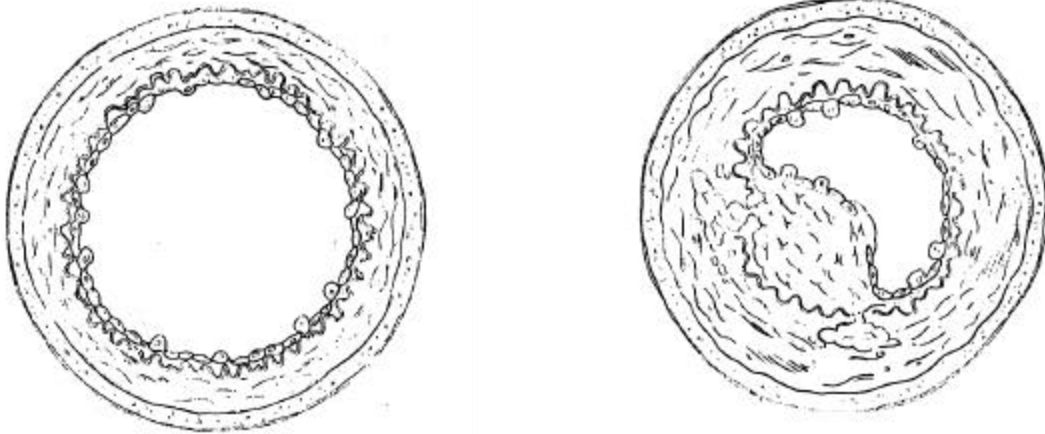


# **IT STARTS IN THE WALL**

*Early Detection of Vascular Disease through Arterial Waveform Analysis*



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## SUMMARY

Significant advances have been made in the prevention and treatment of vascular disease during the past few decades. Widespread awareness of risk factors such as smoking, inactivity, obesity, diabetes, high blood pressure, and high cholesterol has encouraged healthier eating habits and more active lifestyles. Yet vascular disease remains as the leading cause of death in the United States as well as in many other countries.

Current prevention efforts are aimed at either the entire population (smoking cessation, prudent diets, and increased exercise) or those with specific risk factors that can be treated (hypertension, high cholesterol). The whole-population approach imposes lifestyle alterations on a large population, only some of whom are at risk and would benefit from such changes. The so-called high-risk population may or may not ever develop vascular disease. In fact, a history of hypertension is present in less than 40 percent of patients sustaining a heart attack, and high cholesterol levels are present in less than 40 percent of patients sustaining a heart attack.<sup>1</sup> While this approach is clinically useful, it does not identify the actual presence of vascular disease in its early stages. Early identification with current techniques is rare due to cost, invasiveness, lack of specificity, and other factors.

An advanced technology, *Arterial Waveform Analysis*, developed at the University of Minnesota, holds the promise of detecting vascular disease at the earliest stages, when subtle changes in the arterial wall provide what appears to be an early marker for vascular disease.<sup>2</sup> *Arterial waveform analysis* has the potential to assist physicians in positively identifying individuals who exhibit the development of vascular disease and begin appropriate treatment – long before symptoms or clinical signs appear.<sup>3,4</sup> *Arterial waveform analysis* may also help physicians improve management of the pharmacological therapy for their patients and aid in efforts to better utilize healthcare resources by allowing therapy to

begin much earlier in the disease process, when lifestyle changes and/or lower cost treatments are most beneficial.

## UNDERSTANDING THE PROBLEM – WHO REALLY IS AT RISK?

Disease of the blood vessels (vascular disease) accounts for approximately one-half of all deaths in the United States each year and is the primary cause of heart attacks and strokes. Vascular disease can manifest itself in many ways: hypertension, coronary artery disease, peripheral artery disease, atherosclerosis, aneurysm, stroke, kidney failure and retinopathy. According to the American Heart Association, 58 million Americans have some form of cardiovascular disease.

Hypertension is the leading cardiovascular disease. Coronary artery disease affects 13.9 million Americans and is the nation's number one killer. Stroke is ranked number three. According to a 1997 release by the National Heart, Lung and Blood Institute, approximately 50 million adults (approximately 28% of the adult population) in the United States have been diagnosed as suffering from hypertension (defined as blood pressure greater than 140 mmHg systolic pressure and/or greater than 90 mmHg diastolic pressure), with nearly 75% of those not properly treated for the condition. Those who are not properly treated for the condition are facing significantly increased risk for heart and kidney disease and strokes.

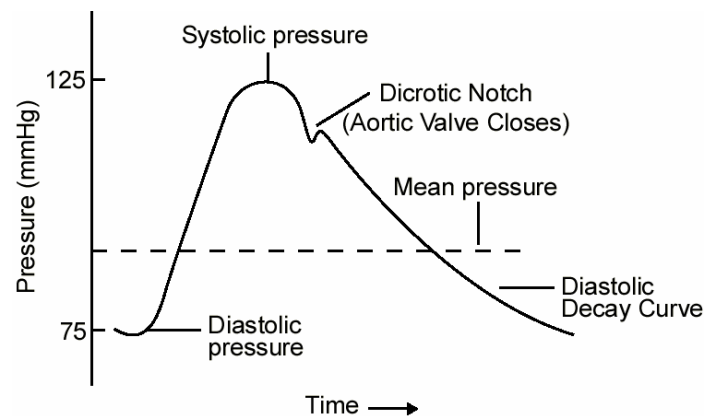
According to the Johns Hopkins White Papers on Hypertension (1998), an additional 30 million Americans are estimated to have “high-normal hypertension” sometimes referred to as “borderline hypertension”, defined as a blood pressure reading at or slightly above 130/85 mmHg. These individuals are twice as likely to develop hypertension and they have a greater risk of cardiovascular events than people with lower blood pressure.<sup>5</sup> In fact, high-normal blood pressure is so common in the United States that the majority of cardiovascular events

attributable to high blood pressure occur in people who demonstrate the condition.

Hypertension is of particular concern to older adults, as levels increase with age – it accounts for 15-20% of all deaths over fifty years of age in the United States.<sup>6</sup> Women also appear to be at increased risk with 33% of deaths attributable to heart disease and 17% to stroke – with half of the women who were affected by stroke exhibiting no symptoms of cardiovascular disease.<sup>7</sup> Since hypertension can easily go undetected, it has been called the “silent killer” because it usually produces no symptoms until after it seriously damages the heart, kidneys, brain or some other organ. The seriousness of this problem increases as the population grows older because individuals with sustained high blood pressure have an increased overall death rate from stroke, heart attack and kidney disease.<sup>8</sup>

The standard and initial test for screening and monitoring patients for vascular disease is use of an upper-arm blood pressure cuff device, or sphygmomanometer, developed in the 1890's. While the cuff yields some information about individuals and patient populations, the information it provides is very limited in terms of positively identifying the presence of blood vessel disease.

The blood pressure cuff is placed on a patient's upper-arm to obtain a measurement of the systolic blood pressure, or the pressure generated during the heart's contraction, and the diastolic pressure, or lowest pressure reached before the next heart beat. The information obtained is highly variable and influenced by many factors, including physical activity, stress or other environmental stimuli. Moreover, clinically important information in the blood pressure waveform – between the peak (systole) and the trough (end diastole) blood pressure values – is discarded (Figure 1).



**Figure 1 - Arterial Blood Pressure Waveform** – An arterial pressure pulse waveform with the limits of the pressure excursion over the cardiac cycle marked. Systolic pressure represents the peak pressure attained while diastolic pressure represents the trough occurring during the cardiac cycle.

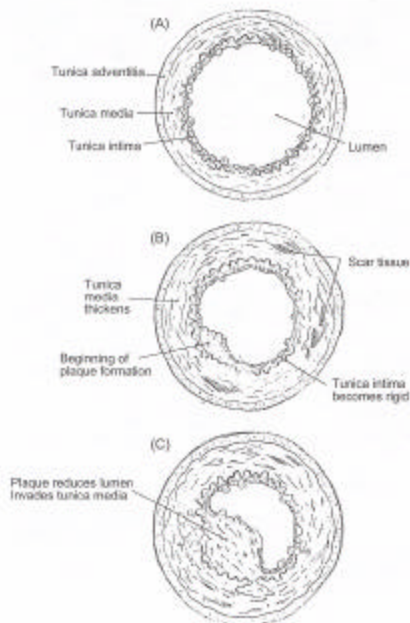
When the aortic heart valve closes after ejecting its stroke volume, the decay of blood pressure prior to the next heart beat describes a waveform which is dependent on the stiffness of the arterial system into which the blood has been delivered. This clinically valuable information contained in the blood pressure waveform can tell a health care professional a great deal about the likelihood of atherosclerosis (the formation of plaque and the accumulation of fatty deposits lining the walls of the artery which affect blood flow).

In the absence of such information, treatment may be initiated for suspected cardiovascular disease for patients with one or more risk factors, though it is entirely possible that many of these patients do not have the disease. Likewise, some patients who are developing atherosclerosis but do not exhibit high blood pressure, high cholesterol or other cardiovascular risk factors, may not receive treatment.

Augmenting current prevention efforts with positive identification of blood vessel disease has the potential to yield significant advances in the screening and diagnosing of patients for arteriosclerosis and atherosclerosis, and thereby reduce the incidence and severity of heart attacks and strokes.

## IT STARTS IN THE WALL

Hypertension is a deadly disease that damages both large and small arteries, leading to pathological changes in the tissues or organs supplied by these damaged arteries, and accelerating the development of atherosclerosis in large blood vessels, and the arteries supplying blood to the brain, heart, kidneys, and legs (Figure 2).



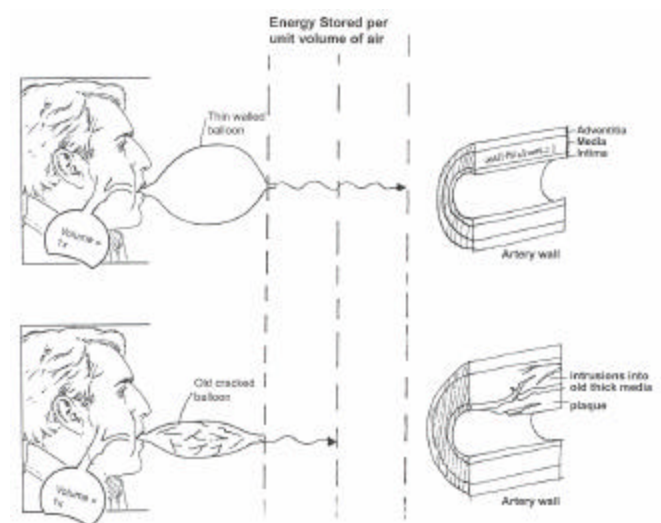
**Figure 2 - Cross Sections of Artery** – (A) normal elastic artery, (B) early stages of atherosclerosis where changes in the arterial wall have begun to impact blood flow and reduce arterial elasticity, and (C) advanced stage of atherosclerosis where arterial elasticity is reduced and plaque formation has restricted blood flow.

Atherosclerotic plaques can cause minimal strokes (transient ischemic attacks) due to diminished blood flow (ischemia) to parts of the brain; angina from partly obstructed coronary arteries; or pain in the leg muscles when walking, a result of poor blood supply to the legs (peripheral arterial disease). Blood clots, which tend to occur at the sites of atherosclerotic narrowing, can totally block a vessel and cause a stroke or heart attack.

The walls of all arteries (large and small) throughout the body are distensible – they expand and contract as blood pressure waves from the heart pass through the lumen, the passageway for blood within the arterial walls.

It is this distensibility that enables the arterial system to act as an elastic reservoir that stores part of the energy of each cardiac contraction, maintaining blood pressure and flow during diastole to perfuse all bodily tissues.

Changes in function and structure of the arterial wall precede the development of obstructive coronary artery disease, and are an early indication of the hypersensitive disease process.<sup>9</sup> Vascular changes in elasticity can be induced by changes in: the smooth muscle; the mass of the smooth muscle collagen, or elastin components of the wall; the infiltration of the wall with cellular or interstitial elements; and/or the change in tissue fluid in the wall (Figure 3).



**Figure 3 - Wall Thickness** – If one imagines blowing the same quantity of air into two balloons with a release valve at the opposite end, the new, supple balloon will store a greater quantity of energy than an old, cracked one. Arterial walls that are more “youthful,” or distensible, will similarly hold a greater quantity of energy than “older” or less distensible arterial walls.

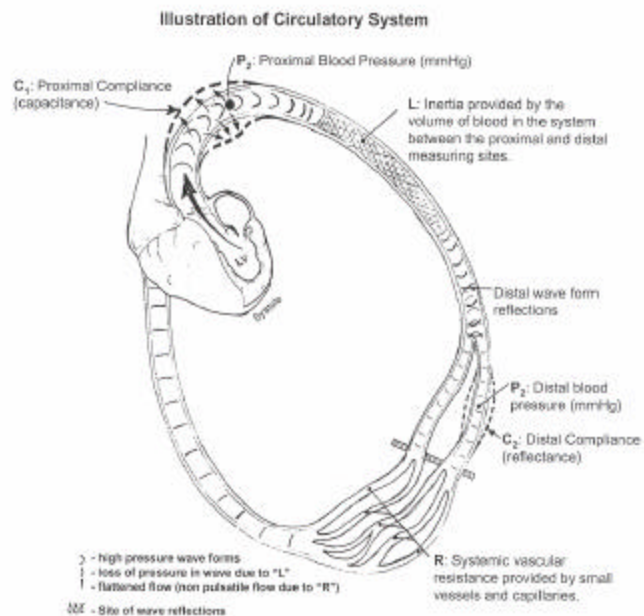
The arterial wall is composed of three concentric zones termed the *tunica intima*, *tunica media*, and *tunica adventitia*. The *tunica intima* consists of the vascular endothelium and a thin layer of collagen and elastin fibers that anchor it to the internal elastin lamina. Recent research has explored the significant role the endothelium plays in the development of blood vessel disease.<sup>10</sup> If the endothelium is thought of as an internal organ, it would be one of the largest organs of the body. Spread over a flat

area, the endothelium cells lining the arteries of a single adult would cover the approximate area of three football fields. Nitric oxide gas is released by the endothelium cells, and relaxation of the arterial walls is believed to be an important result.

The influence of systemic arterial elasticity, or vascular compliance, on circulatory integrity is often not adequately emphasized. The smallest arteries and arterioles are the sites of greatest hemodynamic resistance and act in conjunction with the precapillary sphincters to form a variable resistance that controls the rate of blood flow perfusing all body tissue. An arterial system composed of elastic conduits and high-resistance terminals constitutes a hydraulic filter that converts the intermittent output from the heart into steady capillary flow.

The arterial blood pressure waveform is derived from the complex interaction of the left ventricle stroke volume, the physical properties of the arterial tree and the characteristics of the fluid (blood) in the system. Changes in arterial vascular compliance -- or elasticity of blood vessels -- introduce changes in the arterial system that are reflected in the arterial blood pressure waveform. These changes can be visualized by examining the difference in the arterial pressure waveform of a patient before and after the administration of a pharmacological agent such as nitroprusside or nitroglycerin, which has the effect of increasing vascular compliance.

During systole, only the proximal portion of the aorta becomes distended initially because the inertia of blood hinders the passage of the total stroke volume to the periphery. The radial stretch of the ascending aorta brought about by left ventricle (LV) ejection initiates a blood pressure wave that is propagated down the aorta and its branches. This pressure wave moves at a finite velocity that is considerably faster than the actual forward movement of the blood itself -- the pressure pulse is simply a moving wave of pressure that involves very little forward movements of blood (Figure 4).



**Figure 4 - Illustration of Circulatory System** – the walls of large and small arteries throughout the body expand and contract as blood pressure waves from the heart pass through them. An arterial system that is composed of elastic conduits and high resistance terminals constitutes a hydraulic filter than converts the intermittent output of the heart into a steady capillary flow.

The distortion in the arterial waveform includes a delay in the time of the onset of the initial pressure rise, damping of the high-frequency components of the pulse, and a narrowing and elevation of the systolic portions of the pressure wave.

In the initial portion of the diastolic pressure waveform, a feature referred to as the "dicrotic notch" becomes more prominent as the pulse passes peripherally. These morphologic changes tend to diminish with age as the arteries lose their elasticity or become less compliant. The damping of the high-frequency components of the arterial pulse are largely due to the viscoelastic properties of the arterial walls, though the mechanisms involved in the peaking of the pressure wave are not fully understood.

## **ARTERIAL WAVEFORM ANALYSIS**

Functional and structural changes in the arterial wall precede the development of obstructive coronary artery disease and may be early markers for the hypertensive disease process.<sup>11</sup> Vascular (or arterial) compliance has long been recognized as declining as part of the normal aging process, and as declining at an accelerated rate in people with heart disease.<sup>12</sup> Although the aorta and large arteries can be readily visualized by various x-ray and other techniques, there has been no means to evaluate the flexibility or elasticity of the small and very small arteries throughout the body which become altered in hypertension and with other vascular diseases.

Cardiovascular specialists spend considerable effort on evaluating heart function, including electrocardiograms (EKGs), echocardiograms and stress tests, but have been unable to assess the functional and structural abnormality of the arteries prior to the late phase of arterial obstruction (as determined by angiography).

Clinical research related to arterial waveform analysis has been ongoing at the University of Minnesota Medical School since 1980, and at other clinical investigator sites and medical research centers since about 1988.

The arterial waveform analysis method utilizes a modified Windkessel model, a well-established electrical analog model, which describes the pressure changes during the diastolic phase of the cardiac cycle in the circulatory system. This analysis method provides an independent assessment of the elasticity or flexibility of the large arteries which expand to briefly store blood ejected by the heart, and of the small and very small arteries (arterioles) which produce oscillations or reflections in response to the blood pressure waveform generated during each heart beat.

By assessing the elasticity of the arterial system, clinical investigators have been able to

identify a reduction in arterial elasticity in patients without evidence of traditional risk factors, suggesting the early presence of vascular disease.<sup>13</sup> Furthermore, clinical research data has demonstrated that individuals with heart failure, coronary artery disease, hypertension and diabetes typically exhibit a loss of arterial elasticity.<sup>14</sup> These abnormal blood vessel changes often appear to precede overt signs of cardiovascular disease and the occurrence of a heart attack or stroke by many years. Clinical investigators have also demonstrated an age-related loss of elasticity of both the large and small arteries suggesting that premature stiffening of an individual's arteries is an apparent marker for the early onset of cardiovascular disease.<sup>15</sup>

Dozens of clinical research studies and pharmaceutical trials have already been completed utilizing this technology, involving more than 2,500 subjects, and resulting in more than 30 scientific articles being published in peer-reviewed medical journals.

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