects, resulting in substantial cost savings. 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. LVEF can increase regardless of the initial LVEF. RAN increased LVEF by ≥+7 EFUs in 17/41 (41.5%) systolic CHF patients vs. 9/13 (69%) diastolic 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 or not 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 0.5mg.

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) mainly resulting from a reduction in LFa, a sympatholytic effect. Sympatholytics, such as beta-blockers, are known to be cardio-protective. This protection is at least in part due to a decrease in SB (balance) toward 1.0 indicating less sympathetic activity and a relative increase in parasympathetic activity and it is associated with reduced CAN risk. NORANCHF patients almost doubled their initially high-normal SB as a result of a marked increase in LFa with only a small increase in RFa, 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 doses of beta-blockers and ACE-Is/ARBs CHF patients can tolerate. 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 (parasympathetic) activity changes were very small, consistent with the lack of significant changes in the Time Domain Ratios, and CAN was not, on average, 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 an open enrollment (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. Therefore, high sympathetic activity as indicated by high SB was more predictive of MACE than the change in LVEF. 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. RAN's antioxidant effect would also decrease SB.

Recently, it was proposed that diastolic CHF be defined as CHF with LVEF≥0.50 [52]. 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 pro-arrhythmia [13]. IKr and late INa are inhibited. In addition, RAN has been shown to inhibit the diastolic transient inward current [20] resulting in suppression of after depolarizations. Although the QT interval is prolonged by approximately 6 msec. due to IKr inhibition, there is no transmural dispersion of repolarization, and RAN is protective against torsades de pointes [53]. EAD/DAD are causes of triggered ventricular ectopy [54] and can be induced by late INa that RAN inhibits (13). DAD are due to spontaneous release of Ca^{++} from the sarcoplasmic reticulum, and EAD are directly due to Ca^{++} entry through the Ca^{++} window current, except in Purkinje fibers where EAD are due to late INa window current.

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 [55-61].

Our patients met criteria for VP [62]. 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 1 of 1,300 patients and can be a highly symptomatic arrhythmia which is thought to be caused by EAD/DAD. 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 [63]. A report of two patients responding to adenosine has been published [64]. Dilantin was successful in one patient [65]. Cardiac pacing succeeded in two patients [66]. Amiodarone produced good results in nine patients [67]. 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 phosphoralization 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 (not BP-related, but a direct CNS effect), nausea, or constipation, with no known organ toxicity with the exception of possibly worsening pre-existing severe chronic renal disease, especially in DM. Patients' symptoms improved proportionally to PVC reduction.

In canine ventricular wedge preparations, RAN did not induce torsades de pointes, reduced the action potential duration of M cells, and suppressed EAD induced by d-sotalol [68]. 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 Cmax is doubled (other statin doses may need reduction as well.

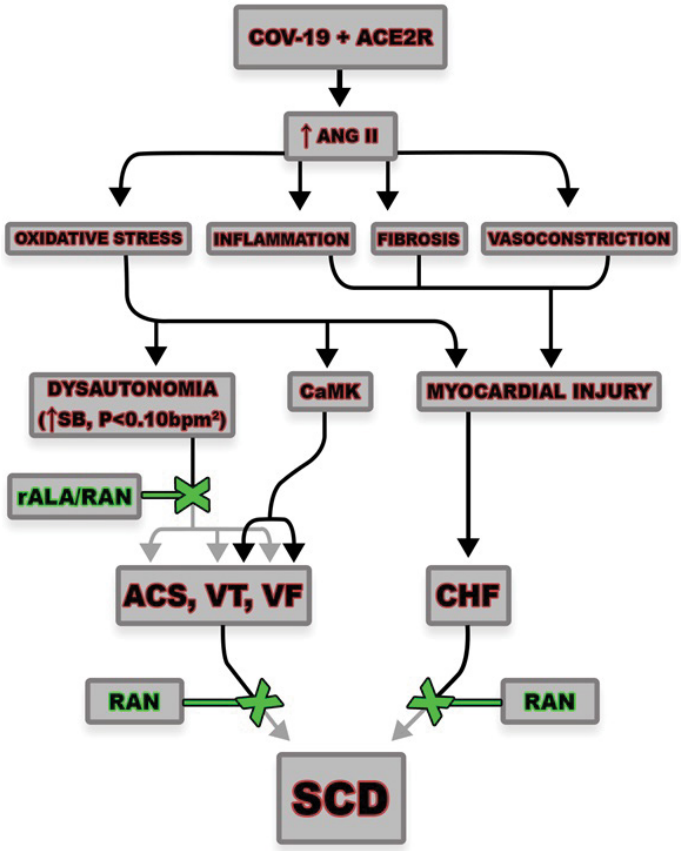
The patient population herein reported seems reasonably typical of adults who would be referred to a cardiology practice primarily for ventricular arrhythmia evaluation and therapy. Patients were essentially Medicare-age with multiple comorbidities, but well-preserved LVEF and highly symptomatic with palpitations, dizziness, and fatigue. Syncope and cardiac arrest were not methods of presentation.

In summary, RAN was found to be highly effective in suppressing triggered VPC. Isolated PVCs were reduced from 13,329 to 3,837, ventricular bigeminy reduced from 4,168 to 851, ventricular couplets reduced from 374 to 81, and VT was reduced from 56 to 5, representing reductions of 71, 80, 78, and 91%, respectively. One of the initial three non-responders demonstrated a remarkable response 1.5 years later with 16,890 PVCs reduced to only 3 PVCs per 24 hours (99% reduction). The presenting symptoms were improved in proportion to PVC reduction (marked decrease in palpitations, fatigue, and dizziness).

SCD IN DM 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); P reduces VT/VF and silent ischemia (4,37,49,51), 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



Abbreviations: (ACE2R: Angiotensin Conversion Enzyme 2 Receptor; ACS: Acute Coronary Syndrome; ANG II: Angiotensin II; CaMK: Ca^{++}/Calmodulin kinase II; CHF: Congestive Heart Failure; bpm^2: Beats per Minute Squared; rALA: (r) Alpha Lipoic Acid; RAN: Ranolazine; SB: Sympathovagal Balance; VF: Ventricular Tachycardia; VT: Ventricular Tachycardia).

Figure 2. CoV-19 and SCD.

NA, p = 0.034).

Since SW and PE can cause both NOH and systemic HTN, 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 S and P abnormalities than treating the BP *per se* (28).

(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 (4). It improves hyperglycemia, endothelial dysfunction, nitric oxide levels (protective against VT/VF, silent ischemia [69,70]), reduces nuclear kappa B, and is essential for certain mitochondrial oxidative enzymes. Decreased nitric oxide levels prolong QTc [71,72].

(r) ALA prevents diabetic-induced reduction of the afferent limb function of the baroreceptor reflex (BR) (5), reducing SCD. 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. 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 an 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. Improved mitochondrial function should reduce SCD also [73].

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

CHF: 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. However, no new information regarding RAN and diastolic CHF would have obtained.

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 [73]. 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 $^{12}_{Iodine}$ 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 [74].

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 weren't 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 DM 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 or disorders. To conclude our example of COVID-19, Figure 2 presents the progression from COVID-19 induced cytokine storms to SCD.

ACE2R =angiotensin conversion enzyme 2 receptor; ACS=acute coronary syndrome; ANG II =angiotensin II; CaMK =Ca^{++}/Calmodulin kinase II; CHF =congestive heart failure; bpm^2 =beats per minute squared; rALA = (r) Alpha Lipoic Acid; RAN =ranolazine; SB =sympathovagal balance; VF =ventricular tachycardia; VT =ventricular tachycardia

Neither has had a death attributed to it and both are extraordinarily safe, should not be used in patients with severe renal disease. Upon hospital admission, all patients could be started on (r) ALA 300 mg bid if P&S testing is unavailable. If troponin, echocardiogram, or cardiac MRI indicate cardiac involvement, RAN 1000 mg po bid, should be given. For ventilator-dependent patients, RAN has been safely administered I.V in animals, and (r) ALA given per feeding tube along with I.V. RAN.

References

1. Wu Lin, Aislinn O'Kane, Hu Peng, Yaguang Bi, et al "SARS-Cov-2 and Cardiovascular Complications: from Molecular Mechanisms to Pharmaceutical Management." *Biochemical Pharmacology* 178 (2020): 114114.
2. Kenney Mickey and Cantos Ganta. "Autonomic Nervous System and Immune System Interactions." *Comprehensive Physiology* 4 (2014): 1177.
3. Murray Gary and Joseph Colombo. "Routine Measurements of Cardiac Parasympathetic and Sympathetic Nervous Systems Assists In Primary and Secondary Risk Stratification and Management of Cardiovascular Clinic Patients." *Clinical Cardiovascular Med* 3 (2019): 27-33.
4. Gomes Brito and Carlos Negrato. "Alpha-Lipoic Acid as A Pleiotropic Compound With Potential Therapeutic Use In Diabetes and Other Chronic Diseases." *Diabetology & Metabolic Syndrome* 6 (2014): 1-18.
5. Gouty Shawn, Jen Regalia, Fang Cai, Cinda Helke et al. "αLipoic Acid Treatment Prevents The Diabetes-induced Attenuation of the Afferent Limb of the Baroreceptor Reflex in Rats." *Autonomic Neuroscience* 108 (2003): 32-44.
6. Murray G. "Oxidative Cardiac Autonomic Neuropathy: A Unifying Paradigm In Adult Sudden Death With Normal Left Ventricular Fraction; Early Diagnosis And Treatment Reduces Sudden Cardiac Death At Least 43%." *EC Cardiology* (2020).
7. Flather Marcus, Salim Yusuf, Lars Køber, Marc Pfeffer, et al. "Long-Term ACE-Inhibitor Therapy In Patients With Heart Failure Or Left-Ventricular Dysfunction: A Systematic Overview Of Data From Individual Patients." *The Lancet* 355 (2000): 1575-1581.
8. Granger CB, McMurray JJ and Yusuf S. CHARM Investigators and Committees. Effects of Candesartan in Patients with Chronic Heart Failure and Reduced Left-Ventricular Systolic Function Intolerant To Angiotensin-Converting-Enzyme Inhibitors: The CHARM-Alternative Trial. *Lancet* 2003: 772-776.
9. Cohn Jay, William Tam, Inder Anand, Anne Taylor, et al. "Isosorbide Dinitrate And Hydralazine In A Fixed-Dose Combination Produces Further Regression Of Left Ventricular Remodeling In A Well-Treated Black Population With Heart Failure: Results From A-Heft." *Journal of Cardiac Failure* 13 (2007): 331-339.
10. Merit-HF Study Group. "Effect Of Metoprolol CR/XL In Chronic Heart Failure: Metoprolol CR/XL Randomised Intervention Trial In-Congestive Heart Failure (MERIT-HF)." *The Lancet* 353 (1999): 2001-2007.
11. Packer Milton, Andrew Coats, Michael Fowler, Hugo Katus, et al. "Effect Of Carvedilol On Survival In Severe Chronic Heart Failure." *New England Journal of Medicine* 344 (2001): 1651-1658.
12. Kadish Alan and Mandeep Mehra. "Heart Failure Devices: Implantable Cardioverter-Defibrillators and Biventricular Pacing Therapy." *Circulation* 111 (2005): 3327-3335.
13. Shryock, J. C., and L. Belardinelli. "Inhibition of Late Sodium Current to Reduce Electrical and Mechanical Dysfunction of Ischemic Myocardium." *British Journal of Pharmacology* 153 (2008): 1128-1132.
14. Aldasoro Martin, Sol Guerra-Ojeda, Diana Aguirre-Rueda, Mª Dolores Mauricio, et al. "Effects of Ranolazine On Astrocytes and Neurons In Primary Culture." *PLoS One* 11 (2016): e0150619.
15. Bradshaw and Patrick C. "Cytoplasmic and Mitochondrial NADPH-Coupled Redox Systems in the Regulation of Aging." *Nutrients* 11 (2019): 504.
16. Cassano Velia, Antonio Leo, Martina Tallarico, Valentina Nesci, et al. "Metabolic And Cognitive Effects Of Ranolazine In Type 2 Diabetes Mellitus: Data From An *In Vivo* Model." *Nutrients* 12 (2020): 382.
17. Wang Kuo, Joanna Calderon and Sho-Ya Wang. "State-And Use-Dependent Block Of Muscle Nav1. 4 And Neuronal Nav1. 7 Voltage-Gated Na+ Channel Isoforms by Ranolazine." *Molecular Pharmacology* 73 (2008): 940-948.
18. Rajamani Sridharan, John Shryock and Luiz Belardinelli. "Block of Tetrodotoxin-Sensitive, Nav1. 7, And Tetrodotoxin-Resistant, Nav 1. 8, Na+ Channels By Ranolazine." *Channels* 2 (2008): 449-460.
19. Murray Gary and Joseph Colombo. "Ranolazine Preserves And Improves Left Ventricular Ejection Fraction and Autonomic Measures When Added To Guideline-Driven Therapy In Chronic Heart Failure." *Heart International* 9 (2014): 5000219.
20. Lindegger N, Hagen BM, Marks AR, Lederer WJ, et al. "Diastolic Transient Inward Current in Long QT Syndrome Type 3 Is Caused By Ca2+ Overload and Inhibited By Ranolazine." *Journal of Molecular and Cellular Cardiology* 47 (2009): 326-334.
21. Murray Gary. "Ranolazine Is an Effective and Safe Treatment of Adults with Symptomatic Premature Ventricular Contractions Due To Triggered Ectopy." *International Journal of Angiology* 25 (2016): 247-251.
22. Burashnikov Alexander, Luiz Belardinelli, and Charles Antzelevitch. "Atrial-Selective Sodium Channel Block Strategy to Suppress Atrial Fibrillation: Ranolazine versus Propafenone." *Journal of Pharmacology and Experimental Therapeutics* 340 (2012): 161-168.
23. Burashnikov Alexander, José Di Diego, Hector Barajas-Martínez, Dan Hu, et al. "Ranolazine Effectively Suppresses Atrial Fibrillation in the Setting Of Heart Failure." *Circulation: Heart Failure* 7 (2014): 627-633.
24. Akselrod Solange, Sarah Eliash, Orna Oz, Sasson Cohen et al. "Hemodynamic Regulation in SHR: Investigation by Spectral Analysis." *American Journal of Physiology-Heart and Circulatory Physiology* 253 (1987): H176-H183.
25. Akselrod and Solange. "Spectral Analysis of Fluctuations in Cardiovascular Parameters: A Quantitative Tool for the Investigation of Autonomic Control." *Trends in Pharmacological Sciences* 9 (1988): 6-9.
26. Adiraju RK, Akselrod S, Arora RR, Aysin B, et al. "Clinical Autonomic Dysfunction Measurement, Indications, Therapies, And Outcomes."
27. Bloomfield Daniel, Elizabeth Kaufman, Thomas Bigger, Joseph Fleiss, et al. "Passive Head-Up Tilt And Actively Standing Up Produce Similar Overall Changes In Autonomic Balance." *American Heart Journal* 134 (1997): 316-320.
28. Murray Gary and Joseph Colombo. "The Feasibility Of Blood Pressure Control With Autonomic-Assisted Hypertension Therapy Versus JNC 8 Therapy." *Clinical Cardiol Cardiovascular Med* 4 (2020): 1-5.
29. Körei Anna, Miklós Kempler, Ildikó Istenes, Orsolya Vági, et al. "Why Not To Use The Handgrip Test In The Assessment Of Cardiovascular Autonomic Neuropathy Among Patients With Diabetes Mellitus?." *Current vascular pharmacology* 15 (2017): 66-73.
30. Kannel William and Arthur Schatzkin. "Sudden Death: Lessons from Subsets in Population Studies." *Journal of the American College of Cardiology* 5 (1985): 141B-149B.
31. Umetani Ken, Donald Singer, Rollin McCraty, Mike Atkinson et al. "Twenty-Four Hour Time Domain Heart Rate Variability And Heart Rate: Relations to Age and Gender Over Nine Decades." *Journal of the American College of Cardiology* 31 (1998): 593-601.
32. Kucharska-Newton Anna, David Couper, James Pankow, Ronald Prineas, et al . "Diabetes and the Risk of Sudden Cardiac Death, the Atherosclerosis Risk in Communities Study." *Acta Diabetologica* 47 (2010): 161-168.
33. Patel Ravi, Moorthy MV, Stephanie Chiuve, Aruna Pradhan, et al . "Hemoglobin A1c levels and risk of sudden cardiac death: a nested case-control study." *Heart Rhythm* 14 (2017): 72-78.
34. Sumner Glen. "Sudden Cardiac Death." *Curr Probl Cardiol* 40 (2015): 133-200.
35. AlJaroudi Wael, Marwan Refaat, Robert Habib, Laila Al-Shaar, et al. "Effect of Angiotensin-Converting Enzyme Inhibitors And Receptor Blockers On Appropriate Implantable Cardiac Defibrillator Shock In Patients With Severe Systolic Heart Failure (From The GRADE Multicenter Study)." *The American Journal of Cardiology* 115 (2015): 924-931.
36. Kucharska-Newton Anna, David Couper, James Pankow, Ronald Prineas, et al. "Diabetes and The Risk Of Sudden Cardiac Death, The Atherosclerosis Risk In Communities Study." *Acta diabetologica* 47 (2010): 161-168.
37. Patel Ravi, Moorthy MV, Stephanie Chiuve, Aruna Pradhan, et al. "Hemoglobin A1c Levels and Risk Of Sudden Cardiac Death: A Nested Case-Control Study." *Heart Rhythm* 14 (2017): 72-78.
38. Sumner Glen. "Sudden Cardiac Death." *Curr Probl Cardiol* 40 (2015): 133-200.
39. AlJaroudi Wael, Marwan Refaat, Robert Habib, Laila Al-Shaar, et al. "Effect of Angiotensin-Converting Enzyme Inhibitors and Receptor Blockers On Appropriate Implantable Cardiac Defibrillator Shock In Patients With Severe Systolic Heart Failure (From The GRADE Multicenter Study)." *The American journal of cardiology* 115 (2015): 924-931.
40. Sattar Naveed, James McLaren, Søren Kristensen, David Preiss, et al ."SGLT2 Inhibition and cardiovascular events: why did EMPA-REG Outcomes surprise and what were the likely mechanisms?" *Diabetologia* 59 (2016): 1333-1339.
41. Roussel Ronan, Florence Travert, Blandine Pasquet, Peter Wilson, et al. "Metformin

Use and Mortality Among Patients With Diabetes And Atherothrombosis." *Archives of internal medicine* 170 (2010): 1892-1899.

42. Simard Patrice, Nancy Presse, Louise Roy, Marc Dorais, et al . "Association between Metformin Adherence and All-Cause Mortality among New Users of Metformin: A Nested Case-Control Study." *Annals of Pharmacotherapy* 52 (2018): 305-313.
43. Costa Eunice Cristina da Silva, Antonio Gonçalves, Miguel Areas, Rafael Gustavo Birochi Morgabel et al. "Effects of Metformin On QT And Qtc Interval Dispersion Of Diabetic Rats." *Arquivos brasileiros de cardiologia* 90 (2008): 254-260.
44. Straus Sabine, Jan Kors, Marie Bruin, Cornelis van der Hooft, et al. "Prolonged Qtc Interval and Risk of Sudden Cardiac Death in a Population of Older Adults." *Journal of the American College of Cardiology* 47 (2006): 362-367.
45. Reinier Kyndaron, Carmen Rusinaru, Sumeet Chugh. "Race, Ethnicity, And The Risk Of Sudden Death." *Trends in cardiovascular medicine* 29 (2019): 120-126.
46. Curtis Brian and James O'Keefe. "Autonomic Tone as a Cardiovascular Risk Factor: The Dangers Of Chronic Fight Or Flight." In *Mayo Clinic Proceedings* 77 (2002): 45-54.
47. Kalla Manish, Neil Herring and David Paterson. "Cardiac Sympatho-Vagal Balance and Ventricular Arrhythmia." *Autonomic Neuroscience* 199 (2016): 29-37.
48. Dib Nabil, Robert Michler, Francis Pagani, Susan Wright, et al. "Safety And Feasibility Of Autologous Myoblast Transplantation In Patients With Ischemic Cardiomyopathy: Four-Year Follow-Up." *Circulation* 112 (2005): 1748-1755.
49. Jay Cohn. "Prognosis in Congestive Heart Failure." *Annual Review of Medicine* 45 (1994): 341-350.
50. Maser Raelene, Braxton Mitchell, Aaron Vinik, Roy Freeman et al. "The Association between Cardiovascular Autonomic Neuropathy And Mortality In Individuals With Diabetes: A Meta-Analysis." *Diabetes care* 26 (2003): 1895-1901.
51. Hunt S, Abraham W, Chin M, Feldman A, et al. "ACC/AHA Guidelines Update for The Diagnosis And Management Of Chronic Heart Failure In The Adult: Summary Article." *Circulation* 115 (2007): 1825-1852.
52. Antoons Gudrun, Avram Oros, Jet Beekman, Markus Engelen, et al. "Late Na+ Current Inhibition By Ranolazine Reduces Torsades De Pointes In The Chronic Atrioventricular Block Dog Model." *Journal of the American College of Cardiology* 55 (2010): 801-809.
53. Li Pan and Yoram Rudy. "A Model of Canine Purkinje Cell Electrophysiology and Ca2+ Cycling: Rate Dependence, Triggered Activity, And Comparison To Ventricular Myocytes." *Circulation Research* 109 (2011): 71-79.
54. Antoons Gudrun, Avram Oros, Jet Beekman, Markus Engelen, et al. "Late Na+ Current Inhibition By Ranolazine Reduces Torsades De Pointes In The Chronic Atrioventricular Block Dog Model." *Journal of the American College of Cardiology* 55 (2010): 801-809.
55. Kujala Kirsi, Jere Paavola, Anna Lahti, Kim Larsson, et al. "Cell Model Of Catecholaminergic Polymorphic Ventricular Tachycardia Reveals Early And Delayed Afterdepolarizations." (2012): e44660.
56. Wolk R "Arrhythmogenic Mechanisms in Left Ventricular Hypertrophy." *EP Europace* 2 (2000): 216-223.
57. Kimura Shinichi, Arthur Bassett, Hongying Xi, Robert Myerburg et al. "Early After depolarizations And Triggered Activity Induced By Cocaine. A Possible Mechanism of Cocaine Arrhythmogenesis." *Circulation* 85 (1992): 2227-2235.
58. Gaur Namit, Yoram Rudy and Livia Hool. "Contributions of Ion Channel Currents To Ventricular Action Potential Changes And Induction Of Early Afterdepolarizations During Acute Hypoxia." *Circulation Research* 105 (2009): 1196-1203.
59. Xie Lai-Hua, Fuhua Chen, Hrayr Karagueuzian, James Weiss et al. "Oxidative Stress–Induced Afterdepolarizations And Calmodulin Kinase II Signaling." *Circulation Research* 104 (2009): 79-86.
60. Song Yejia, John Shryock, Stefan Wagner, Lars Maier, et al. "Blocking Late Sodium Current Reduces Hydrogen Peroxide-Induced Arrhythmogenic Activity And Contractile Dysfunction." *Journal of Pharmacology and Experimental Therapeutics* 318 (2006): 214-222.
61. Castellanos A, Sandudi N, Myerberg R. Parasystole. In Zipes D, JalifeJ, eds. Cardiac Electrophysiology: From Cell to Bedside. 3rd ed. Philadelphia, PA: WB Saunders; (2000): 690–696.
62. Lipnitskiĭ TN, Denisiuk VI, Kolesnik PF, Sizova MP, et al. "The Clinical Efficacy of Verapamil In Ventricular Extrasystolic Arrhythmia And Parasystole." *Terapevticheskii Arkhiv* 65 (1993): 42-44.
63. Tomcsányi János, József Tenczer and Lajos Horváth. "Effect of Adenosine on Ventricular Parasystole." *Journal of electrocardiology* 29 (1996): 61-63.
64. Zanini S, and Rossi R. "Ventricular Parasystole: Successful Treatment with Diphenylhydantoin." *Giornale italiano di cardiologia* 2 (1972): 575-578.
65. Furuse Akira, Goki Shindo, Haruo Makuuchi, Masahiro Saigusa, et al. "Apparent Suppression of Ventricular Parasystole by Cardiac Pacing." *Japanese Heart Journal* 20 (1979): 843-851.
66. Paleev NR, IKel'man IM, Kovaleva LI, Nikiforova TB, et al. "Cordarone Treatment of Parasystole." *Kardiologiia* 20 (1980): 19-21.
67. Sossalla, Samuel, Nora Wallisch, Karl Toischer, Christian Sohns, Dirk Vollmann, Joachim Seegers, Lars Lüthje, Lars S. Maier, Markus Zabel et al. "Effects Of Ranolazine on Torsades De Pointes Tachycardias in A Healthy Isolated Rabbit Heart Model." *Cardiovascular Therapeutics* 32 (2014): 170-177.
68. Horinaka Shigeo, Naohiko Kobayashi, Akihisa Yabe, Hiroshi Asakawa, et al . "Nicorandil Protects Against Lethal Ischemic Ventricular Arrhythmias And Up-Regulates Endothelial Nitric Oxide Synthase Expression And Sulfonylurea Receptor 2 Mrna In Conscious Rats With Acute Myocardial Infarction." *Cardiovascular Drugs and Therapy* 18 (2004): 13-22.
69. Hino Yoshiaki, Takashi Ohkubo, Yasuhiro Katsube, Shunichi Ogawa et al. "Changes in Endothelium-Derived Vascular Regulatory Factors during Dobutamine-Stress-Induced Silent Myocardial Ischemia in Patients With Kawasaki Disease." *Japanese Circulation Journal* 63 (1999): 503-508.
70. Eijgelsheim Mark, Adrianus Aarnoudse, Fernando Rivadeneira, Jan Kors, et al. "Identification of a common variant at the NOS1AP locus strongly associated to QT-interval duration." *Human Molecular Genetics* 18 (2009): 347-357.
71. Rakhit Amit, Colin Maguire, Hiroko Wakimoto, Josef Gehrmann, et al. "*In Vivo* Electrophysiologic Studies In Endothelial Nitric Oxide Synthase (Enos)-Deficient Mice." *Journal of Cardiovascular Electrophysiology* 12 (2001): 1295-1301.
72. DePace NL and Colombo J. "Autonomic and Mitochondrial Dysfunction in Clinical Diseases: Diagnostic, Prevention, And Therapy." (2019).
73. Boogers Mark, Caroline Veltman and Jeroen Bax. "Cardiac Autonomic Nervous System in Heart Failure: Imaging Technique And Clinical Implications." *Current Cardiology Reviews* 7 (2011): 35-42.
74. Allely Maxine and Alps BJ. "The Effects of the Novel Anti-Anginal Compound RS 43285 on Myocardial Conduction in the Anaesthetized Dog." *British Journal of Pharmacology* 93 (1988): 375-382.

How to cite this article: Gary L. Murray. "Is an Easy, Safe Management Strategy for the Life-Threatening Cardiac Complications of COVID-19 Right Under our Noses?". *J Cardiovasc Dis Diagn* 9 (2021) 461