Improving the Identification and Management of Patients with Cardiovascular Disease

The Development of Cardiovascular Disease

CONTRIBUTING FACTORS
- Aging
- Diet
- Smoking
- Inactivity
- Diabetes
- High Cholesterol
- High Blood Pressure
- Stress
- Genetics

TREATMENT
- Lifestyle Modifications: Diet & Exercise
- Diabetic - High Blood Lipids - High Blood Pressure
- End-Stage Disease: Treated by your doctor with surgical procedures.

MARKERS
- HeartSavers™ measures small artery elasticity
- HeartSavers™ measures large artery elasticity
- Calcium Score
- Ankle Brachial Index
- Pulse Wave Velocity
- C-Reactive Protein
- Left Heart Enlargement
- Heart Attack
- Chest Pain
- Stroke
- Kidney Damage

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The Cost of Cardiovascular Disease

Cardiovascular disease is the #1 cause of death in the United States – a disease that claims more lives than the next four causes of death combined. According to the American Heart Association, one-third of deaths in the United States are attributable to cardiovascular disease and approximately 50% of individuals under 65 die within eight years of their initial heart attack.¹

Overall, 83 million Americans (1 in 3) have some form of cardiovascular disease and $444 billion² is spent per year on their care, representing approximately one-third of total U.S healthcare spending (with costs anticipated rising to $818 billion by 2030).

The Problem of Cardiovascular Disease Detection

Until recently, the ability to identify individuals with cardiovascular disease has been limited to an assessment of risk factors (e.g., blood pressure, cholesterol, or family history) or late-stage cardiovascular disease events that confirmed the presence of the disease (e.g., obstructed arteries, heart attack, stroke, or multiple symptoms of the disease).

In an attempt to identify as many individuals as possible prior to a life-altering cardiovascular event, risk factor measurements are standard practice. But, there are significant limitations associated with these “risk factor” assessments in that:

- Most heart attacks strike with no warning;
- 50% of heart attack victims have normal blood pressure and normal cholesterol; and,
- 75% of stroke victims have normal blood pressure.

The limitations associated with blood pressure measurement rest in the fact that it is not always an indication of disease. A rise in blood pressure might be attributable to such non-disease influences such as caffeine, a high-fat meal, certain medications, nicotine, stress, or a combination of these factors. Alternatively, a normal blood pressure is not necessarily an indication of health, as indicated by the many patients who suffer a heart attack or stroke and have clinically normal blood pressures. Similarly, cholesterol testing lacks precision in identifying those with disease in that 50% of heart attack victims present with normal cholesterol levels.

At best, therefore, using risk factor assessments to identify early signs of cardiovascular disease means 50% or more of the people who need to be helped are overlooked.

The Framingham Heart Study Risk Score

The Framingham Heart Study is the origin of the term “risk factor.” Prior to this study, clogging of the arteries and hardening of the arteries was believed to be a normal part of aging.³ ⁴ ⁵ ⁶

In 1948, Thomas Royle Dawber began studying 5,209 adults aged 30 to 62 from Framingham, Massachusetts in an attempt to learn more about factors that influence disease. The Framingham Study data was used to develop a Framingham Risk Score intended to provide a cardiovascular risk estimate specifically for future coronary heart disease events. The Framingham Risk Score does not, however, predict risk for stroke, transient ischemic attack (TIA), or heart failure. Additionally, it is important to note that the Risk Score can overestimate
(or underestimate) risk in populations other than the U.S. population, and within U.S. populations other than European Americans and African Americans, (e.g. Hispanic Americans and Native Americans).

Since this scoring system estimates who is most likely to develop cardiovascular disease, it can be useful to indicate who is likely to benefit from prevention practices. But, prevention advice is a useful admonition for all individuals; however, the Framingham Risk Score does not identify those individuals with actual disease – only those who may be at risk for developing disease later in life.

**Changing the Disease Identification Paradigm - A Major Scientific Breakthrough**

On October 12, 1998, three Americans, Drs. Furchgott, Ignarro, and Murad, were awarded the Nobel Prize for their discovery of nitric oxide (NO) as a signaling molecule in the cardiovascular system - now considered one of the most important discoveries in the history of cardiovascular medicine. Their work revealed that a healthy endothelium, the innermost layer of cells that line the blood vessels throughout the body, releases NO in response to the natural rhythms of the body.

NO acts as a signaling molecule that tells the blood vessels to relax. An ample supply of NO allows the blood vessels to be relaxed and elastic. The relaxation of the blood vessels increases blood flow and reduces blood pressure similar to several vasodilating drugs. But NO is a natural vasodilator that prevents hardening of the arteries and prevents platelets (particles in the blood that can form blood clots) and white blood cells from sticking to the blood vessel wall.

Current research studies point to the fact that atherosclerosis is caused by a dysfunctional endothelium and smoking, high cholesterol, obesity, high blood pressure, diabetes, a sedentary lifestyle, and/or an inherited predisposition impair the functional characteristics of the endothelium that produce NO. When the endothelium makes less NO or when the blood vessel absorbs less NO, the blood vessel becomes sticky and stiff – which is commonly referred to as “hardening of the arteries.”

Measuring the concentration of NO in the blood vessel wall would be an ideal way to assess the presence or absence of cardiovascular disease, but the detection of NO in biological tissues is particularly difficult. Due to the short lifetime and concentration of these molecules in blood, the half-life of NO in blood ranges from 0.05 to 1.8 milliseconds.

The human body is the optimal machine for NO production and when NO is produced at optimal levels, blood flows with little resistance through elastic vessels to nourish vital organs. Over the course of a lifetime, the endothelium can become damaged by unhealthy lifestyle, illness such as high blood pressure, high cholesterol, or high blood glucose, environmental toxins such as pollution or cigarette smoke, and age. Relatively early in the progression of vascular disease, these factors cause a dysfunction of the endothelium. When the endothelium becomes damaged or dysfunctional, NO production decreases, blood vessels stiffen, and blood flow is reduced.

Concurrent with the discovery of NO, research scientists at the University of Minnesota observed that the blood pressure waveforms of patients with heart failure were noticeably different than those of normal, healthy patients. Their research indicated that the rate and shape of decay in a blood pressure waveform correlated with the disease severity or health
status of patients studied. That is, the blood pressure waveform of a healthy individual was noticeably different than that of a patient with disease. With this finding, scientists realized that if there was a way to accurately measure alterations in a patient's blood pressure waveform, it would prove valuable as a marker for disease and as a marker for patients not at risk for events and, therefore, not in need of therapy. Furthermore, a focus on “vascular dysfunction” rather than identification of “risk factors” had the potential to improve the precision of therapeutic intervention to prevent future events.

A New Way to Measure Endothelial Dysfunction

In 1998, three factors supported the creation of a breakthrough blood pressure waveform analysis tool: the development of a non-invasive sensor that could replace invasive sensors used to obtain high-fidelity blood pressure waveforms, the development of an algorithm that could differentiate between blood pressure oscillations derived from stiff (diseased) or elastic (healthy) arteries, and the computer processing power to analyze these waveforms.

With this new tool, researchers demonstrated that the loss of arterial elasticity was predictive of cardiovascular events,\(^{12}\) that stiffness of the microvasculature (small arteries) was the earliest predictor of hypertension and coronary heart disease,\(^{13}^{14}\) that blood vessel elasticity could be improved with some therapies,\(^{15}\) and that the loss of blood vessel elasticity was a marker for atherosclerotic plaque burden.\(^{16}\)

Although several large-scale therapeutic studies such as LIFE\(^{17}\), HOPE\(^{18}\) and CAPPP\(^{19}\) demonstrated significant improvement in patients who received ACEs and ARBs as part of their therapy, several studies also demonstrated that these same drugs significantly increased blood vessel elasticity (or reduced blood vessel stiffness).\(^{20}^{21}^{22}\) Of considerable value was research that compared several different techniques for measuring blood vessel stiffness and found that the measurement of small artery elasticity was a sensitive marker for endothelial dysfunction.\(^{23}\)

Evaluating Comparative Test Results

Subsequently, in 2000, the National Heart Lung and Blood Institute (NHLBI) of the National Institutes of Health (NIH) sponsored a large clinical study called the Multi-Ethnic Study of Atherosclerosis (MESA), to investigate the characteristics of cardiovascular disease before it has produced clinical signs and symptoms, and risk factors that predict progression of the disease in a diverse population-based sample of 6,500 men and women aged 45–84 years who were of white, African-American, Hispanic, and Asian descent.

Study participants are being followed over a 10-year period and tested with four diagnostic technologies: (1) coronary computed tomography (sometimes referred to as a CAT Scan or a Heart Scan) which uses radioactive X-rays to look for calcium deposits in the coronary arteries, (2) carotid intima media thickness (sometimes referred to as Carotid IMT or carotid ultrasound) which utilizes high frequency ultrasound waves to image the arteries that supply blood to the brain; (3) magnetic resonance imaging (sometimes referred to as MRI) which utilizes a powerful magnetic field to visualize the elasticity of the ascending aorta; and, (4) a research version of the CVProfiler\(^{\circ}\), a non-invasive blood pressure waveform analysis tool which provides an assessment of the elasticity of the C2-small and C1-large arteries throughout the entire body.
When preliminary results from these tests were recently compared relative to the development of hypertension and cardiovascular disease in the MESA study population, the measurement of C2-small artery elasticity as demonstrated by the CVProfiler® was shown to be the earliest predictor of incident hypertension and the most predictive indicator of coronary heart disease. These findings provided strong evidence that the measurement of C2-small artery elasticity could predict hypertension and heart disease better and earlier than more expensive MRI, IMT, or CAT imaging technologies.

**Improving the Effectiveness of Cardiovascular Disease Identification**

Knowing that the blood vessel plays a primary role in cardiovascular disease progression, scientists at the University of Minnesota undertook a study designed to identify which cardiac and vascular and cardiac tests provided information on early vascular abnormalities likely to progress and to measure risk contributors susceptible to therapy. Ten tests were utilized: (i) C1 Large Artery Elasticity, (ii) C2-Small Artery Elasticity, (iii) resting blood pressure, (iv) an exercise-induced change in blood pressure, (v) optic fundus photos, (vi) microalbuminuria, (vii) ankle-brachial index, (viii) electrocardiogram, (ix) left-ventricular ultrasound, and (x) plasma B-type peptide concentration.

The study screened 396 normal, healthy individuals who presented with no signs or symptoms of cardiovascular disease and used a scoring system from 0 (no disease) to 20 (advanced disease) – with each abnormal test contributing a score of 2 and each borderline test contributing a score of 1.

Of those tested, 75% exhibited cardiovascular disease abnormalities not recognized by their primary care physician and 49% exhibited abnormalities sufficient to initiate or change medical therapy (a score of ≥ 5). Only 7% were free from any abnormalities by virtue of a score of 0.

Upon further analysis of the data, four of the ten tests yielded sensitive predictive value in cardiovascular functional and structural evaluation that outperformed individual test screening: (i) C1-Larger Artery Elasticity, (ii) C2-Small Artery Elasticity, (iii) resting blood pressure, and (iv) exercise-induced blood pressure measurement. Substituting a 3-test measurement (i.e., eliminating the exercise blood pressure measurement) or a 5-test measurement (adding microalbuminuria) only served to reduce sensitivity and specificity. Additionally, the ankle-brachial index proved insensitive in an asymptomatic population.

In a second study of 633 individuals, the 10-test disease scoring system outperformed the Framingham Risk Score in predicting future cardiovascular morbid events. The subjects were divided into three scoring categories based on their disease assessment scores: (i) <3, (ii) 3-5, and (iii) ≥6.

No events occurred over six years in the <3 group, events began accumulating in the 3-5 group after 4 years, and events in the ≥6 group began immediately after the evaluation – demonstrating that disease scoring based on abnormalities of cardiovascular function and structure were far superior to individual tests of early vascular disease in discriminating between individuals at no risk and those at high risk for future morbid events.
The Value of Early Detection

Maintaining endothelial health is essential in the fight against vascular disease of all kinds. A damaged endothelium can be repaired and atherosclerosis can be reversed. More importantly, when the endothelium is healthy or when endothelial health is restored, heart attacks and strokes can be prevented.

Identifying and treating early signs of cardiovascular disease are, therefore, key to reducing a patient’s risk for heart attack, stroke and heart failure. The traditional approach to reduction of risk for cardiovascular disease events has been two-fold: (1) Screen the healthy population for “risk factors” and intervene when measurements are above a level defined as “normal;” and (2) intervene aggressively in individuals who have suffered from a cardiovascular event aimed at secondary prevention.

Unfortunately, the current primary preventive approach that relies on “risk factor” screening captures individuals who have no vascular precursors of atherosclerosis and misses many individuals destined to develop progressive atherosclerosis.

Consequently, aggressive therapeutic intervention based on risk factors can be costly, risky and generally ineffective – providing some patients with therapy who don’t need it and failing to treat other patients as aggressively as may be required. Identification of individuals without early disease who do not require intervention may be as important as is the aggressive intervention in the population with early disease.

Focusing on the vasculature, therefore, improves the detection specificity and sensitivity among individuals in need of therapy to prevent progression of the vascular disease. In such individuals, guidelines now recommend aggressive treatment of risk factors to levels well below the traditional standards for risk factor interventions.

But, since all individuals do not possess the same degree of risk for cardiovascular disease progression, a screening methodology that consists of two phases – (1) Early vascular disease assessment; and, (2) Modifiable disease contributor assessment, provides a cost-effective means by which to determine who might benefit from therapy to prevent future morbid events.

Early Disease Assessment - Cardio 101™

In an effort to provide a sensitive, specific and yet inexpensive method for screening adults, four non-invasive tests have been shown to be effective at assessing the earliest possible evidence of cardiovascular disease.

(1) Large Artery Elasticity Index: Blood pressure waveform analysis provided by the CVProfiler® allows a separate assessment of the elasticity (stiffness) of the C1-Large conduit arteries which are a clear indication of late-stage disease.

(2) Small Artery Elasticity Index: Blood pressure waveform analysis provided by the CVProfiler® allows a separate assessment of the elasticity (stiffness) of the C2-Small arteries. The C2-small artery elasticity index describes the status of the very small arteries and arterioles just before the capillary bed – providing a surrogate marker for endothelial function. A premature loss of small artery elasticity has been shown to be correlated with early macro-vascular and micro-vascular complications.
A premature reduction in C2-small artery elasticity has been shown to be a sensitive and early predictor of cardiovascular disease morbidity and mortality. One such study indicated that a reduced C1-large artery elasticity and a reduced C2-small artery elasticity were univariate predictors of events and, after adjusting for age, indicated that for every 2-unit decrease in C2-small artery elasticity, there was a 50% increase in cardiovascular events. Because endothelial dysfunction would appear to be the earliest manifestation of vascular disease likely to progress to atherosclerosis and vascular dysfunction, comparisons of C1-Large Artery Elasticity and C2-Small Artery Elasticity have been demonstrated to be useful in identifying patients with cardiovascular disease, the severity of disease (the small arteries are the first to show signs of disease and the large arteries are a clear indication of late-stage disease) and/or correlating risk factors for cardiovascular disease.

(3) Blood Pressure at Rest – Resting sitting blood pressure is recorded using a standard sphygmomanometer, a procedure that has been well established in the identification of cardiovascular risks.

(4) Blood Pressure During Exercise – The patient stands on a treadmill and exercises for three minutes at five metabolic equivalents workload. The exercise induced change in blood pressure is recorded in that a brisk rise in blood pressure has been shown to correlate with reduced arterial elasticity.

Recent data on the value of these four tests indicate that of 1,806 asymptomatic patients tested, 39% had scores indicative of advanced disease. Of those referred for additional testing, 73% were in need of aggressive treatment and 27% were in need of an individualized lifestyle prescription. There were no incidents of false-positive test results; i.e., test results indicating the absence of disease in individuals with disease.

The test results are accomplished in 20 minutes and the results are designed to either confirm or deny the presence of cardiovascular disease.

**Modifiable Disease Contributor Assessment – Cardio1000™**

Confirmation of the presence of disease is the first step in effective treatment, but certainly not the last.

Since cardiovascular disease is a progressive disease that begins years or decades before symptoms of the disease become evident, precise identification of the cause and its severity is critical in determining proper treatment. To be successful at preventing cardiovascular morbid events and to effectively slow its progression, it is important to know where on the continuum of cardiovascular disease the patient is and the factors contributing to the disease.

For those with clear evidence of disease, a Modifiable Disease Contributor Assessment is utilized to identify aggressive treatment of modifiable factors that contribute to disease progression. This type of testing may also be appropriate in high-risk individual; e.g., patients with diabetes even if early disease cannot be identified. But, before an effective treatment plan can be created, it is important to first determine the severity, location and contributors to that disease.
The answer to the questions on disease severity, location and contributors can be difficult to determine and, at times, even more difficult to interpret. The solution to these problems rests in clinical support resources that quickly and easily answer clinical questions at the point of care – helping physicians provide better care.

The Cardio1000™ 10-test methodology is designed to identify contributing disease factors and disease severity in support of an individualized treatment plan – synthesizing patient information that can be easily delivered to the point of care with specific, actionable recommendations that ensure clinical questions are answered quickly and accurately to support the best care management decisions.

Individual treatment plans are needed because everyone has a different physiological response to diet, exercise and pharmaceutical therapies – i.e., one treatment plan does not fit all individuals. As an example, the American Heart Association estimates that more than 52% of hypertension patients are not properly treated. To a significant degree, these treatment problems stem from population based treatment plans that fail to identify the root cause of the disease, fail to prescribe the proper therapy, failure of the patient to take the medication prescribed, or some combination of all three.

The Cardio1000™ program takes approximately 1-2 hours and includes more detailed non-invasive tests to determine the location and severity of disease. The results of these 10-tests, which include blood and urine tests, provide the basis for an individualized treatment plan that may include changes in diet and exercise, pharmaceutical prescriptions, and possibly other treatments.

The important thing is that, if detected and treated early, heart disease progression is reversible. Early identification and an individualized treatment plan can help stop – maybe even eliminate – heart disease.

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