**WEBSITE CONTENT**

**Healthcare Provider Content**

The heart is a special muscle and as all other muscles in the body, the heart is controlled by nerves. However like the heart, these are special nerves as well. The nerves are the parasymapathetic and sympathetic (P&S) branches of the autonomic nervous system (ANS). Together with the P&S nerves, there are three factors in the control of the function of the heart:

1. The mechanical or pump function, as measured by echocardiogram;
2. The electrical features of the heart muscle itself, as measured by EKG; and
3. The P&S nervous system input to the heart, as measured by P&S monitoring.

Dysfunction in any one or more of these features of the heart is assocaited with heart disease.

The blood vessels, including the arteries and veins, are also intimately involved in heart function. This is why vascular disease is also associated with heart disease.

Many well known heart diseases are evident Echo and EKG. The heart diseases evidencw from P&S Monitoring may not be well know, and include: syncope, orthostatic dysfunction, autonomic imbalance, many unexplained symptoms, and cardiovascular autonomic neuropathy (CAN). While some of these are sometimes evidenced by tilt-table testing and other autonomic testing, objective, quantitative, independent and simultaneous measures of P&S function has heretofore been difficult.

There are lifestyle, medical history, genetic, and other risk factors that may contribute to heart disease. Risk factors in heart disease are based on the potential for developing Atherosclerosis. Atherosclerosis is a hardening of the arteries. It is a common disorder in which plaques form that narrows arteries, reducing blood flow and causing problems throughout the body. Plaques may lead to Atherothrombosis [[[1]](#endnote-1)] which can have unpredictable and life-treatening consequences, including acute coronary syndromes and (ACS) and cardiovascular or sudden death.

There are two general categories of risk factors: Traditional and non-traditional. Epidemiological studies [[[2]](#endnote-2),[[3]](#endnote-3),[[4]](#endnote-4),[[5]](#endnote-5),[[6]](#endnote-6),[[7]](#endnote-7),[[8]](#endnote-8),[[9]](#endnote-9),[[10]](#endnote-10)] confirm traditional risk factors for the development of atherosclerotic heart disease. They demonstrate that atherosclerosis often leads to coronary heart disease (CHD), Cerebral Vascular Disease (including stroke and transient ischemic attack); Peripheral Artery Disease (including intermittent claudication and ischemia to the lower extremities); and Atherosclerosis of the Aorta, which may lead to aneurysm formation [[[11]](#endnote-11)]. Risk factors in heart disease are categorized into:

* **Traditional Risk Factors**: 1) age[[12]](#footnote-1); 2) Diabetes; 3) smoking; 4) high blood pressure (BP) or Hypertension[[13]](#footnote-2); 5) Dyslipidemia[[14]](#footnote-3), low high-density lipoprotein (HDL) cholesterol[[15]](#footnote-4), or Hypertriglyceridemia[[16]](#footnote-5); and 6) family history of premature coronary artery disease (CAD[[17]](#footnote-6)).
* **Non-Traditional Risk Factors**: 1) abnormal Ankle-Brachial Index (ABI); 2) chronic inflammation as indicated by abnormal levels of C-Reactive Protein (CRP), Fibrinogen, Lipoprotein (a), Brain Natriuretic Peptide (BNP), or Human immunodeficiency virus (HIV); 3) Homocysteine elevation; 4) Microproteinuria[[18]](#footnote-7); 5) Microalbuminaria[[19]](#footnote-8); 6) Metabolic Syndrome; 7) elevated serum insulin levels; 8) Renal Disease; 9) abnormal Calcium Score; 10) Carotid Intima-Media Thickness; 11) left ventricular (LV) hypertrophy; 12) psychosocial stresses; 13) alcohol; 14) abnormal diet; 15) clinical depression; 16) obesity[[20]](#footnote-9); 17) sedentary lifestyle; 18) various types of infections; and 19) collagen vascular diseases.
* **Modifiable Risk Factors** (those that may be treated and negated, reversed, or diminished): smoking, Dyslipidemia, Hypertension, sedentary lifestyle, diet, obesity, type 2 Diabetes Mellitus or impaired glucose tolerance, and CRP.
* **Non-Modifiable Risk Factors**: age, gender, genetic abnormalities, and family history of premature atherosclerosis.

**RISK SCORES**

For many decades, physicians and epidemiologists have attempted to develop equations, scoring systems, and algorithms to risk stratify and predict which individual patients are at risk for cardiac events. The first landmark system was derived from prospective follow-up of approximately 20 years of a cohort of individuals that resided in Framingham, MA. The Framingham Risk Score projects future risk of cardiovascular disease (CVD) for up to ten years [7]. This risk score system incorporates several risk factors which are commonly seen in a large cohort of individuals (traditional risk factors). These risk factors include: diabetes, hypertension, lipid elevations, cigarette smoking, and age. While the Framingham Risk Score was an excellent beginning and is still widely used in clinical medicine today, it has a number of short-comings. Current longer life expectancies need a prediction model that extends beyond ten years. Furthermore, large sub-populations develop complications from heart disease and are not identified by these scoring systems [10,[[21]](#endnote-12),[[22]](#endnote-13)]. Family history of premature coronary artery disease, a risk factor not incorporated into the Framingham risk score, is an addition important factor in risk stratification for cardiac events.

The family history of premature CAD with inflammation (*e.g.*, as measured by CRP) added to the Framingham Score (the Reynolds Risk scoring system), improves upon the Framingham system. The Reynolds risk scoring system is based on age, BP, cigarette smoking, CRP, and family of history of cardiac event prior to 60. The improvement in this scoring system is based on the fact that the Reynolds scoring system reclassifies almost half of the intermediate risk women into high and low risk groups [10]. Here again, however, the Reynolds Risk scoring system only predicts out to ten years.

Recently, research into risk scoring has focused on non-traditional risk factors which have been shown to improve scoring. In addition to CRP, ultrasound, doppler, and other imaging-derived measurements, such as carotid intimal thickness, ABI, and cardiac CT scan calcium scores, have also yielded addition information in risk stratification [10,12,13,[[[23]](#endnote-14)],[[24]](#endnote-15),[[25]](#endnote-16),[[26]](#endnote-17),[[27]](#endnote-18)]. Another risk factor which predisposes patients to adverse cardiac events is autonomic neuropathy, specifically cardiovascular autonomic neuropathy (CAN) [[[28]](#endnote-19),[[29]](#endnote-20),[[30]](#endnote-21),[[31]](#endnote-22),[[32]](#endnote-23),[[33]](#endnote-24),[[34]](#endnote-25),[[35]](#endnote-26),[[36]](#endnote-27),[[37]](#endnote-28),[[38]](#endnote-29),[[39]](#endnote-30),[[40]](#endnote-31),[[41]](#endnote-32),[[42]](#endnote-33),[[43]](#endnote-34)]. CAN is associated with other risk factors [[[44]](#endnote-35)], including 1) low ejection fraction [[[45]](#endnote-36),[[46]](#endnote-37)]; 2) poor cardiac output [[[47]](#endnote-38)]; 3) arrhythmias [[[48]](#endnote-39)],[[49]](#endnote-40)]; 4) cardiomyopathies [[[50]](#endnote-41),[[51]](#endnote-42)], including chronic heart failure [[[52]](#endnote-43)]; 5) poor circulation [[[53]](#endnote-44)], including poor cardiac circulation (Angina or CAD) [[[54]](#endnote-45)]; 6) greater mortality [20]; and 7) greater morbidity [[[55]](#endnote-46)], including silent MI and early cardiac death [20,[[56]](#endnote-47)]. Often, very low parasympathetic activity leads to the need for cardiac intervention or an implanted cardiac device. With supplemental information from parasympathetic and sympathetic monitoring, which identifies CAN, appropriate treatment modalities, including pharmacological and cardiac device therapy, may reduce adverse cardiac outcomes. By restoring proper P and S balance [[[57]](#endnote-48)], morbidity and mortality may be reduced [19,20,[[58]](#endnote-49)].

**CARDIOVASCULAR RISKS ASSOCIATED WITH AUTONOMIC NEUROPATHY**

**Autonomic Neuropathy is Associated with Cardiac Mortality Risk**

Heart rate is normally not constant. For younger, healthier individuals, instantaneous heart rate varies with respiration and is known as respiratory sinus arrhythmia (RSA). RSA declines with age and chronic illness or injury. The field of beat-to-beat changes in heart rate is known as heart rate variability (HRV) and has been known since the seventeen hundreds [[[59]](#endnote-50)]. The study of HRV (or similarly beat-to-beat blood pressure, brbBP) is a study of total autonomic nervous system (ANS) activity. However, we need to go deeper to understand the P&S branches of the ANS. For this we need to add to HRV (or btb BP) [51,52,[[60]](#endnote-51),[[61]](#endnote-52)]. Researchers at MIT and Harvard proved that the addition is the analysis or respiratory activity [[[62]](#endnote-53),[[63]](#endnote-54),[[64]](#endnote-55),[[65]](#endnote-56)]. “Functional imbalances between the sympathetic and parasympathetic nervous systems are discerned with respiratory modulation.” [20] This observation is supported by a large body of literature (*e.g.*,[31,32,33,34,[[66]](#endnote-57),[[67]](#endnote-58),[[68]](#endnote-59)]). Analyzing both HRV and respiratory activity, simultaneously, is P&S monitoring [[[69]](#endnote-60),[[70]](#endnote-61)].

Respiratory activity (*e.g.*, from impedance plethysmography) helps to identify the cardio-vagal response which is respiratory sinus arrhythmia (RSA). Conceptually, this technique separates RSA from the other HR changes that are observed in the cardiogram. This technique is sensitive enough to identify RSA even in sick patients when it is not visible to the human in the cardiogram, irrespective of patient history, state, or activity. Specific P&S function testing has the ability to provide the clinician with supplemental information to document and differentiate which agents or therapeutic modalities are needed. For example, more is not always better, such as intensive glucose control for diabetic patients [[[71]](#endnote-62),[[72]](#endnote-63),[[73]](#endnote-64)].

Decreased HRV, specifically very low resting parasympathetic activity as measured by P&S monitoring, defines CAN[[74]](#footnote-10) [20, [[75]](#endnote-65),[[76]](#endnote-66),[[77]](#endnote-67)]. Meta-analyses strengthen the association of CAN with cardiac mortality [20,65,66]. When more measures defining CAN are fulfilled, the mortality rate is higher [20,65,66,83]. Curtis and O’Keefe [19] show that associations of CAN with high mortality rates are consistent across study groups, patient cohorts, testing modalities, autonomic dysfunction, and disease definitions. Subsequent studies demonstrate the association with multi-variant analyses [65,[[78]](#endnote-68),[[79]](#endnote-69)].

Epidemiological studies strengthen the association between CAN and mortality risk [[[80]](#endnote-70),[[81]](#endnote-71),[[82]](#endnote-72),[[83]](#endnote-73)]. After assessing for age, gender, cigarette smoking, diabetes, and other relevant risk factors, P&S measurements offer significant prognostic information beyond that provided by evaluation of traditional cardiovascular risk factors. Tsuji and coworkers studied all-cause mortality in elderly participants, and subsequently addressed the general population [67]. A predicted risk increase for sudden cardiac event was found in 2,501 men and women who were without clinically apparent heart disease and with reduced autonomic activity. A biologically feasible mechanism for this is based on the fact that patients who have heart disease with increased sympathetic activity, or decreased parasympathetic activity, are predisposed to ventricular fibrillation.

Twelve studies of diabetic patients, with and without CAN, show that CAN diabetics are 280% more likely to suffer silent MI than non-CAN diabetics (See Figure 1) [20]. Using a definition of severe autonomic failure that includes abnormalities of autonomic reflex function, Barthel and coworkers [[[84]](#endnote-74)] identify at-risk patients and demonstrate very poor prognoses. In their risk model, autonomic dysfunction predicts history of previous MI, arrhythmia, poor glucose control, and LV ejection fraction less than 30%. This highlights the importance, even in the low risk patients, of performing P&S testing to risk stratify for MACE, including cardiac death. In general, abnormal cardiac autonomic activity as assessed by autonomic monitoring is associated with a post MI mortality, sudden death, and all-cause mortality.

In a population-based prospective study, Liao and coworkers [[[85]](#endnote-75)] demonstrate that autonomic dysfunction, especially lower parasympathetic activity, is associated with the risk of developing CHD. This expands the application of monitoring autonomic dysfunction to a much larger patient base and the general population. Liao *et al*. find that autonomic dysfunction may be a predictor of subsequent development of CAD. This is an extremely important finding, highlighting autonomic dysfunction as a potentially important risk factor for newly developing CAD. Therefore, not only is identifying abnormal autonomic function and CAN important for secondary prevention, it is also important for primary prevention. Furthermore, autonomic dysfunction is correlated with progression of CAD [[[86]](#endnote-76)], and with silent ischemia, which leads to sudden unexpected cardiac death and unexpected MI. Wackers and coworkers [[[87]](#endnote-77)] find that myocardial ischemia is associated with abnormal Valsalva response with a risk ratio of 5.6. Males demonstrate a risk ratio of 2.5, and patients diagnosed with diabetes demonstrated a risk ratio 5.2. All other traditional cardiac risk factors, including inflammatory and pro-thrombotic markers, are not predictive. The emerging cardiac risk factors in this thorough study are not associated with abnormal stress tests or computed tomography imaging. By contrast, CAD is a strong predictor of ischemia.

CAN is associated with a denervated heart, leaving patients unaware of cardiac events. This demonstrates a compelling need to assess P&S function in asymptomatic patients, especially given silent ischemia or sudden cardiac death (SCD). Without P&S Monitoring, critical information concerning the asymptomatic patient’s risk of silent ischemia will be lacking, including clinical trending information to document patients’ responses to therapy. The fact that coronary atherosclerosis may progress with CAN [80], and that silent ischemia may occur with a higher incidence with CAN [19,49,79,80,81], suggests that CAN is either a risk factor or an etiological factor for these subclinical events. Asymptomatic patients, despite having other traditional risk factors, should have autonomic function assessed.

**Stratifying Autonomic Neuropathy Risk**

CAN indicates an autonomic condition in which a sympathetically medicated ventricular tachyrhythm may not be sufficiently slowed by parasympathetic activity to prevent ventricular fibrillation or worse. CAN may be normal for geriatric and long standing chronic disease patients [49]. For example, based on Framingham risk factors, an 85 year-old has a greater mortality risk than a 45 year-old. More, but not excessive, parasympathetic activity relative to sympathetic activity is known to be cardio-protective and reduce mortality risk [49]. Chronic sympathetic activation is known to increase cardiovascular risk [19]. Depression is known to elevate mortality risk in heart disease [[[88]](#endnote-78)], and depression is associated with abnormally high levels of parasympathetic activity relative to sympathetic activity.

The relationship between P&S activity at rest is known as sympathovagal balance (SB) [[[89]](#endnote-79)]. CAN risk (the risk associated with very low-parasympathetic activity with respect to sympathetic activity) may be stratified based on SB. High SB indicates relative resting sympathetic excess. CAN with high SB is considered high risk [21,24,25]. Low SB indicates a relative resting parasympathetic excess. Very low SB (< 0.4) is associated with (sub-clinical) depression and elevates CAN risk [81]. Normal SB, indicating a balanced ANS, is associated with much lower CAN risk [19]. Low-normal SB, indicating more parasympathetic activity, is associated with minimal CAN risk [49].

**Diabetes Risk and Autonomic Neuropathy**

It is well established that Diabetes Mellitus is a major risk factor for heart disease. Diabetic Autonomic Neuropathy (DAN) is a very serious and common complication in diabetes [20]. Symptoms of DAN include: 1) resting tachycardia, 2) exercise intolerance, 3) orthostatic hypotension, and 4) may also include a glycemic autonomic failure [[[90]](#endnote-80)]. DAN is often misperceived as asymptomatic and the symptoms considered in isolation. DAN imposes a burden on an individual whose cardiac reserve may be compromised by underlying atherosclerosis or LV abnormalities. The most studied and clinically important advanced form of DAN is CAN [20]. CAN may be present at diagnosis of diabetes (one in three), and prevalence increases with age, duration of diabetes, and poor glycemic control. CAN encompasses damage to the autonomic nerve fibers that innervate the heart and blood vessels, resulting in abnormalities in heart control and vascular dynamics. Autonomic neuropathy is not restricted to diabetics. Advanced autonomic dysfunction (*i.e.*, a form of DAN in non-diabetics) may occur in those without diabetes, with similar burdens, including CAN. A symptom of CAN is an increased threshold to chest pain during MI (Silent MI), which can lead to SCD.

Various tests of autonomic function have been used to define CAN and have been studied by numerous investigators who compared mortality risk among diabetic patients with and without CAN [[[91]](#endnote-81)]. Tests may include the provocative Ewing challenges [[[92]](#endnote-82)]: changes in posture, Valsalva maneuvers, and paced breathing. These autonomic challenges have been shown to stimulate one or the other or both branches of the autonomic nervous system through changes in HBI and respiratory activity. The Ewing challenges have become the standard for clinical autonomic testing [low, 1997]. Fifteen studies of 2,900 patients with and without CAN showed a 230% higher risk of mortality for the CAN diabetics (See Figure 2) [20]. These data are supported by Ewing’s findings. He demonstrated a 53% mortality risk after five years in patients with CAN [85]. He also compared the mortality rate of abnormal autonomic function tests to a mortality rate of only 15% over a five-year period among diabetic patients with normal autonomic function tests. Half of the deaths of individuals that have abnormal autonomic function were from renal failure and 29% from SCD. CAN increases morbidity and mortality in diabetes and may have greater predictive power than traditional risk factors for cardiovascular events. Significant morbidity and mortality is attributed to dysregulation of cardiovascular function from P&S imbalance. Consider frequent screening for and treating P&S imbalance (dysfunction) [[[93]](#endnote-83),[[94]](#endnote-84)].

**Non-Traditional Risk Factors and Autonomic Neuropathy**

CRP is a useful marker of increased long-term risk of SCD. After 17 years of follow-up study, including Homocysteine and lipid values, CRP was the only significant biomarker that had predictive potential with SCD [[[95]](#endnote-85)]. CRP is associated with decreased autonomic function, even after controlling for traditional risk factors that decrease CAD. Autonomic dysregulation may represent one pathway leading to CAD, even with treatment of risk factors to prevent the development of CAD [[[96]](#endnote-86)]. Dyslipidemia (a traditional risk factor) significantly contributes to atherosclerosis in some cases. Inflammation is also a significant contributor towards atherosclerosis and is a non-traditional risk factor with incremental value [89]. The association of diminished autonomic function with elevated CRP levels is potentially significant. In multi-variant analysis, autonomic variables remain independently associated with CRP while norepinephrine concentrations did not [89]. In a recent work by Vinik, inflammatory markers were correlated with diminished HRV measures and independent measures of low P&S activity with high SB (See Figure 3) [20].

Microalbuminuria has been associated with an increased risk of cardiovascular mortality independently of other known coronary artery risk factors [[[97]](#endnote-87)]. Endothelial function and low-grade inflammation have been proposed to explain the increased risk of cardiovascular mortality in individuals with microalbuminuria [[[98]](#endnote-88)]. The Hoorn study [[[99]](#endnote-89)] (498 individuals, ages 50 to 75 yrs, followed for a median period of 13.6 years) demonstrated that with an albumin to creatinine ratio greater than 2·0 mg/mmol, patients’ CAN was independently associated with cardiovascular mortality. Their conclusions suggest that microalbuminuria and CAD are associated with cardiovascular mortality in an elderly Caucasian population of individuals with normal glucose tolerance.

Again, some of these researchers find that CAN is treatable with more information from P&S monitoring [48,[[100]](#endnote-90)].

**TREATMENTS TO SLOW THE PROGRESSION OF AUTONOMIC NEUROPATHY**

There are no approved pharmaceuticals that specifically target the parasympathetic or sympathetic nerves. Some common agents, however do effect one or the other ANS branch. Beta-blockers (*i.e.*, beta1-adrenergic antagonists), Alpha-blockers (*i.e.*, alpha-adrenergic antagonists), Vasopressors (*i.e.*, alpha1-adrenergic agonists), and Bronchodilators (*i.e.*, beta2-adrenergic agonists) are some of the agents that effect sympathetic (adrenergic) activity. Most anti-hypertensives, including ACE-Is, ARBs, and calcium channel blockers, also effect sympathetic activity. Most anti-depressants (including Tri-cyclics, SNRIs, and SSRIs), anxiolytics, benzodiazepines, and GI motility and sleep medications have anti-cholinergic properties and effect parasympathetic activity. While many of these are used in very low doses to establish and maintain P&S balance, they may be accompanied with undesired side-effects at clinical doses.

Some supplements have been well researched and studied to positively affect autonomic changes, including: Alpha-Lipoic Acid (ALA), Coenzyme Q-10 (CoQ-10), Vitamin B6 (Pyridoxine), Vitamin B12 (Methylcobalamin), Vitamin D (Cholecalciferol), Magnesium Oxide, and Omega-3 Fatty Acids. All of these supplements are found in CardioNeuro Plus.

Alpha-Lipoic Acid (ALA) is a vitamin-like chemical called an antioxidant. It seems safe for most adults. It should not be used in children without medical supervision. In patients with diabetes, it may lower blood sugar. In patients with Thyroid disease it may interfere with treatment. ALA has been show to work well in slowing the progression of autonomic neuropathy in patients with diabetes, diabetic nerve pain, and many other chronic diseases, including heart disease. ALA is used in the body to break down carbohydrates and to make energy for the other organs in the body. It seems to work as an antioxidant, and seems to be selective for nerves, including the nerves innervating the heart helping to relieve the affects of CAN in patients with heart disease or risks for heart disease (*e.g.*, diabetes). ALA might provide protection to the brain under conditions of damage or injury. The antioxidant effects might also be helpful in certain liver diseases.

Coenzyme Q-10 (CoQ10) is a vitamin-like substance found throughout the body, but especially in the heart, liver, kidney, and pancreas. It seems safe for most adults. It should not be used in children without medical supervision. Given it role in producing ATP, CoQ10 may help increase energy. It also seems to have antioxidant activity. Aging, length of chronic disese and smoking decreases stores of CoQ10. In some diabetics CoQ10 has been shown to decrease blood sugar levels. It may help to lower blood pressure.

Vitamins B6 and B12, and Magnesium are known to selectively increase parasympathetic activity, especially in patients with diseases that lead to (relative) sympathetic excesses (*e.g.*, Hypertension, Diabetes, Heart Disease, COPD and Asthma, Sleep Apnea, Chronic Pain). They seem safe for most adults and children at FDA recommended daily allowances. They are known to help improve cognitive function, reduce some dementias, elevate mood, and reduce anxiety. Vitamin B6 is required for the proper function of sugars, fats, and proteins in the body. It is also required for the proper growth and development of the brain, nerves, skin, and many other parts of the body. Vitamin B12 is required for the proper function and development of the brain, nerves, blood cells, and many other parts of the body. Magnesium is present in relatively large amounts in the body. It is important in more than 300 chemical reactions that keep the body working properly. Magnesium is required for the proper growth and maintenance of bones. It is also required for the proper function of nerves, muscles, and many other parts of the body. In the stomach, magnesium helps neutralize stomach acid and moves stools through the intestine.

Vitamin D can be found in small amounts in a few foods, including fatty fish such as herring, mackerel, sardines and tuna. It seems safe for most adults and children at FDA recommended daily allowances. Most Vitamin D (approximately 85% of what is acquire by the body) is obtained through exposure to sunlight. Vitamin D is required for the regulation of the minerals calcium and phosphorus found in the body. It also plays an important role in maintaining proper bone structure. Vitamin D is used for preventing and treating rickets and osteoporosis. Vitamin D may be used for conditions of the heart and blood vessels, including high blood pressure and high cholesterol. It is also used for diabetes, obesity, muscle weakness, multiple sclerosis, rheumatoid arthritis, chronic obstructive pulmonary disease (COPD), asthma, bronchitis, premenstrual syndrome (PMS), and tooth and gum disease. It is also used for boosting the immune system, preventing autoimmune diseases, and preventing cancer.

Omega-3 Fatty Acids (Omega-3s) are not produced in the body. They are acquired from fish oils. They seem safe for most adults and children, unless there are allergies, expecially to shellfish. Omega-3s reduce pain and swelling, making them possibly effective for rheumatoid arthritis, psoriasis and dry eyes. They also prevent the blood from clotting easily and may lower triglycerids levels, making them helpful for some heart conditions.

**Patient Content**

The heart is a special muscle, but still a muscle. As all other muscles in the body, the heart is controlled by nerves. However like the heart, these are special nerves as well. The nerves are the parasymapathetic and sympathetic (P&S) branches of the autonomic nervous system (ANS). Together with the parasymapathetic and sympathetic (P&S) nerves, there are three factors in the control of the function of the heart:

1. The mechanical or pump function, as measured by echocardiogram;
2. The electrical features of the heart muscle itself, as measured by EKG; and
3. The P&S nervous system input to the heart, as measured by P&S monitoring.

Dysfunction in any one or more of these features of the heart is assocaited with heart disease.

The blood vessels, including the arteries and veins, are also intimately involved in heart function. This is why vascular (blood vessel) disease is also associated with heart disease.

* Heart diseases that are evident from the Echocardiogram include, heart valve dysfunction, cardiomyopathy, infarction and ischemia.
* Heart diseases that are evident from the EKG include, arrhythmia and conduction defects.
* Heart diseases that are evident from the vasculature (blood vessels) include, high blood pressure, hypertension, hyperlipidemia, poor circulation and atherosclerosis.
* Heart diseases that are evident from the P&S monitoring include, syncope, orthostatic dysfunction, autonomic imbalance, and cardiovascular autonomic neuropathy (CAN).

There are lifestyle, medical history, genetic, and other issues that may contribute to heart disease. These are called risk factors. Risk factors in heart disease are based on the potential for developing Atherosclerosis. Atherosclerosis is a hardening of the arteries. It is a common disorder that narrows arteries reducing blood flow. Atherosclerosis occurs when fat, cholesterol, and other substances build up in the walls of arteries and form hard structures called plaques. Over time, these plaques can block the arteries and cause problems throughout the body. Sometimes these plaques trap a blood clot. When this happens the condition is called Atherothrombosis. Atherothromboses can have unpredictable and life-treatening consequences, including heart attack, stroke or sudden death.

There are two general categories of risk factors: Traditional and non-traditional.

* **Traditional Risk Factors**: 1) age[[101]](#footnote-11); 2) Diabetes; 3) smoking; 4) high blood pressure (BP) or Hypertension[[102]](#footnote-12); 5) Dyslipidemia[[103]](#footnote-13), low high-density lipoprotein (HDL) cholesterol[[104]](#footnote-14), or Hypertriglyceridemia[[105]](#footnote-15); and 6) family history of premature coronary artery disease (CAD[[106]](#footnote-16)).
* **Non-Traditional Risk Factors**: 1) abnormal Ankle-Brachial Index (ABI); 2) chronic inflammation as indicated by abnormal levels of C-Reactive Protein (CRP), Fibrinogen, Lipoprotein (a), Brain Natriuretic Peptide (BNP), or Human immunodeficiency virus (HIV); 3) Homocysteine elevation; 4) Microproteinuria[[107]](#footnote-17); 5) Microalbuminaria[[108]](#footnote-18); 6) Metabolic Syndrome; 7) elevated serum insulin levels; 8) Renal Disease; 9) abnormal Calcium Score; 10) Carotid Intima-Media Thickness; 11) left ventricular (LV) hypertrophy; 12) psychosocial stresses; 13) alcohol; 14) abnormal diet; 15) clinical depression; 16) obesity[[109]](#footnote-19); 17) sedentary lifestyle; 18) various types of infections; and 19) collagen vascular diseases.
* **Modifiable Risk Factors** (those that may be treated and negated, reversed, or diminished): smoking, Dyslipidemia, Hypertension, sedentary lifestyle, diet, obesity, type 2 Diabetes Mellitus or impaired glucose tolerance, and CRP.
* **Non-Modifiable Risk Factors**: age, gender, genetic abnormalities, and family history of premature atherosclerosis.

**RISK SCORES**

For many decades, physicians and epidemiologists have attempted to develop equations, scoring systems, and algorithms to risk stratify and predict which individual patients are at risk for cardiac events. The Framingham Risk Score projects future risk of heart disease for up to ten years. These risk factors include: diabetes, hypertension, lipid elevations, cigarette smoking, and age. While the Framingham Risk Score was an excellent beginning and is still widely used in clinical medicine today, it has a number of short-comings. Current longer life expectancies need a predictor that extends beyond ten years, and there are family history and other complications that add to risks that are not included in the Framingham scoring systems.

Family history and inflammation were added to the Framingham score and called the Reynolds Risk score. The improvement enables the Reynolds scoring system to identify almost half of the women at risk that were not identified earlier. However, the Reynolds scoring system still only predicts out to ten years.

Risk scoring research continues with new technologies able to easily measure other aspectos of the cardiovascular system (heart, vessels, and blod chemistry). However, only one technology provides information directly the P&S nervous systems as two separate systems. This technology is P&S monitoring. P&S monitoring sensitively and specifically identifies cardiovascular autonomic neuropathy (CAN). CAN is measured as very low parasympathetic activity. The loss of P&S activity level, especially parasympathetic activity, is often asymptomatic. This is a main reason why heart attacks and sudden death are still surprises. Very low parasympathetic activity is like having little or no brakes left on your car. The parasympathetics, in part, function to slow the heart and protect the heart (and body) from stresss. With very low parasympathetic activity there may not be enough activity to prevent the sympathetics (like the accelerator on your car) from over stimulating the heart into a dangerous rhythm. By restoring proper P and S balance, these risks are normalized.

**CARDIOVASCULAR RISKS ASSOCIATED WITH AUTONOMIC NEUROPATHY**

**Autonomic Neuropathy is Associated with Cardiac Mortality Risk**

Your heart rate is normally not constant. Your pulse, as measured by the nurse at your doctor’s office is actually an average rate. Your true heart rate varies by increasing a little when you breath in and decreasing a little when you breath out. This change in heart rate is called respirator sinus arrhythmia. It is the only arrhythmia you want. It is more significant when you are younger and healthier and declines with age and chronic illness or injury. The field of beat-to-beat changes in heart rate is known as heart rate variability (HRV) and has been known since the seventeen hundreds. The study of HRV (or similarly beat-to-beat blood pressure, brbBP) is a study of total autonomic nervous system (ANS) activity. However, we need to go deeper to understand the P&S branches of the ANS. For this we need to add to HRV (or btb BP). Researchers at MIT and Harvard proved that the addition is the analysis or respiratory activity. “Functional imbalances between the sympathetic and parasympathetic nervous systems are discerned with respiratory modulation.” Analyzing both HRV and respiratory activity, simultaneously, is P&S monitoring. Specific P&S function testing has the ability to provide the clinician with more information to determine which agents or therapeutic modalities are needed for you as an individual. For example, more is not always better, such as intensive glucose control for diabetic patients. Doctors from the Mayo Clinic, Rochester, MN show that associations of CAN with high mortality rates are consistent across many groups of patients and disease definitions. Researchers from Boston, MA, found that after assessing for age, gender, cigarette smoking, diabetes, and other relevant risk factors, P&S measurements offer significant prognostic information beyond that provided by traditional risk factors. A biologically feasible mechanism for this is based on the fact that patients who have heart disease with increased sympathetic activity, or decreased parasympathetic activity, are predisposed to heart disease, heart attack, or sudden death.

CAN is associated with a denervated heart, leaving patients unaware of cardiac events. This demonstrates a compelling need to assess P&S function in asymptomatic patients, especially given the higher risk of silent ischemia or sudden cardiac death (SCD) in these patients. Without P&S Monitoring, critical information concerning the asymptomatic patient’s risk of silent events will be lacking, including clinical trending information to document patients’ responses to therapy. The fact that coronary atherosclerosis may progress with CAN, and that silent events may occur with a higher incidence with CAN, suggests that CAN is important. Asymptomatic patients, despite having other traditional risk factors, should have P&S function assessed.

**TREATMENTS TO REDUCE OR NORMALIZE THE AFFECTS OF AUTONOMIC NEUROPATHY**

There are no approved pharmaceuticals that specifically target the parasympathetic or sympathetic nerves. Some common agents, however do effect one or the other ANS branch. Beta-blockers, Alpha-blockers, Vasopressors, and Bronchodilators are some of the agents that effect sympathetic activity. Most anti-hypertensives, including ACE-Is, ARBs, and calcium channel blockers, also effect sympathetic activity. Most anti-depressants, anxiolytics, benzodiazepines, and gastrointestinal motility and sleep medications have anti-cholinergic properties and effect parasympathetic activity. While many of these are used in very low doses to establish and maintain P&S balance, they may be accompanied with undesired side-effects at clinical doses.

Some supplements have been well researched and studied to positively affect autonomic changes, including: Alpha-Lipoic Acid (ALA), Coenzyme Q-10 (CoQ-10), Vitamin B6 (Pyridoxine), Vitamin B12 (Methylcobalamin), Vitamin D (Cholecalciferol), Magnesium Oxide, and Omega-3 Fatty Acids. All of these supplements are found in CardioNeuro Plus.

Alpha-Lipoic Acid (ALA) is a vitamin-like chemical called an antioxidant. It seems safe for most adults. It should not be used in children without medical supervision. It is found in small amounts in yeast, liver, kidney, spinach, broccoli, and potatoes, but not enough to provide clinical benefit. In patients with diabetes, it may lower blood sugar. In patients with Thyroid disease it may interfere with treatment. ALA has been show to work well in slowing the progression of autonomic neuropathy in patients with diabetes, diabetic nerve pain, and many other chronic diseases, including heart disease. ALA is used in the body to break down carbohydrates and to make energy for the other organs in the body. It seems to work as an antioxidant, and seems to be selective for nerves, including the nerves innervating the heart helping to relieve the affects of CAN in patients with heart disease or risks for heart disease (*e.g.*, diabetes). ALA might provide protection to the brain under conditions of damage or injury. The antioxidant effects might also be helpful in certain liver diseases. As a result, some people use alpha-lipoic acid for memory loss, chronic fatigue syndrome (CFS), HIV/AIDS, cancer, liver disease, diseases of the heart and blood vessels (including a disorder called cardiac autonomic neuropathy) and Lyme disease.

Coenzyme Q-10 (CoQ10) is a vitamin-like substance found throughout the body, but especially in the heart, liver, kidney, and pancreas. It seems safe for most adults. It should not be used in children without medical supervision. It is eaten in small amounts in meats and seafood, but not enough to provide clinical benefit. Given it role in producing ATP, a molecule in the body’s cells that transfers energy, as a result CoQ10 may help increase energy. It also seems to have antioxidant activity. Aging, length of chronic disese and smoking decreases stores of CoQ10. In some diabetics CoQ10 has been shown to decrease blood sugar levels. It may help to lower blood pressure. Many people use CoQ10 for heart and blood vessel conditions such as congestive heart failure (CHF), chest pain (Angina), high blood pressure, and heart problems linked to certain [cancer](http://www.webmd.com/cancer/) drugs. It is also used for diabetes, gum disease (both taken by mouth and applied directly to the gums), breast cancer, Huntington’s disease, Parkinson’s disease, muscular dystrophy, increasing exercise tolerance, chronic fatigue syndrome (CFS), Lyme disease and mitochondrial disorders. Some people have also used coenzyme Q-10 for strengthening the immune systems of people with HIV/AIDS, male infertility, and migraine headache.

Vitamins B6 and B12, and Magnesium are known to selectively increase parasympathetic activity, especially in patients with diseases that lead to (relative) sympathetic excesses (*e.g.*, Hypertension, Diabetes, Heart Disease, COPD and Asthma, Sleep Apnea, Chronic Pain). They seem safe for most adults and children at FDA recommended daily allowances. They are known to help improve cognitive function, reduce some dementias, elevate mood, and reduce anxiety. Vitamin B6 is required for the proper function of sugars, fats, and proteins in the body. It is also required for the proper growth and development of the brain, nerves, skin, and many other parts of the body. It can be found in certain foods such as cereals, beans, vegetables, liver, meat, and eggs. Vitamin B6 is used for preventing and treating “tired blood” (anemia), heart disease; high cholesterol; reducing blood levels of homocysteine, a chemical that might be linked to heart disease; and helping clogged arteries stay open. Vitamin B12 is required for the proper function and development of the brain, nerves, blood cells, and many other parts of the body. It is used to treat pernicious anemia, memory loss; Alzheimer’s disease; boosting mood, energy, concentration and the immune system; and slowing aging. It is also used for heart disease, lowering high homocysteine levels, male infertility, diabetes, sleep disorders, depression, mental disorders, weak bones (osteoporosis), swollen tendons, AIDS, inflammatory bowel disease, asthma, and allergies. Vitamin B12 is found in meat, fish, and dairy products. Magnesium is present in relatively large amounts in the body. It is important in more than 300 chemical reactions that keep the body working properly. Magnesium is required for the proper growth and maintenance of bones. It is also required for the proper function of nerves, muscles, and many other parts of the body. In the stomach, magnesium helps neutralize stomach acid and moves stools through the intestine. Magnesium is found in foods that are high in fiber, including legumes, whole grains, vegetables (especially broccoli, squash, and green leafy vegetables), seeds and nuts (especially almonds), dairy products, meats, chocolate, and coffee. Some people use magnesium for diseases of the heart and blood vessels including chest pain, irregular heartbeat, high blood pressure, high levels of “bad” cholesterol called low-density lipoprotein (LDL) cholesterol, low levels of “good” cholesterol called high-density lipoprotein (HDL) cholesterol, heart valve disease (mitral valve prolapse), and heart attack. Magnesium is also used for treating attention deficit-hyperactivity disorder (ADHD), anxiety, chronic fatigue syndrome (CFS), Lyme disease, fibromyalgia, restless leg syndrome, and multiple sclerosis.

Vitamin D can be found in small amounts in a few foods, including fatty fish such as herring, mackerel, sardines and tuna. It seems safe for most adults and children at FDA recommended daily allowances. Most Vitamin D (approximately 85% of what is acquire by the body) is obtained through exposure to sunlight. Vitamin D is required for the regulation of the minerals calcium and phosphorus found in the body. It also plays an important role in maintaining proper bone structure. Vitamin D is used for preventing and treating rickets and osteoporosis. Vitamin D may be used for conditions of the heart and blood vessels, including high blood pressure and high cholesterol. It is also used for diabetes, obesity, muscle weakness, multiple sclerosis, rheumatoid arthritis, chronic obstructive pulmonary disease (COPD), asthma, bronchitis, premenstrual syndrome (PMS), and tooth and gum disease. It is also used for boosting the immune system, preventing autoimmune diseases, and preventing cancer.

Omega-3 Fatty Acids (Omega-3s) are not produced in the body. They are acquired from fish oils (*e.g.*, mackerel, tuna, salmon, sturgeon, mullet, bluefish, anchovy, sardines, herring, trout, menhaden, and krill). They seem safe for most adults and children, unless there are allergies, expecially to shellfish. Omega-3s reduce pain and swelling, making them possibly effective for rheumatoid arthritis, psoriasis and dry eyes. They also prevent the blood from clotting easily and may lower triglycerids levels, making them helpful for some heart conditions. They are also used for high cholesterol, high blood pressure, stroke, cancer, osteoarthritis, depression, premenstrual syndrome (PMS), and painful menstrual periods.

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14. Too much “bad” cholesterol, defined as high low-density lipoprotein (LDL) cholesterol > 99 mg/dL [↑](#footnote-ref-3)
15. HDL is the “good” cholesterol, < 40 mg/dL [↑](#footnote-ref-4)
16. > 150 mg/dL [↑](#footnote-ref-5)
17. < 65 yrs old in Females and < 55 yrs old in Males [↑](#footnote-ref-6)
18. urinary protein excretion between 80 and 300 mg/24h, including Albumin to Creatinine ratio > 30 mg/mmol or albumin concentration > 200 mg/L. [↑](#footnote-ref-7)
19. Albumin to Creatinine ratio > 2.5 mg/mmol in men or > 3.5 mg/mmol in women, or albumin concentration > 20 mg/L. [↑](#footnote-ref-8)
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103. Too much “bad” cholesterol, defined as high low-density lipoprotein (LDL) cholesterol > 99 mg/dL [↑](#footnote-ref-13)
104. HDL is the “good” cholesterol, < 40 mg/dL [↑](#footnote-ref-14)
105. > 150 mg/dL [↑](#footnote-ref-15)
106. < 65 yrs old in Females and < 55 yrs old in Males [↑](#footnote-ref-16)
107. urinary protein excretion between 80 and 300 mg/24h, including Albumin to Creatinine ratio > 30 mg/mmol or albumin concentration > 200 mg/L. [↑](#footnote-ref-17)
108. Albumin to Creatinine ratio > 2.5 mg/mmol in men or > 3.5 mg/mmol in women, or albumin concentration > 20 mg/L. [↑](#footnote-ref-18)
109. particularly of the abdominal male type, [↑](#footnote-ref-19)