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Mini Review

Oxidative Stress Cardiac Autonomic Neuropathy: A Unifying Paradigm in Adult Sudden Death with Normal Left Ventricular Ejection Fraction; Early Diagnosis and Treatment Reduces Sudden Death at Least 43%

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Abstract

This commentary on our current paradigms' inability to predict and prevent sudden cardiac death (SCD), responsible for 15 - 20% of all deaths in the general population, is inspired by the results of our 12 year study of 133 type II diabetics (DM) in whom we identified SCD risk with one autonomic screening and addressed it, reducing SCD 43% (p = 0.0076). We are currently ascertaining if this applies to non-diabetics. The SCD reduction in DMII was due to screening and treating even mild (69% of patients) oxidative cardiac autonomic neuropathy. Since oxidative stress, and secondary dysautonomia, is a common thread of all major cardiac disease, and there is preventative therapy, a new paradigm of oxidative-stress cardiac dysautonomia as a major common final pathway to SCD should be considered. The general population should be screened autonomically and preventive measures initiated.

Keywords: *Autonomic Nervous System; Alpha Lipoic Acid; Sudden Death*

Introduction

Current SCD/major adverse cardiac events (MACE) risk stratification

Eighty-five % of SCDs occur in patients not previously diagnosed with heart disease or in those with a history of stable heart disease and left ventricular ejection fraction (LVEF) > 40%; our ability to predict these SCDs using current paradigms is limited to poor [1]. Although many mention dysautonomia as one of many risk factors, it's never heavily emphasized.

Oxidative stress, cardiac disease, dysautonomia

Oxidative-stress, and its role in the development and progression, of the major adult cardiac diseases (coronary artery [CAD], hypertension [HTN] and congestive heart failure [CHF]) have long been recognized but likely underappreciated as risk factors for SCD except in DMII [2,3] which has high oxidative stress.

We all know heart rate variability (HRV) and cardio-protective parasympathetic tone (P) are decreased, while sympathetic tone (S) is harmfully increased (resulting in platelet activation, hemodynamic stress, oxidation of LDL, ventricular arrhythmias). But none of this is addressed except in DMII with its up to 3.25x increased SCD and CHF (beta blockers).

What has prevented considering dysautonomia as a major predictor and cause of SCD?

Inaccurate measurement of HRV, P and S

Probably mainly due to difficulty in directly measuring P, all non-invasive ANS measurements have only measured total autonomic activity (heart rate variability [HRV]), resulting in assumptions and approximations of the independent contributions of S and P to total HRV. Since HRV= S + P, both S and P must be identified accurately.

A technologic breakthrough accomplished this, developed, validated and verified by the 1st joint Bio-Medical Engineering program group from Massachusetts Institute of Technology and Harvard [4-8] and is now available for user-friendly routine use. It is P&S Monitoring. The breakthrough quantifies the independent contribution of S and P to total HRV through two simultaneous measurements: (1) ECG recording which establishes total HRV (Low Frequency area [0.04 - 0.15 Hz] under the HR time-frequency spectral curve), simultaneously with (2) Impedance Plethysmography which independently quantitates P (a 0.12 Hz-wide window area under the HRV spectral curve centered on the modal peak of the time-frequency Respiratory Activity [RA] spectral curve; HRV due to RA is solely P-dependent). Therefore, S = HRV - P; where P is no longer assumed to be the area under the HR curve between a wide, noise-containing 0.15 - 0.40 Hz band, but is quantitatively measured as the Respiratory Frequency area.

The curves are analyzed using continuous wavelet transforms rather than the frequency-only fast Fourier transforms. The latter, although accurate for stationary signals, compromises time and frequency resolution due to the fixed length windows used in analysis.

Utilizing this new technique, the Framingham study revealed P < 0.10 bpm^2 as high risk for SCD [9]. Sympathovagal balance (SB) > 2.5 outperformed myocardial perfusion imaging and 2D echocardiography (p = 0.001) as a predictor of MACE (including SCD,V T/VF) in 483 patients (127 with risk factors, 224 known CAD, 132 chronic CHF) followed a mean 4.92 yrs with a sensitivity of 0.59,OR = 7.03 (CI: 4.59 - 10.78), specificity of 0.83, PPV = 0.64, and NPV = 0.80 [10].

Now that we have two accurate autonomic targets indicating increased SCD risk, can we reduce SCD medically?

Yes. In 2006, 133 consecutive DMII patients with any abnormality screened using this new technique were offered (r)alpha lipoic acid, a powerful, natural autonomic neuro-protective antioxidant dietary supplement.

Eighty-three agreed, 50 patients refused. Ten non-autonomic risk factors for SCD slightly favored survival of the 50 patients, as did their initial autonomics. Only 31% of the 133 patients initially had SB > 2.5 and/or P < 0.10 bpm^2.

After 12 years, median f/u 5 years, SCD was reduced by 43% (p = 0 0076) in the 83 patients, accompanied by a 62% reduction in SB > 2.5 and 38% reduction in P < 0.10 bpm^2.

Only (r)ALA survivors demonstrated an increase in final, resting P (and HRV); P reduces VT/VF and silent ischemia [11-14], increasing 36.2%, vs. a 7.6% decrease for non-(r)ALA survivors, a 10.5% decrease in (r)AlA SCD, and a 67.5% decrease in non-(r)ALA SCD victims**.** The progressive increase in the decline of resting P indicated mortality, from the lowest decline in resting P in non- (r)ALA survivors, to the next greater decline in (r)ALA SCD, to those with the greatest decline, non-(r)ALA SCD subjects (p < 0.001). Changes in P were proportional to (r)ALA dose**.** These trends were not found in the other physiologic measures: BMI, LVEF and QTc. The only other intervention that could reduce SCD 43% in this or the general population would be implantation of a defibrillator.

Conclusion

Oxidative-stress dysautonomias, major adult cardiac diseases, and autonomic SCD are major common enemies of survival (Figure 1). When we consider SCD, we focus on acute coronary thrombosis or electrophysiologic studies, not dysautonomias. Perhaps a new screening paradigm, including emphasizing an autonomic profile, should be employed in all adults.

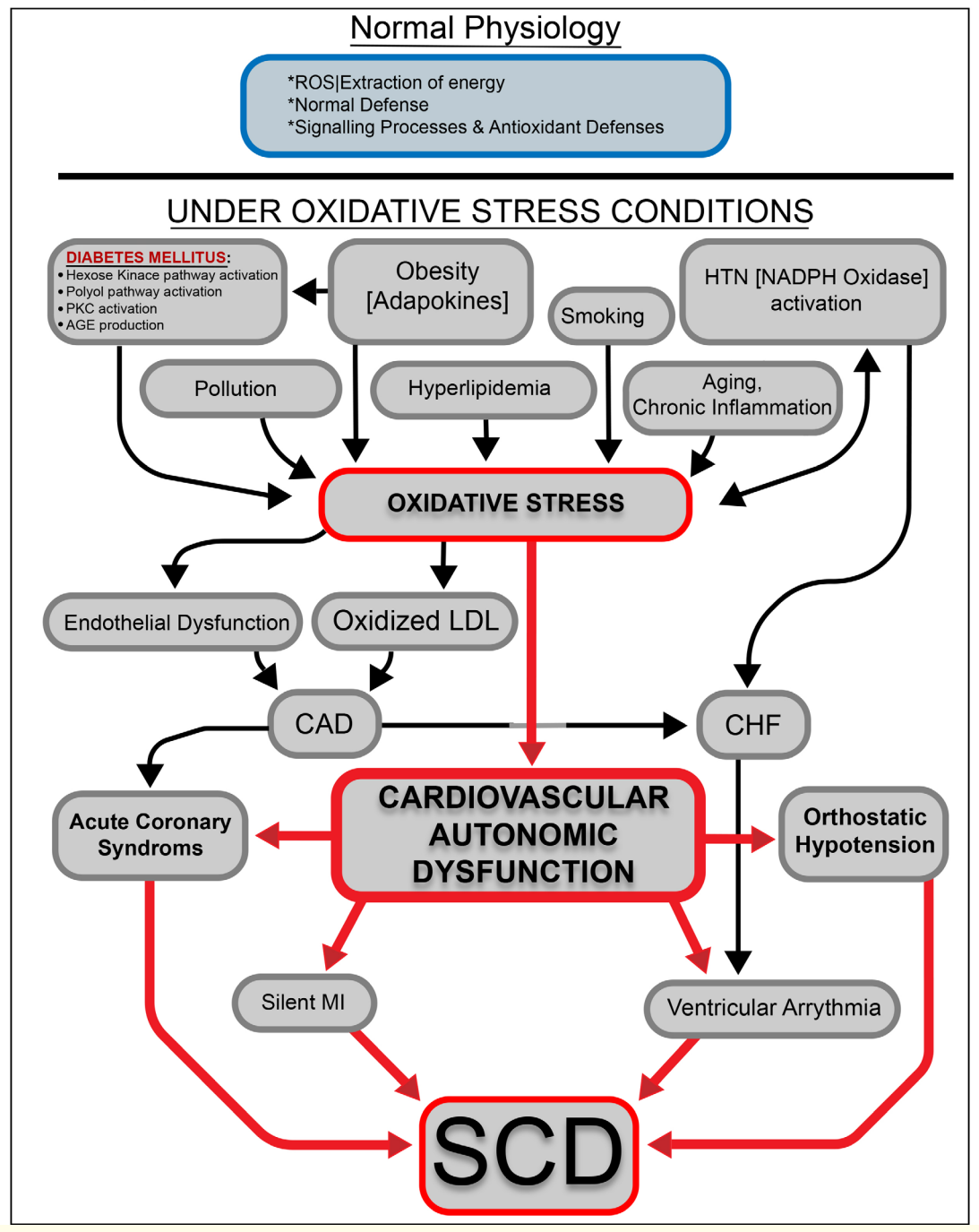

Figure 1: *Oxidative stress, cardiovascular autonomic dysfunction and sudden cardiac death.*

AGE: Advanced Glycation Endproducts; CAD: Coronary Artery Disease; CHF: Congestive Heart Failure; HTN: Hypertension; LDL: Low Density Lipoprotein; MI: Myocardial Infarction; NADPH: Nicotinamide Adenine Dinucleotide Phosphate; PKC: Protein Kinase C; ROS: Reactive Oxygen Species; SCD: Sudden Cardiac Death.

If even minimal dysautonomia is detected, it should be addressed by appropriate lifestyle changes and antioxidant therapy considered, titrated by serial autonomic testing. High Lipoprotein-associated Phospholipase A2 or hsCRP suggest oxidative stress. We recommend (r) ALA as initial therapy, 300 mg - 600 mg daily, as its autonomic neuro-protection should not be DMII-dependent [14].

Limitations of the Study

Obviously, a large autonomic screening and treatment of a general population should be accomplished.

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