Clinical Autonomic and Mitochondrial Disorders

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Diagnosis, Prevention, and Treatment for Mind-Body Wellness

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To our wives and families, our motivation in all things.
Thank you!

Foreword

The nervous system comprises the central nervous system (CNS) and the peripheral nervous system (PNS). The peripheral nervous system (PNS) is composed of three parts: the somatic, autonomic, and enteric. The somatic portion functions to control voluntary movement, while the autonomic and enteric function involuntarily to control various bodily functions. The autonomic nervous system (ANS) includes the parasympathetic and sympathetic (P&S) nervous systems. The sympathetics are the "fight or flight system" or the "accelerator of the body," while the parasympathetics act as the "brakes of the body" or the "rest and digest system." Some have coined it the "feed and breed" system. Together, the P&S nervous systems control or coordinate every cell in the body and, thereby, control homeostasis of the entire body, including cardiovascular and respiratory activity, digestion, urination and bowel function, sexual function, sweating, sleep, and ability to maintain upright position. Many physicians, including ourselves, consider the enteric nervous system (ENS) as actually a part of the ANS, specifically the parasympathetic nervous system. It is the most independent functioning component of the ANS and controls gastrointestinal function (secretion and peristalsis).

Anatomically, the ANS is located in both the central and peripheral parts of the nervous system, even though it is considered part of the PNS. Collectively, the P&S are regulated by, and in turn regulate (through feedback), the hypothalamus and the central autonomic network. In the CNS, the P&S are located predominately in the forebrain and brain stem. Therefore, the "mind-to-body" connection by the P&S operates from central (the brain) to peripheral (the body) and back again. The hypothalamus is the highest level of P&S integration under the control of the limbic (emotional influence) and cortical (voluntary influences) structures. By integrating the brain and the body, the P&S controls heart rate regulation, blood pressure regulation (vasomotor), and reflexes such as swallowing, sneezing, vomiting, and coughing.

It is simplistic to state that the sympathetics excite and the parasympathetics inhibit bodily functions since there are exceptions. The "brakes" and "accelerator" concept of the P&S helps the patient better understand the symptoms they are experiencing when a P&S imbalance or dysfunction occurs. P&S imbalances or dysfunctions are known as dysautonomias. They are conditions in which the P&S systems are not functioning properly and are not in balance or not coordinating properly. The P&S can be equated to being a "seesaw" where both ends of the "seesaw" should be level (in balance) or

opposing each other when active (one end being high and the other low). There are various abnormalities in which one end of the "see-saw" is too much higher than the other or, at times, the "see-saw" is broken where both ends are up at the same time or are too low at the same time.

Dysautonomia affects the function of the heart, intestine, bladder, pupils, sweat glands, blood vessels, and virtually all organs of the body as the P&S supplies innervation of the smooth muscles and glands throughout the body. Again, the P&S are the regulator of cardiovascular function, arterial baroreceptor reflex, standing response, sweating, gastrointestinal tract motility, and sleep cycle. Imbalance, or malfunction, of the P&S may cause hyperhidrosis and anhydrosis, lightheadedness or dizziness and orthostatic intolerance, and even syncope, high or low heart rates, blood pressure fluctuations, urinary incontinence and retention, insomnia, and swallowing difficulties. Common symptoms of dysautonomia cause exercise intolerance, chronic fatigue, muscle aches and pains, headache or migraine, diffuse sleep, tunnel vision, weakness, blurred vision, constipation, diarrhea, cognitive difficulties, and brain fog. Word-finding difficulties and short-term memory lapses can occur. Gastroparesis is also a common and disabling problem.

Most common symptoms are due to orthostatic intolerance. Standing is a major challenge for a healthy P&S. Gravity causes venous pooling in the lower extremities and lowers central pressures and venous return to the heart. The normal functioning ANS first withdraws the parasympathetics to potentiate and facilitate the sympathetics and then activates the sympathetics. Parasympathetic withdrawal immediately upon standing increases venous return to the heart and also increases heart rate on the initial stand response and avoids venous pooling. In orthostatic-intolerant (OI) individuals, due to dysautonomia, this mechanism is defective. The sympathetics constrict the lower extremity vessels and promote blood flow centrally to the heart. Sympathetic withdrawal inappropriately occurs, blood pools in the legs, and cardiac output and venous return are impaired. The patient may have a drop in blood pressure and orthostatic hypotension or an inappropriate increase in heart rate, overcompensating as in postural orthostatic tachycardia syndrome (POTS), or simply brain fog, fatigue, and exercise intolerance without significant changes in blood pressure or heart rate. The latter is more commonly seen in patients, especially younger patients at presentation. It is estimated that 4 million people in the United States have OI, and this is a major cause of disability and may be responsible for many of the symptoms that we classify as fibromyalgia-type or chronic fatigue. OI and chronic fatigue occur simultaneously.

To treat various forms of dysautonomia, including OI, pharmacology along with lifestyle changes, diet and salt intake, physical maneuvers and compression garments, fluids, stress reduction techniques, and neural feedback may be indicated depending on the patient's symptoms, history, and type of dysautonomia. Experimental pacing and stimulating devices have often been used in various circumstances. Surgical procedures occasionally are indicated, for example, bilateral sympathectomies, for various hyperhidrosis states. Patients with hypermobility syndromes, such as Ehlers-Danlos syndrome (EDS) and other related disorders, are often a significant challenge

and occasionally are referred for orthopedic or neurosurgical interventions. Gastroparesis is particularly troublesome, as there may be mixed components of imbalance in the autonomic nervous system affecting the GI tract as compared to other organs, and one pharmacological agent instituted to treat one organ disorder may adversely affect the other. Therefore, pharmacologic treatment of dysautonomia is very complex, and not always successful.

However, one must get at the "root of the problem." Increased oxidative stress is often the real trigger event for causes of mechanism at the cellular level. Deficiency of ATP production and mitochondrial dysfunction leads to significant impairment of neuron function and abnormalities of myelin sheath (neurons are very rich in mitochondrial density). Also, small fibers (the type C fibers, which are sensory and P&S fibers) are susceptible to oxidative stress. Nitric oxide deficiency also contributes to many of the neurological and vascular features of autonomic function and dysfunction. A "cocktail" of antioxidants, anti-inflammatories, and nitric oxide-enhancing agents have been advocated and may be useful empirically, especially at appropriately titrated doses.

When a patient presents to our autonomic center with symptoms consistent with dysautonomia, they have usually seen a minimum of 14 physicians, and a diagnosis has not been made. In fact, most patients arrive at the diagnosis by doing their own independent research on the Internet. Many patients are referred to us via Internet research and not by direct physician referral. One patient, an Indian/Asian young male, stated that he had seen 99 physicians prior to seeing us. These patients with dysautonomia have various presentations. They have oftentimes been labeled with the diagnosis of anxiety and have not had any types of autonomic assessment tests performed, such as sweat testing (sudomotor) or combined heart rate and respiratory variability testing, which are easy noninvasive tests to do in the outpatient center. Most have not had a tilt test performed. There is an obvious problem with identifying these patients due to physicians not being educated in this area sufficiently, both in medical school and within the medical literature. While autonomic dysfunction has in the past been the domain of the neurologist, the cardiologist is also beginning to learn more about it, as many of the diagnostic tests have a cardiac basis and many of the patients present to a cardiologist with shortness of breath, chest pain, and palpitations, which are manifestations of autonomic dysfunction and not intrinsic cardiac disease. In addition, endocrinologists and rheumatologists are beginning to have more awareness of autonomic dysfunction, especially in the diabetic, pain, myalgia, and hypermobility populations.

In fact, the hypermobility populations, which include benign hypermobility and any one of the number of variants of Ehlers-Danlos syndrome, osteogenesis imperfecta, Stickler syndrome, pseudoxanthoma elasticum, and Marfan syndrome, may be the most recent to greatly benefit from the improved autonomic dysfunction/dysautonomia awareness. It has long been known that both Ehlers-Danlos syndrome and dysautonomia are associated with small fiber neuropathy. Recently, testing for both small fiber neuropathy and dysautonomia has become commercially available. It is often difficult to determine which hypermobility disorder the patient suffers from due to the

heterogeneity and the expense of gene testing. The Ehlers-Danlos varieties typically have COL1A1 gene abnormalities, while Marfan's has abnormal fibrillin. We have not seen the patient with any of the above disorders that has not suffered from dysautonomia. Some of the more common features, which we recognize, include vascular pooling which mimics Raynaud syndrome, flushing, anxiety, hyperhidrosis, fatigue, and loss of consciousness or POTS.

In this text, we detail the symptoms and diagnoses of dysautonomia and the universal mechanism at the cellular level that causes or contributes to autonomic dysfunction. We propose a six-prong treatment approach that has been useful empirically in clinical practice. This involves not simply pharmacology and physical measures and maneuvers but also diet, an anti-inflammatory approach, an antioxidant approach, and a stress reduction approach. An integrative approach to the treatment of dysautonomia should be holistic. It is our goal to stimulate further research in this area and further education and recognition of this disease entity. Not just physicians and healthcare workers but also the public needs to be educated as to the existence and prevalence of dysautonomia and the related morbidity and mortality risks and the treatment entailed.

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About the Authors

Nicholas L. DePace is board certified in cardiology, echocardiography, internal medicine, lipidology, and nuclear cardiology, with nearly 40 years of clinical practice experience in cardiovascular medicine. He was trained at Mount Sinai Medical School in New York City, and Hahnemann Hospital in Philadelphia. He runs cardiovascular and autonomic practices in south Philadelphia and southern New Jersey. He is a Clinical Professor of medicine at Hahnemann Hospital, with cardiology affiliations and privileges at Jefferson Health Hospitals, NJ, and Pennsylvania Hospital/University Pennsylvania Health System, Philadelphia, PA. In addition to his many hours in clinic and rounding at the hospital, he teaches medical students, interns, and residents and continues to promote research in several fields associated with cardiovascular medicine and autonomic dysfunction. He has published over 100 medical journal articles, abstracts, book chapters, and books in cardiovascular diseases and neurocardiology. He previously served for 10 years on the editorial board of the American Journal of Cardiology. He has many achievements and has received many professional honors and awards throughout his career including being a Fellow of the American College of Cardiology and a Fellow of the American College of Chest Physicians. He has also received honors and awards for his acts of community service. He is a husband of over 35 years and a father of one with one grandchild.

Joseph Colombo is trained in neurology with a background in electrical and mechanical engineering. His doctorate from the University of Rochester, NY, is in neuroscience and biomedical engineering. Dr. Colombo currently serves as Chief Technology Officer and Senior Medical Director of TMCAMS, Inc.; and Parasympathetic and Sympathetic Nervous System Consultant, Franklin Cardiovascular Associates, PA. He has been an Adjunct Professor in medicine and lectures worldwide on clinical applications of, and disorders of, the parasympathetic and sympathetic (P&S) nervous systems. His career has included over 17 years developing aircraft crew systems and life support systems for NASA, Military, and FAA, and sensory-neural prostheses, including: digital hearing aids, cochlear implants, cochlear nucleus implants, visual prostheses, and vestibular measures. He is a signal processing expert. He has also been involved in developing tele-healthcare and tele-medicine systems. For over 25 years, Dr. Colombo has developed P&S nervous system technologies and has researched and published clinical applications and outcome studies in uses of noninvasive P&S monitoring in critical care (trauma and

sepsis), anesthesiology, cardiology, endocrinology, family medicine, internal medicine, pain management, neurology, psychiatry, pulmonology, sleep medicine, and more as positive, patient outcomes data are available. He has (co-)authored over 100 journal articles internationally, book chapters and medical text book on clinical applications of, and outcomes from, noninvasive P&S guided therapy. Dr. Colombo continues to participate in more than 50 clinical research projects worldwide and consults with physicians, clinically, on a global scale. He has a wife of 34 years and two married children, with over 30 years of mentoring hundreds of youths and students.

Preface

In 1983, I (Dr. DePace) first met, Dr. Jerry Lemole, who was the premier cardiothoracic surgeon in the Philadelphia area at the time. He had previously worked at the Baylor University, Texas Heart Institute, on the team that did the first heart transplant in the United States, and subsequently served as chief of Cardiothoracic Surgery at Temple University Hospital in Philadelphia and Deborah Heart Center in New Jersey. He was renowned for his very quick cross-clamp time and excellent surgical technique.

I noticed that Dr. Lemole's patients had excellent results. Empirically, I compared his results with other cardiothoracic surgeons using stress radionuclide angiography, which we did in our office on our postoperative patients. I noted that his patients had much better left ventricular resting function and reserve compared to other surgeons. This is in an era when cardioplegia[1] was now being perfected and better cardioplegia techniques were making even mediocre surgeons have good results. Therefore, I attempted to understand how Dr. Lemole would get such good results on his patients. Perhaps, he was more fully revascularizing them, and his technique was still far superior to others, which was true at the time, in my opinion. However, I noticed that he put most of his postoperative patients on a coenzyme Q preparation.

I was not familiar with coenzyme Q10 (CoQ10), nor did I know or have any idea about its biological feasibility. There was not really much evidence-based medicine behind its use then. CoQ10 is an essential lipid-soluble antioxidant, which protects cellular membranes and also circulates lipoproteins against free radical-induced oxidative stress, and has significant oxidative stress-reducing properties.

CoQ10 is an essential component of the electron transport chain and is an electron carrier as well as an antioxidant. It made sense that it would be useful in situations where there were deficiencies of mitochondrial energy generation as well as situations in which low cellular antioxidant capacity could be prevalent, such as in the postoperative period.

Significant research has been done since Dr. Lemole first started using CoQ10 (see "coenzyme Q10" section and any of the many references). Of course, Dr. Lemole was not aware of this information or data published as he was using CoQ10 10–20 years before the publication of these data. He was clearly ahead of his time. However, he understood the biological feasibility and advantages of using an antioxidant such as CoQ10 to protect against

[1] Intentional and temporary cessation of cardiac activity, primarily for cardiac surgery.

cardioplegia and postoperative oxidative stress, for these could impair left ventricular function. It is my belief that this is why his patients' postoperative stress radionuclide angiogram studies showed much higher ejection fractions than many of his colleagues' patients at that time.

Heart failure is also due to loss of contractility of the myocardium and is a consequence of a lack of energy in the myocardium. Chronic heart failure patients do show decreased CoQ10 levels on serum studies and endomyocardial biopsies (see "Oxidative Stress in Cardiovascular Diseases"). This research came from Dr. Cooley's lab at Baylor; therefore, Dr. Lemole was probably privy to this research, as he himself had trained at the Texas Heart Institute where Dr. Cooley was operating prior to 1983. Dr. Cooley's data supports that CoQ10 improves the efficiency of energy production, and quantity of energy produced, in human hearts when used as an adjunct to standard medical therapy and heart failure. CoQ10 decreases substances measured that indicate oxidative stress. In heart failure, CoQ10, a neuroprotective against lesions and a significant important antioxidant in both mitochondria and lipid membranes, scavenges free radicals and improves ATP regeneration in cardiac muscles and skeletal muscles in Friedreich's ataxia, another neurodegenerative disease. Data in toto reflects that antioxidant protection with agents, such as CoQ10, is protective in cardiac and neurodegenerative diseases.

In the early 1980s, Dr. Lemole provided me my first introduction to the possibility of using antioxidant therapy in a cardiac setting such as postoperative surgery. I was empirically impressed with the results I saw with my patients postoperatively. Recently, literature has shown that there is increasing interest in introducing CoQ10 for treatment of mitochondrial disorders. Since then, we have had great success in establishing and maintaining wellness in our patients and traditionally carrying lower hospitalizations and pharmaceuticals (and thereby healthcare cost) than most of our colleagues. We believe that this success has everything to do with our cooperative patients, largely adopting and remaining with the Mind-Body Wellness Program described in this book.

Sewell, NJ, USA Nicholas L. DePace

Contents

Summary

This book details the science behind the Mind-Body Wellness Program and highlights our clinical successes with the program over the past one and a half decades. This is truly a supplemental approach to standard pharmaceutical, noninvasive, and invasive therapies. An example of its application as a supplemental program is provided in the next paragraph. The program should never be taken as a replacement for standard therapy and may not be for everyone. This program or any portions of this program should be started under close physician supervision.

Someone in the United States dies of a heart disease every 90 seconds. Despite taking statins and lowering cholesterol by 33%, two-thirds (67%) of at-risk patients still have major adverse cardiac events (MACE, e.g., heart attack, sudden death) or stroke, including repeat events. Patients, for example, are not protected from MACE or stroke just because they are on a statin. These patients' disease includes autonomic and mitochondrial dysfunction. A six-pronged approach is used to treat and prevent autonomic and mitochondrial dysfunction and includes the amino acids L-arginine and L-citrulline, as well as inorganic nitrates from beet root and spinach. These amino acids and nitrates may help to protect the two-thirds of the subpopulation, thereby closing that gap. Unfortunately, this will never be heard from the pharmaceutical industry. However, there are peer-reviewed articles in prestigious medical journals that support a lifestyle and supplement (non-pharmaceutical) approach. The pharmaceutical industry will not promote a lifestyle and supplement program because it will detract from their economic profits and require less of their product.

This is just one example of such gaps. Stress, including psychosocial stress, and stress due to anxiety, depression, diabetes, being overweight, excessive consumption of processed and fast foods, sedentary lifestyles, pain, etc., may all lead to chronic diseases, including heart and vascular diseases. While there are pharmaceuticals designed to treat all of these conditions, typically, that is all they do. They only treat these conditions. They do not cure them. In another example, there is a television commercial that says to take another antidepressant if the one prescribed is not (fully) effective. This is another gap, and in this case, the additional antidepressant may only serve to make a bad situation worse. The fish oils, antioxidants (e.g., alpha-lipoic acid), olive oil, and exercise may do more than any (or both) antidepressants, without the myriad of side effects, including suicide risk.

Our point is that despite pharmaceuticals, our patients are still suffering. They suffer from poor quality of life (QoL) due to increased morbidity risk and from reduced longevity due to increased mortality risk. It may be argued that a younger adults' basic definition of QoL is upper GI health, restful sleep, lower GI and bladder health, proper erectile function and vaginal lubrication, and no lightheadedness upon standing. Nowadays, normal blood pressure, cognitive function (including no "brain fog"), and proper energy levels should probably be added. Even when these functions are diminished with time, older adults' QoL would include having the energy and cognitive faculties to spend time with grandchildren, even if the rest of their QoL functions are suffering. By normalizing autonomic and mitochondrial dysfunction, morbidity and mortality risk is minimized, thereby optimizing QoL and possibly longevity. It may also reduce the prescription medication load required to maintain health and establish wellness.

As another example, the vast majority of patients with anxiety, diabetes, heart and kidney diseases, and more have high blood pressure (BP). High BP is arguably the most common condition measured and is not a diagnosis. Consider it more of a warning. High BP is not a problem to be diagnosed until it becomes chronic. Chronic high BP is known as the "silent killer" and is diagnosed as hypertension. High BP must be demonstrated in two or more consecutive doctor visits before a diagnosis of hypertension. Chronic high BP (hypertension) will:

- Damage the organs of the body, like the kidneys (increased morbidity risk), leading to renal failure (increased mortality risk)
- Damage the blood vessels (increased morbidity risk) leading to atherosclerosis, aneurysms, and stroke (increased mortality risk)
- Overwork the heart (increased morbidity risk), leading to heart failure or heart attack (increased mortality risk)
- Damage the nerves and nervous tissue, including the brain (increased morbidity risk) leading to dementia (e.g., Alzheimer's or Parkinson's disease) and autonomic neuropathy (increased mortality risk)

Chronic high BP accelerates the aging process, making one look and feel older before their time.

Over 50% of patients with hypertension are not adequately controlled. They suffer from autonomic and mitochondrial dysfunction causing one or more of headaches or migraines; cognitive difficulties, including "brain fog"; fatigue; lightheadedness or dizziness; anxiety or panic attacks; sleep disorders; and more. A piece of the puzzle is missing. The six prongs of the Mind-Body Wellness Program (Fig. 1) address the autonomic and mitochondrial dysfunction and, thereby, the chasm between well-controlled and current state of most patients. These are (1) a Mediterranean diet, (2) exercise, (3) reduced psychosocial stress, (4) increased nitric oxide to provide better circulation to all cells, (5) decreased oxidative stress to increase energy production and prevent chronic disease or slow its progression, and (6) increased "good" fats to get the energy to all parts of the body.

The six-pronged approach includes three nutraceutical compounds, which are required together for optimal health because all three help support nervous and cardiovascular system health through different mechanisms. One com-

Fig. 1 The lifestyle and supplement prongs that together comprise a Mind Body-Wellness Program. (Illustrations by Elysian Creative Studio, www.elysiancreativestudio.com, Lizzy Colombo)

pound includes omega-3 fatty acids as obtained from fish oils, for example. These are membrane stabilizers, as well as an anti-inflammatories and antioxidants. Omega-3 or fish oils are provided separately to establish and maintain healthy cell membranes and endothelial function. A nitric oxide compound is included. Nitric oxide, indirectly, supports the heart and vasculature. Both need to be supported at the same time. By providing a nitric oxide compound, nitric oxide production is supported, which promotes endothelial health. The endothelium is the sheet of cells that line all of the blood vessels of the body. Endothelial health promotes proper (smooth) blood flow and flexible and more relaxed blood vessels, both of which may lower blood pressure. Smooth blood flow and lower blood pressure help to protect the heart. Nitric oxide, acting as an antioxidant, together with fish oil, will establish and maintain a healthy lipid balance as supported and perpetuated by the combination of the Mediterranean diet providing more omega-3 fatty acids and exercise inducing additional antioxidant activity. The third compound is an antioxidant compound which supports the brain and the nervous system, especially the autonomic nervous system (ANS), including the parasympathetic and sympathetic (P&S) nervous systems, which are the two components of the ANS. The antioxidant compound includes alpha-lipoic acid (ALA) and coenzyme Q10 (CoQ10), two of the most powerful antioxidants

produced in the body. Unfortunately, due to stress, chronic disease, and aging, the body produces less and less of these antioxidants. Fewer antioxidants accelerate the aging process. A high stress lifestyle may reduce the levels of these powerful antioxidants. Levels have been documented as having been reduced to that of a normal 80-year-old individual by the time one is 40 years old. This then reduces QoL and longevity. Diabetes, for example, does the same. It causes a 60-year-old individual with diabetes to have 80-year-old blood vessels. The antioxidant compound, with fish oils and nitric oxide production, provides nutrients and antioxidants to establish and maintain brain and nerve health, thereby reducing psychosocial stress (including anxiety and depression), cognitive difficulties, decreasing oxidative stress, and increasing energy production. It also delays the onset of and reduces the severity of dementia.

> The person who takes medicine must recover twice, once from the disease and once from the medicine. (Sir William Osler, Bt)

The Mind-Body Wellness Program, in part, focuses on the P&S (autonomic) nervous systems. This is the portion of the nervous system that forms the brain-heart (Fig. 2 [1]) and mind-body connection. The P&S nervous sys-

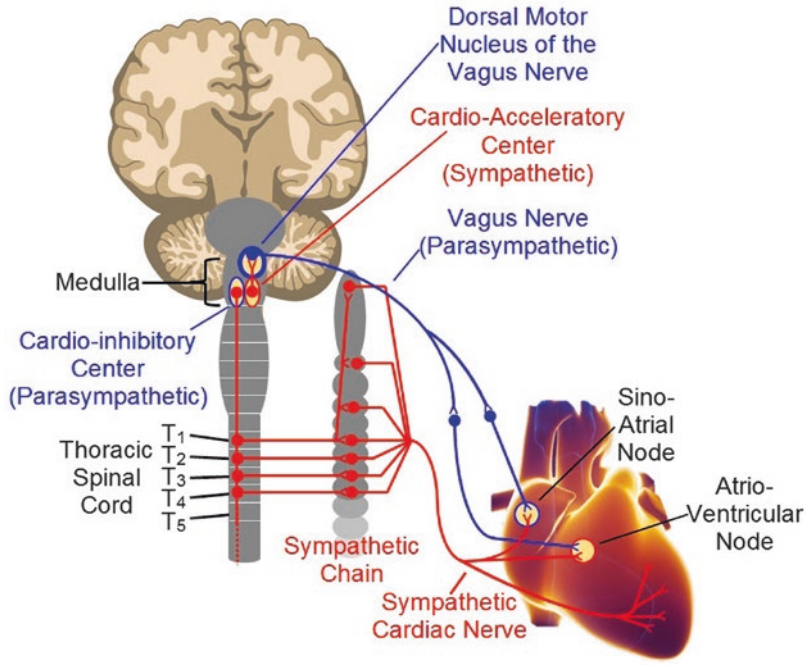

Fig. 2 Parasympathetic and Sympathetic innervation of the heart: anatomy. Efferent fiber (Vagus) comprises A-beta, A-delta, and unmyelinated C fibers. Coronal Cut illustration modified from Royalty-free stock vector images ID: 1203177505. Coronal and sagittal cut of the human brain. Diagram. Vector illustration, by Olga Bolbot. Heart illustration adapted from Shutterstock Royalty-free stock illustration ID: 82159072 by CLIPAREA l Custom media. (Source: [1]. Reproduced from Martini FH. Fundamentals of Anatomy and Physiology. 8th ed. 2006. Chapter 20, by permission of Pearson Education, Inc Prentice Hall, copyright © 2006. Alternate Source: Agarwal SK, Norby FL, Whitsel EA, Soliman EZ, Chen LY, Loehr LR, Fuster V, Heiss G, Coresh J, Alonso A. Cardiac Autonomic Dysfunction and Incidence of Atrial Fibrillation: Results from 20 years follow-up. JACC. 2017; 69(3): 291–9)

tems regulate blood pressure, heart rate, airway size, airflow to lungs, digestion, bladder and sexual function, depression, anxiety, gland and hormone function, and all of the rest of the body functions. In fact, the P&S nervous systems control or coordinate virtually all cells of the body and all organ and organ systems of the body. The sympathetic nervous system is the reactionary nervous system (known as the "fight or flight" nervous system), responding to stresses and generally expending energy. The parasympathetic nervous system is the protective nervous system (known as the "rest and digest" nervous system) and generally conserves energy. The health of, and balance between, the P&S nervous systems defines QoL, including morbidity and mortality risks.

For example, if the sympathetic nervous system becomes over-reactive, it may damage the parasympathetic nervous system. This may amplify pain reactions and reaction to simple stimuli, causing, in the extreme, anxiety-like, fibromyalgia, or post-traumatic stress disorder symptoms. Prolonged, excess sympathetic activation also leads to chronic inflammation. The P&S systems work together. Excess activity in one branch wears on the other. Most commonly, the overactivation of sympathetic activity, due to the typical stresses of everyday American lifestyles, accelerates the onset of parasympathetic neuropathy leading to early, and persistent, morbidity and mortality risk. The converse has also been noted. Patients that exercise their parasympathetic nervous system too much, through meditation, yoga, and the like, or sympathectomies, have had sympathetic imbalances that also effect morbidity and mortality risk [1]. The main problem is that P&S imbalance increases MACE risk (including stroke). Specifically, low parasympathetic activity levels, especially when compounded by (relatively) high sympathetic activity levels, increase the 5-year mortality rate to over 50% [2]. Clinically speaking, the parasympathetics are not strong enough to prevent a sympathetically mediated ventricular tachy-rhythm from becoming fibrillation or death.

Proper mitochondrial function, including proper amounts of adenosine triphosphate (ATP) produced from the mitochondria, is fundamental to health and wellness. Nerves, including the brain, require lots of energy. Just sitting there, the brain consumes about 70% of the energy produced in the body to control all of the functions of the body. During periods of high activity (whether running or swimming, having an emotional experience like love or rage, or taking a final exam), the brain consumes up to 85% of the energy produced in the body to also control the additional activities. Many cognitive disorders may involve both autonomic and mitochondrial dysfunctions. ATP is needed for all nerve functions and muscle contractions, including cardiovascular muscle contractions.

A lack of ATP causes many mitochondrial and autonomic disorders. Mitochondria produce a significant amount of reactive oxygen species (ROS, a type of free radical). One to three percent (1–3%) of all ROS leak out of the electron transport chain within the mitochondria. ROS damage tissue, including the mitochondria themselves. ROS must be reduced by antioxidants, or they cause damage to proteins, lipids, and cell membranes. In this way, ROS may create atherosclerosis, as well as other damages. Atherosclerosis often blocks blood flow, leading to MACE or stroke. ROS is also associated with various forms of cancer, dementia, and many other diseases and disorders.

ALA and CoQ10 reduce oxidative stress by collecting and neutralizing free radicals, including ROS, that literally burn cell membranes and other structures, including mitochondria. Normally, within the mitochondrial electron transport chains, up to 3% of the time oxygen is incompletely reduced and ROS are produced. Normally, the body's naturally occurring ALA and CoQ10 neutralize these ROS. While there are other antioxidants in the body (i.e., vitamins A, C, and E), these are the most powerful and versatile. They are designed to support P&S and mitochondrial health; they already exist within the nerves and mitochondria, and they recycle vitamins A, C, and E. However, as people age (normally or due to stress, disease, or injury), there are fewer endogenous antioxidants available, and more free radicals leak out of the mitochondria and into the cells, damaging both.

Oxidative stress often causes mitochondrial dysfunction. Mitochondrial dysfunction includes a loss of efficiency, including fewer ATP produced in the electron transport chain and fewer mitochondria to produce ATP. Less ATP means less energy. This is at the core of how chronic stress leads to fatigue and depression. Another result is an increase in free radical production, thereby damaging cells throughout the body. This is a characteristic of aging and is a result of all chronic diseases. Mitochondrial dysfunction can affect all body parts and organs. Oxidative stress can accelerate aging and promote tumor genesis, as well as most chronic diseases, including diabetes, Parkinson's and other neurological diseases, certain types of dementia, and kidney and cardiovascular diseases. Antioxidants react with ROS to prevent or repair damage to tissues.

Because mitochondrial dysfunction relates directly to the aging process, it has been suggested as playing a role in atherosclerotic cardiovascular disease. Mitochondrial DNA copy numbers (mtDNA-CN) are statistics derived from the number of mitochondria per cell and the number of mitochondrial genomes per mitochondria. Analyzing mtDNA-CN in patients at risk for cardiovascular disease could help clinicians predict sudden cardiac death and heart failure in patients up to a decade before anything happens, including symptoms [3, 4]. These findings pave the way for improved outcomes in cardiac patients. The study stated that blood testing for mitochondrial DNA measurements could lead to early detection of cardiovascular disease (CVD) and, therefore, allow at-risk patients to take preventative measures against developing heart problems in the future.

Approximately two out of every three people who experience sudden cardiac death show no symptoms that could have warned their physician of their risk [5]. P&S monitoring already provides a risk indicator for sudden cardiac death, stroke, or other MACE. The P&S indicator is Cardiovascular Autonomic Neuropathy (CAN), which predicts the 5-year risk for MACE [6]. As a risk measure, CAN is more specific when the risk is stratified by Sympathovagal Balance (SB[2]); predicting the 2-year mortality risk [1]. The

[2]SB is the ratio of resting sympathetic activity (S) to resting parasympathetic activity (P); {SB = S/P: normal adult range: $0.4 < SB < 3.0$}. It is a ratio of averages, rather than an average of ratios. It is a more specific measure of the relative P&S levels as compared to the traditional heart rate variability (HRV) low- to high-frequency ratio (L/H). In P&S

P&S nervous systems rely heavily on mitochondrial function. The lower mitochondrial DNA-CN numbers were, the more at risk a patient was for suffering an adverse CVD event. MTDNA-CN could more accurately predict a 10-year risk for heart failure and augments the P&S findings of CAN with abnormal SB, helping to improve specificity of those who would require early intervention to minimize morbidity and mortality risk, maintain quality of life, reduce hospitalizations and rehospitalizations, reduce healthcare costs, and improve patient outcomes.

The study drew 21,870 participants from the databases of the Cardiovascular Health Study, the Atherosclerosis Risk in Communities Study, and the Multiethnic Study of Atherosclerosis; 92% were CVD-free at baseline. Mitochondrial DNA levels were measured against nuclear DNA levels in these patients, and that number was input into the American College of Cardiology/American Heart Association's Heart Risk Calculator. The calculator includes a patient's cholesterol levels, blood pressure, smoking history, family medical history, weight, and more to predict a 10-year risk for heart attacks and other adverse cardiac events. The study correctly predicted that 6 patients who otherwise wouldn't have been recommended for heart treatment went on to have a life-threatening heart event and 139 patients who would have been recommended for statin treatment under current guidelines actually didn't suffer from CVD.

> One of the first duties of the physician is to educate the masses not to take medicine. (Sir William Osler, Bt)

Nutrients included in the Mind-Body Wellness Program are listed below, in no particular order, with a brief description of their function or benefit:

- *Alpha Lipoic Acid (ALA)* – an anti-inflammatory and an antioxidant. At the cellular level, ALA (1) reduces oxidative stress; (2) scavenges (through chelation) and sequesters free radicals, including ROS; (3) brings products to mitochondria; (4) regenerates other antioxidants, including vitamins C and E; (5) increases nitric oxide production; and (6) boosts energy (ATP) production. At the system level, ALA (1) aids in P&S and sensory nervous system function; (2) lowers blood pressure (BP); and (3) slows or relieves the progression of autonomic neuropathy in diabetes and possibly in other chronic diseases [7]. Natural ALA levels in the body decline with age and duration of chronic disease.
- *Coenzyme Q10 (CoQ10)* – an antioxidant. At the cellular level, CoQ10 (1) sequesters active ROS, (2) increases energy (ATP) production, (3) limits electron leak in the electron transport chain (also increasing (ATP) energy production), and (4) reduces mitochondrial dysfunction. At the system level, CoQ10 (1) decreases cholesterol, (2) increases immune function, (3)

terms, "L" is a measure of both P&S activities, but not necessarily all of the P-activity, only that which happens to be in the low-frequency region at the time. "H" is a measure of the rest of the P-activity not in the low-frequency region, plus noise, due to the fact that the high-frequency region is a broad-band, fix measure that may not capture any P-activity. In summary, L/H is approximately (S + P)/(P + noise) and requires assumption and approximation to hypothesize S/P = SB [1].

increases cardiac function by supporting cardiac muscle health, (4) supports skeletal muscle health, (5) reduces inflammation (including reducing inflammatory markers), and (6) lowers BP. A very important note: natural CoQ10 levels in the body decline with age [8].

- *Vitamin B*, vitamins B_6 and B_{12}, with *magnesium (Mg)* are the potent supporters of parasympathetic nervous system health and thereby help to elevate mood, and protect the heart, among other benefits, such as helping to improve mental health [9].
  - B_6 *(Pyridoxine)* – supports nervous system function and boosts energy (ATP) production.
  - B_{12} *(Cobalamin)* – supports nervous system function and boosts energy (ATP) production.
  - *Folic acid* (B_9) – cofactor in producing nitric oxide, cofactor in citric acid cycle to trap electrons, and cofactor in reducing the toxin homocysteine. High dose Folic Acids helps to slow or reverse the progression of small fiber disease.
  - B_1 *(Thiamine),* B_2 *(Riboflavin),* B_3 *(Niacin),* B_5 *(Pantothenic Acid), and* B_9 *(Folic Acid)* – boosts energy (ATP) production, is a cofactor in citric acid cycle to trap electrons, and attenuates the abnormal effects of asymmetric dimethylarginine (ADMA) by competing with *L-arginine* for nitric oxide synthase (NOS). The arginine part of ADMA, by replacing L-arginine in reactions with NOS, enables ADMA to impair NOS and the synthesis of nitric oxide.
- *Vitamin* D_3 – helps to strengthen the bones and teeth and helps to decrease diabetes [9].
- *Vitamin E* – a fat-soluble antioxidant that protects cell membranes from ROS, thereby slows the aging process [9].
- *Vitamin K* – supports vascular health, reducing arterial calcification (specifically Vitamin K2), supports healthy blood clotting, and can slow cancer growth [9].
- *Minerals:*
  - *Magnesium (Mg)* – supports parasympathetic nervous system function, boosts energy (ATP) production and reduces anxiety
  - *Zinc (Zn)* – supports immune function and memory, decreases severity of chronic diseases that are age-related, and supports wound healing by contributing to collagen synthesis and epithelialization
  - *Copper (Cu)* – involved in collagen synthesis, supports energy (ATP) production, and increases absorption of iron
  - *Manganese (Mn)* – supports nerve function, involved in fat and carbohydrate metabolism, helps to form connective tissue in bones, and supports blood clotting factors
  - *Selenium (Se)* – an antioxidant that boosts energy (ATP) production
  - *Iron (Fe)* – key to red blood cell function, supports the immune system and involved in energy (ATP) production
- *Amino Acids:*
  - *Glutathione* – an antioxidant that scavenges free radicals and heavy metals and boosts energy (ATP) production.
  - *N-Acetyl Cysteine* – boosts *glutathione* levels.
  - *L-Arginine* – produces nitric oxide naturally through the endogenous nitric oxide synthase (NOS) system. By giving L-arginine exogenously

as well, the L-arginine to ADMA ratio may be increased and tissue damage decreased.
  - *L-Citrulline* – easily absorbed in the liver. L-citrulline is converted to L-arginine and nitric oxide, thereby helping to maintain nitric oxide levels.
  - *L-Carnitine Tartrate* – (1) increases nitric oxide signaling, (2) improves endothelial function, (3) reduces oxidative stress, (4) is important as rate-limiting step in fatty acid oxidation that produces ATP, and (5) supports the metabolism of fat.
  - *L-Lysine* – precursor[3] to *L-carnitine*, boosting *L-carnitine* levels.
- *Beet Root* – a potent, alternate, exogenous source of nitric oxide promoting compounds that does not use the traditional nitric oxide synthesis pathways that involve amino acids.
  - In the body, nitric oxide is generated quickly and dissipates quickly under normal situations. Systemically, it increases endothelial function, thereby enhancing exercise tolerance and lowering blood pressure. It is a natural vasodilator and increases blood flow and circulation. It also inhibits the oxidation of ("bad") LDL cholesterol into "foam cells" that are the precursors to atherosclerosis; as a result, it helps to reduce or lower atherosclerosis. In addition, nitric oxide also (1) kills bacteria, (2) enhances immune function, (3) aids neurotransmission, (4) decreases inflammation, (5) may dilate bronchioles, (6) is an antithrombotic, (7) may promote better cerebral circulation, (8) increases Vagal (parasympathetic) tone, (9) slows heart rate, and (10) lowers blood pressure. By increasing parasympathetic tone, including slowing heart rate and lowering blood pressure, nitric oxide is therefore cardioprotective. However, it diminishes with age. By 60 years of age, people have lost, on average, 85% of their nitric oxide production abilities.

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[3] …with Methionine…

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Disclaimer

Over the years, Drs. DePace and Colombo have worked to avoid, and have even resisted, developing supplements or nutraceuticals. While we recognize that, sometimes, some supplements and nutraceuticals may work for some people, their general reliability in improving patient outcomes, population wide, is less than that for pharmaceuticals. Please understand that the difference between pharmaceuticals and supplements and nutraceuticals is that the FDA ensures that pharmaceuticals work at least 80% of the time (the other 20% may end up in the courts, claiming bad drugs), whereas supplements and nutraceuticals are more a 50-50 proposition. The difference is important to physicians in helping to convince patients that a proposed therapy plan should work. In addition, the lack of scientific rigor and validity and statistical relevance or the poor reputation of many supplements and nutraceuticals turned us off from becoming involved. Do not get us wrong if patients had no other choice or were willing to try supplements and nutraceuticals, then we were were happy to assist. We are not sold out to the pharmaceutical approach either. What we are sold out to is lifestyle modifications: exercise (yes *exercise*, it is not a bad word, especially when we mean an active lifestyle, not necessarily beating one's self up in the gym), the Mediterranean diet, stress reduction (especially reducing psychosocial stress), and building an antioxidant reserve to address what cannot be controlled.

However, recently, many have asked us to create a supplement and nutraceutical program to augment the lifestyle program we have been recommending, including incorporating the antioxidants. So we endeavored to research the literature for those agents that are not only purported to be beneficial but had also the scientific and statistical evidence behind it to validate them. In this way, we have convince ourselves that these agents have a better than 50-50 chance of helping our patients. These are the origins of this book.

While we have packaged the supplements and nutraceuticals with quantities that we recommend for the convenience of our patients, we are not promoting our supplement and nutraceutical package through this book. In fact, we recommend that people choose for themselves and select the ingredients that they wish, after conferring with their physician. For example, a portion of our product includes a nitric oxide supplement, the same benefits of which may be obtained from the product SuperBeets® from human^{n} which has been studied by cardiologists and published in the *Journal of the American College of Cardiology*. In fact, as a matter of convenience, we have modeled our product after the published product.

Again, this book is *not* meant to be an advertisement for our product(s). It is meant to be a promotion for the lifelong adoption of the six-pronged Mind-Body Wellness Program, which includes (1) omega-3 fatty acids, (2) nitric oxide, (3) oxidative stress reduction, (4) Mediterranean diet, (5) exercise, and (6) psychosocial stress reduction, that is used to treat and prevent autonomic and mitochondrial dysfunction. Again, the first three prongs may be purchased anywhere. This book is the first of a series of publications designed to help the physician and the patient find reliable and validated forms of omega-3 fatty acid, nitric oxide, and antioxidant products (supplements and nutraceuticals) that have the best chance of helping.

To be clear and for total transparency in this disclaimer, our products include:

- Cardio-Neuro-Mito™, an antioxidant compound
- Vasso-Plus ™, a nitric oxide compound
- Omega-3 Fish Oil

We wish all a lifetime of health and wellness. Enjoy!

Abbreviations

AAD	Advanced Autonomic Dysfunction
ACE-I	Angiotensin-converting enzyme inhibitor
ADD/ADHD	Attention deficit disorder/attention deficit hyperactivity disorder
ADMA	Asymmetric dimethylarginine
ADP	Adenosine diphosphate
AFib	Atrial fibrillation
ALA	Alpha-lipoic acid
ALLA	Alpha-linoleic acid
ANS	Autonomic nervous system
ARB	Angiotensin receptor blocker
ATP	Adenosine triphosphate
BP	Blood pressure
btb	Beat-to-beat
CABG	Coronary artery bypass grafting
CAN	Cardiovascular Autonomic Neuropathy
CASS	Composite autonomic scoring scale
CBD	Cannabidiol
CFS	Chronic fatigue syndrome
cGMP	Cyclic guanosine monophosphate
CHF	Congestive heart failure
CNS	Central nervous system
COPD	Chronic obstructive pulmonary disease
CoQ10	Coenzyme Q10
CRP	C-reactive protein
CRPS	Chronic regional pain syndrome
CVD	Cardiovascular disease
DAN	Diabetic Autonomic Neuropathy
DB	Deep breathing
DHA	Docosahexaenoic acid
DNA	Deoxyribonucleic acid
ED	Erectile dysfunction
EEG	Electroencephalogram
EKG	Electrocardiogram
EPA	Eicosapentaenoic acid
GERD	Gastroesophageal reflux disorder
GI	Gastrointestinal

HDL	High-density lipoproteins
HPA	Hypothalamic-pituitary-adrenal
HR	Heart rate
HRV	Heart rate variability
HSP	Heat shock proteins
LDL	Low-density lipoproteins
LOX-1	Oxidized LDL 1 receptor
MACE	Major adverse cardiovascular event
MAO	Monoamine oxidase
NAC	N-acetylcysteine
NMDA	N-methyl-D-aspartate
NOS	Nitric oxide synthase (three types: e-, c-, n-, endothelial, constitutive and neural, respectively)
OH	Orthostatic hypotension
ox-LDL	Oxidize low-density lipoproteins
P	Parasympathetic
P&S	Parasympathetic and sympathetic nervous systems
PAN	Peripheral autonomic neuropathy
PC	Postural change
PE	Parasympathetic excess
PNS	Peripheral nervous system
POTS	Postural orthostatic tachycardia syndrome
PTSD	Post-traumatic stress disorder
PUFA	Polyunsaturated fatty acid
QoL	Quality of life
QSART	Quantitative Sudomotor Axon Reflex Test
RAAS	Renin-angiotensin-aldosterone system
RNS	Reactive nitrogen species
RONS	Reactive oxygen nitrogen species
ROS	Reactive oxygen species
RVLM	Rostral ventrolateral medulla
S	Sympathetic
SB	Sympathovagal balance
SE	Sympathetic excess
SNRI	Serotonin-norepinephrine reuptake inhibitors
SOD	Superoxide dismutase
SSRI	Selective serotonin reuptake inhibitors
SW	Sympathetic withdrawal
THC	Delta-9-tetrahydrocannabinol
TMJ	Temporomandibular joint
TNF	Tumor necrosis factor
VEGF	Vascular endothelial growth factor
VNS	Vagal nerve stimulation