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Re-print: Maintenance (r) Alpha Lipoic Acid Reduces Sudden Cardiac Death in Geriatric Diabetes Mellitus II Patients

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Abstract

Background: Diabetes carries a two-fold risk of Sudden Cardiac Death (SCD). Diabetic Autonomic Neuropathy (DAN), often progressing to Cardiovascular Autonomic Neuropathy (CAN, critically low parasympathetic tone [P]), increases death 3.5-fold over 5 years, half sudden or non-renal. Oxidative stress is a major cause of DAN. Also, increased sympathetic tone (S), High Sympathovagal Balance [SB>2.5] increases SCD risk.

Objective: Dysautonomic diabetic II patients were treated with the antioxidant (r) Alpha Lipoic Acid (ALA), autonomic function followed, and Sudden Death (SD) compared to untreated patients.

Methods: 133 patients (mean age 66y/o) with DAN or CAN, diagnosed using the ANX 3.0 Autonomic Monitor (Physio PS, Inc., Atlanta, GA) was offered (r)-ALA: 83 agreed (Group 1), and 50 refused (Group 2). P and S were re-measured up to 3 times/yr (mean f/u 6.31 yrs); SCDs were recorded.

Results: A 43% Relative Risk Reduction (RRR) in SCD occurred with (r)-ALA (25% SCD Group 1 vs. 44% SCD Group 2, p=0.0076). Initial to final patients with high SB or CAN were 21.7%-12% (p=0.010), 10.8%-15.7% (p=0.045), Group 1 vs. 24%-22% (p=ns), 6%-12% (p=0.083), Group 2. Only Group 1 survivors increased mean resting P. The progressive increase in P’s decline, increasing CAN risk, in the other patients correlated with mortality (p<0.001) and (r) ALA dose. Initially, Group 1 had insignificantly less high SB (p=0.449) and significantly more CAN (p=0.013) vs. Group 2. Finally, Group 1 had significantly less high SB (p=0.0967) vs. Group 2, also improving to insignificantly more CAN (p=0.261).

Conclusion: (r)-ALA was associated with a 43% RRR of SCD and favorable P and S changes.

Keywords: (r)-ALA was associated with a 43% RRR of SCD and favorable P and S changes.

Abbreviations:

SCD-Sudden Cardiac Death,
DAN-Diabetic Autonomic Neuropathy,
CAN-Cardiovascular Autonomic Neuropathy,
P-Parasympathetic tone,
S-Sympathetic tone,
ALA-Alfa Lipoic Acid,
SD-Sudden Death,
NOH-Neurogenic Orthostatic Hypotension,
DMII-Type 2 Diabetes,
RA-Respiratory Activity,
HRV-Heart Rate Variability,
RFa-Respiratory Frequency area,
FRF-Fundamental Respiratory Frequency,
LFa-Low Frequency area,
ACS-Acute Coronary Syndrome,
VT/VF-Ventricular Tachycardia/Fibrillation,
CART-Cardiovascular Autonomic Reflex Test,
BMI-Body Mass Index, Bx-Baseline,
dBP-Diastolic Blood Pressure,
HL-Hyperlipidemia,
HR-Heart Rate,
LVEF-Left Ventricular Ejection Fraction,
PE-Parasympathetic Excess,
QTc-corrected QT,
SB-Sympathovagal Balance,
sBP-systolic BP,
SW-Sympathetic Withdrawal,
CKD-Chronic Kidney Disease.

Introduction

Diabetics have a two-fold increased risk of Sudden Cardiac Death (SCD), the most common cause of death in adult diabetics. Subgroup analyses have not explained this adequately [1]. Diabetic Autonomic Neuropathy (DAN) [2], carries a 53% 5yr. mortality, half of the deaths sudden [3]. DAN can progress to Cardiovascular Autonomic Reflex Test (CART) w/o isometric grip (grip variability (HRV), as we detailed previously [11].

Methods

In 2006, 133 consecutive DMII referrals for cardiovascular evaluation underwent P and S testing via ANX 3.0 Autonomic Monitoring (P&S Monitoring, Physio PS, Inc., Atlanta, GA). P&S were computed simultaneously and independently by concurrent, continuous time-frequency analysis of Respiratory Activity (RA) and Heart Rate Variability (HRV), as we detailed previously [11]. P&S renormalized; sitting LFa and RFa=0.5 to 10.0 bpm2; SB is age dependent=0.4 to 1.0 for geriatrics; stand LFa is ≥ 10% increase with respect to (wrt) sit; stand RFa is a decrease wrt sit. High SB is defined as>2.5, as established in our Framingham Study [5]. Hyperglycemic- oxidative stress causes dysautonomia [6-8]. We hypothesized (r)-ALA, a natural, potent antioxidant, might reduce SCD in Type 2 Diabetics (DMII) with dysautonomias. We have shown previously (r)-ALA improves autonemics in Hypertension (HTN) [9] as well as Neurogenic Orthostatic Hypotension (NOH) [10].

Results

Figure 1: Sudden Death Mortality risk of a Diabetic type 2 cohort from a south-central USA cardiology practice. (r)ALA (blue curve) reduced this cohort’s relative risk ratio (RRR) by 43% (p=0.0076) as compared to controls (brown curve).

Demographics

Table 1 Survivor demographics Group AA had significantly more males and higher final A1C; their initial LVEF was insignificantly lower, factors not favoring survival [20-24]; tending to favor survival were insignificantly fewer with CAD (although all AA and NA patients were vascularized with normal stress tests), less Chronic Kidney Disease (CKD); and significantly more Angiotensin blocker therapy (ACEI or ARB, p<0.100) [20,25]. 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 [26-29].
CAD vs. survivors, CAD prevalence was insignificantly different in Groups AD, ND.

**Group AA vs. Group ND:** Improved Group AA survival occurred despite Group ND having a normal final BMI (p=0.067), less HTN (p=0.021), greater use of Empagliflozin (p<0.100), Metformin (p<0.100), lower final A1C (p=0.034), and fewer males (p<0.100), all favoring less SCD in Group ND. DMII attenuates gender differences in SD [22]. 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 (1sustained) vs. 14.3% non-sustained in Group ND, p=0.3559.

Note: 2° Dx=Secondary Diagnosis; ACEI=Angiotensin Converting Enzyme Inhibitor; ARB=Angiotensin Renin Blocker; BB=Beta-Blocker; CCB=Calcium Channel Blocker; HL=Hyperlipidemia; Rx=therapy.

### Table 1: Survivor Patient Demographics.

<table>
<thead>
<tr>
<th>Group AA</th>
<th>Group NA</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>62</td>
<td>28</td>
</tr>
<tr>
<td>Male</td>
<td>61%</td>
<td>39%</td>
</tr>
<tr>
<td>Age (mean yrs)</td>
<td>67</td>
<td>64</td>
</tr>
<tr>
<td>Ethnicity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>74%</td>
<td>73%</td>
</tr>
<tr>
<td>African Am</td>
<td>23%</td>
<td>24%</td>
</tr>
<tr>
<td>Other</td>
<td>3%</td>
<td>2%</td>
</tr>
<tr>
<td>2 Dx</td>
<td>95.00%</td>
<td>86.00%</td>
</tr>
<tr>
<td>HTN</td>
<td>80.00%</td>
<td>82.00%</td>
</tr>
<tr>
<td>CAD</td>
<td>24.00%</td>
<td>37.00%</td>
</tr>
<tr>
<td>CHF</td>
<td>21.00%</td>
<td>20.00%</td>
</tr>
<tr>
<td>CKD</td>
<td>25.00%</td>
<td>35.00%</td>
</tr>
<tr>
<td>Smoker</td>
<td>5.00%</td>
<td>4.00%</td>
</tr>
<tr>
<td>AODM Rx</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insulin</td>
<td>25.00%</td>
<td>14.00%</td>
</tr>
<tr>
<td>Metformin</td>
<td>14.50%</td>
<td>36.00%</td>
</tr>
<tr>
<td>Sulfonylurea</td>
<td>9.70%</td>
<td>11.00%</td>
</tr>
<tr>
<td>Sitagliptin</td>
<td>5.00%</td>
<td>7.00%</td>
</tr>
<tr>
<td>Empagliflozin</td>
<td>1.50%</td>
<td>11.00%</td>
</tr>
<tr>
<td>Liraglutide</td>
<td>5.00%</td>
<td>36.00%</td>
</tr>
<tr>
<td>Pioglitazone</td>
<td>5.00%</td>
<td>0%</td>
</tr>
<tr>
<td>Anti-HTN Rx</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACEI/ARB</td>
<td>64%</td>
<td>41%</td>
</tr>
<tr>
<td>CCB</td>
<td>39%</td>
<td>30%</td>
</tr>
<tr>
<td>BB</td>
<td>36%</td>
<td>35%</td>
</tr>
<tr>
<td>Clonidine</td>
<td>3%</td>
<td>3%</td>
</tr>
<tr>
<td>(r)ALA (mean mg)</td>
<td>534 ± 458.5</td>
<td>0</td>
</tr>
<tr>
<td>Initial</td>
<td>Final</td>
<td>Initial</td>
</tr>
<tr>
<td>BMI (mean kg/m2)</td>
<td>31.6 ± 5.6</td>
<td>32.1 ± 6.6</td>
</tr>
<tr>
<td>A1C (mean %)</td>
<td>6.22 ± 0.9</td>
<td>6.61 ± 0.9</td>
</tr>
<tr>
<td>LVEF (mean %)</td>
<td>60 ± 11.1</td>
<td>60 ± 11.0</td>
</tr>
<tr>
<td>QTc (mean msec)</td>
<td>373 ± 47.5</td>
<td>380 ± 50.3</td>
</tr>
</tbody>
</table>

**Table 2** Non-Survivors. Group AD had significantly more males and higher A1C; there were insignificantly higher final BMI [24], lower LVEFs, more CHF, and less Metformin use, all tending unfavorably regarding survival. But 9% more took ACEI/ARBs (p<0.100). Control Group ND was 4 years older (p>0.100); QTc had no significance on SD, as SD increases when QTc is >450ms in males or >470ms in females [30]. Insignificantly more Group ND African Americans tends to favor SD [31]. CAD causes most adult SDs [24]. Although more SD patients had

Note: HCTZ, hydrochlorothiazide. See Table 1 or Methods for other abbreviations.

### Table 2: Non-Survivor Patient Demographics (Sudden Death Patients).

<table>
<thead>
<tr>
<th>Group AD</th>
<th>Group ND</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>21</td>
<td>22</td>
</tr>
<tr>
<td>Male</td>
<td>91%</td>
<td>41%</td>
</tr>
<tr>
<td>Age (mean yrs)</td>
<td>66 ± 12.3</td>
<td>70 ± 11.5</td>
</tr>
<tr>
<td>Ethnicity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>81%</td>
<td>73%</td>
</tr>
<tr>
<td>African Am</td>
<td>11%</td>
<td>28%</td>
</tr>
<tr>
<td>2° Dx</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HTN</td>
<td>68.00%</td>
<td>59.00%</td>
</tr>
<tr>
<td>HL</td>
<td>96.00%</td>
<td>86.00%</td>
</tr>
<tr>
<td>CAD</td>
<td>67.00%</td>
<td>73.00%</td>
</tr>
<tr>
<td>CHF</td>
<td>38.00%</td>
<td>23.00%</td>
</tr>
<tr>
<td>CKD</td>
<td>27.00%</td>
<td>30.00%</td>
</tr>
<tr>
<td>Smoker</td>
<td>5.00%</td>
<td>4.50%</td>
</tr>
<tr>
<td>AODM Rx</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insulin</td>
<td>42.00%</td>
<td>45.00%</td>
</tr>
<tr>
<td>Metformin</td>
<td>10.00%</td>
<td>45.00%</td>
</tr>
<tr>
<td>Sulfonylurea</td>
<td>19.00%</td>
<td>13.60%</td>
</tr>
<tr>
<td>Sitagliptin</td>
<td>11.00%</td>
<td>9.00%</td>
</tr>
<tr>
<td>Empagliflozin</td>
<td>5.00%</td>
<td>13.60%</td>
</tr>
<tr>
<td>Pioglitazone</td>
<td>5.00%</td>
<td>0%</td>
</tr>
<tr>
<td>Anti-HTN Rx</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACEI/ARB</td>
<td>73%</td>
<td>64%</td>
</tr>
<tr>
<td>CCB</td>
<td>27%</td>
<td>11%</td>
</tr>
<tr>
<td>BB</td>
<td>50%</td>
<td>64%</td>
</tr>
<tr>
<td>(r)ALA (mean mg)</td>
<td>5.4± 3.68</td>
<td>0</td>
</tr>
<tr>
<td>Initial</td>
<td>Final</td>
<td>Initial</td>
</tr>
<tr>
<td>BMI (mean kg/m2)</td>
<td>30.7 ± 10.3</td>
<td>32.4 ± 11.2</td>
</tr>
<tr>
<td>A1C (mean %)</td>
<td>7.74 ± 0.1</td>
<td>6.3 ± 0.6</td>
</tr>
<tr>
<td>LVEF (mean %)</td>
<td>57 ± 10.5</td>
<td>48 ± 9.1</td>
</tr>
<tr>
<td>QTc (mean msec)</td>
<td>350 ± 51.2</td>
<td>430 ± 54.6</td>
</tr>
</tbody>
</table>
LVEFs (60% vs. 48%, p<0.100), fewer males (p<0.100), and less CAD (p<0.100; revascularized with normal stress tests), mostly favoring survival. Fewer in Group NA took insulin (p<0.100). Initially, Group NA had 0% non-sustained VT vs. 16.7% in Group AD, p=0.1661.

**Autonomic Measures:** Table 3: 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 5590 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, SW (-24.4% vs. -13.8% [p=0.066]), indicating greater Bar receptor Reflex dysfunction, which increases SCD risk. PE upon standing developed more significantly in survivors (+65%) vs. SCD (+29%) because initial to final standing RFa increased in survivors vs. decreasing in SCD (p=0.022). In parallel, SCD patients experienced a dramatic 59.5% decrease in resting P in addition to SW. All P- and S-final values were lower in SCD, the lowest being resting P. Since HRV=S+P, HRV was lower in SCD (p<0.0001) mainly due to lower P.

**Survivors**

**Group-AA, Survivors with (r)-ALA:**(Table 4) AIC 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.

<table>
<thead>
<tr>
<th>N</th>
<th>Survivors</th>
<th>Sudden Cardiac Death</th>
</tr>
</thead>
<tbody>
<tr>
<td>90</td>
<td>Initial</td>
<td>Final</td>
</tr>
<tr>
<td>Sitting (Rest)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LFa (bpm²)</td>
<td>1.25 ± 2.19</td>
<td>1.1 ± 1.55</td>
</tr>
<tr>
<td>RFa (bpm²)</td>
<td>1.2 ± 2.33</td>
<td>1.35 ± 1.50</td>
</tr>
<tr>
<td>SB, 1.23 ± 1.50</td>
<td>2.07 ± 1.47</td>
<td>1.76 ± 1.49</td>
</tr>
<tr>
<td>Standing</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LFa (bpm²)</td>
<td>1.16 ± 2.05</td>
<td>1 ± 1.22</td>
</tr>
<tr>
<td>RFa (bpm²)</td>
<td>0.97 ± 1.70</td>
<td>1.75 ± 1.95</td>
</tr>
</tbody>
</table>

Note: HCTZ, hydrochlorothiazide; Standing represents positive head-up posture, equivalent to head-up tilt. See Table 1 or Methods for other abbreviations.

**Table 3:** Comparison between Survivors and Sudden Cardiac Death patients, Mean P&S Measures. See Methods for parameters’ normal ranges.
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 BxRFa (Table 4). Group AA’s final RFa increased 36.2%, correlating with the dose of (r)-ALA (p=0.014). Group AA’s increase in resting BxLFa (Table 4) was mitigated by the increase in resting BxRFa, so the SB change was insignificant. Group NA had no CAN initially; increasing to 3.6%. This group’s average resting BxLFa decreased (34.5%); BxRFa 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 4 and 5, Group AA’s BxLFa and BxRFa were initially lower than Group NA’s (p<0.100), indicating lower HRV. Group AA increased both, decreasing mortality risk (Table 4). Group NA decreased both BxLFa (Table 5) (p=0.075) and BxRFa (p=ns), indicating an accelerated progression towards increased mortality risk (decreased HRV).

Non-Survivors

Group AD, Non-Survivors with (r)-ALA: (Table 6) 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 [21,32-36]; seven progressed to CAN (p=0.080), not surprising since initial BxRFa was so severely depressed. Group AD was beyond help. Standing, 57% of Group AD initially progressed towards increased mortality risk (decreased HRV).

Group ND, Non-Survivors without (r)-ALA: (Table 7) Initial resting BxLFa, resting BxRFa, were normal; SB high for age (but not >2.5). Final BxLFa decreased, p=0.100; BxRFa severely decreased, p=0.020. Two more patients (67%) developed CAN (p=0.033) and 57% with ended with (p=0.037) indicative of BRS dysfunction (increased SCD). Finally, Group AD’s, average stand LFa was SW. These Sym pathetic results are significantly similar to Group AA (p=0.061). However, the P-responses, are different (p=0.185).

Mortality Risk: Resting BxRFa decreased in both Groups (Tables 6&7): 10.5%, Group AD and 67.5%, Group ND (p=0.033); a higher risk of developing CAN. Final SB was >2.5 in both, which we have shown increases MACE 700% [18]. 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. BxLFa increased in Group AD (Table 6) by 109.1% vs. decreasing 38.6% in Group ND (Table 7, p=0.100), causing increased SB in Group AD.

In Group ND, despite the decrease in S, the severe decrease in resting BxRFa 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 BxLFa and BxRFa fell severely to the 2nd lowest among all Groups. CAN and high SB were most frequent in Groups AD and ND.

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

Discussion
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 [21,32-
36], 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 greatest
decline in Group AD, to those with the greatest decline, Group ND
(p<0.001). Changes in P were proportional to (r)ALA dose. These trends
are not found in the other physiologic measures: BMI, LVEF, and QTc;
and only different between the survivors’ A1Cs (Group AA vs. Group
NA, p=0.034). Since SW and PE can cause both NOH and systemic HTN
[9,10], DMII patients not on (r)ALA might experience orthostasis, or
labile HTN. HTN could be secondary (neurogenic), and is over twice as
well controlled treating the primary SW ± PE [9] than treating the BP per se.
(r)ALA preserved P and S, especially P, in survivors and non-
survivors. (r)ALA is a natural, powerful thiol antioxidant. (r)ALA restores
and recycles vitamins A,C,E and glutathione [9,10,34].

It improves hyperglycemia, endothelial dysfunction, nitric oxide levels
(protective against VT/VF, silent ischemia [37-40]), reduces nuclear
kappa B, and is essential for certain mitochondrial oxidative enzymes.
(r)ALA prevents diabetic-induced reduction of the afferent limb function
of the baroreceptor reflex (BR) [41], reducing MACE. SW, found in 50%
to 74% of patients, failed to correct in 88% of Group NA and all SCD
patients. SW disappeared substantially only in Group AA, 59.7% reduced
to 53.2%, p=0.097, decreasing SCD risk. The other most common, and
most important, P&S finding was low resting P in 56% to 81% of patients,
improving only in Group AA (initial 56%, final 9%; p=0.070), vs. Group
NA (initial 29%, final 43%; p=0.098), and worsening most severely in
Group ND patients, a 67% reduction in RFa vs. 10.5% reduction in Group
AD (p=0.020).

CAN decreased 37.5% in Group AA vs. an increase of 67% in Group ND.
29% of Group AD had high SB vs. 50% in Group ND (p=0.037). More
CAN in Group 2 increased mortality; high SB increased mortality risk in
Group 1. Group 1’s autonomic profiles generally stabilized or improved
(HRV); Group 2’s deteriorated, especially a 59.5% decrease in resting P,
reducing Group 2’s ability to combat VT/VF, silent ischemia, and life
stresses. Standard deviations decreased over time, with the most decreases
 correlating with the (r)ALA dosage. The pleotropic effects of (r)ALA
likely contributed to
SCD reduction. Increased nitric oxide improves P&S, endothelial
dysfunction, protects against VT/VF and silent ischemia [37-40].
Decreased nitric oxide levels prolong QTc [37]. Improved mitochondrial
function should reduce SCD also [42]. 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.

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