Clinical Application of the CVProfilor®

The Value of Arterial Elasticity Assessment in Clinical Practice

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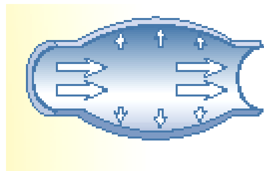
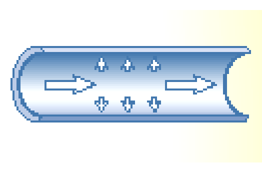


Elastic arteries expand and distend as blood pulses through with each heart beat

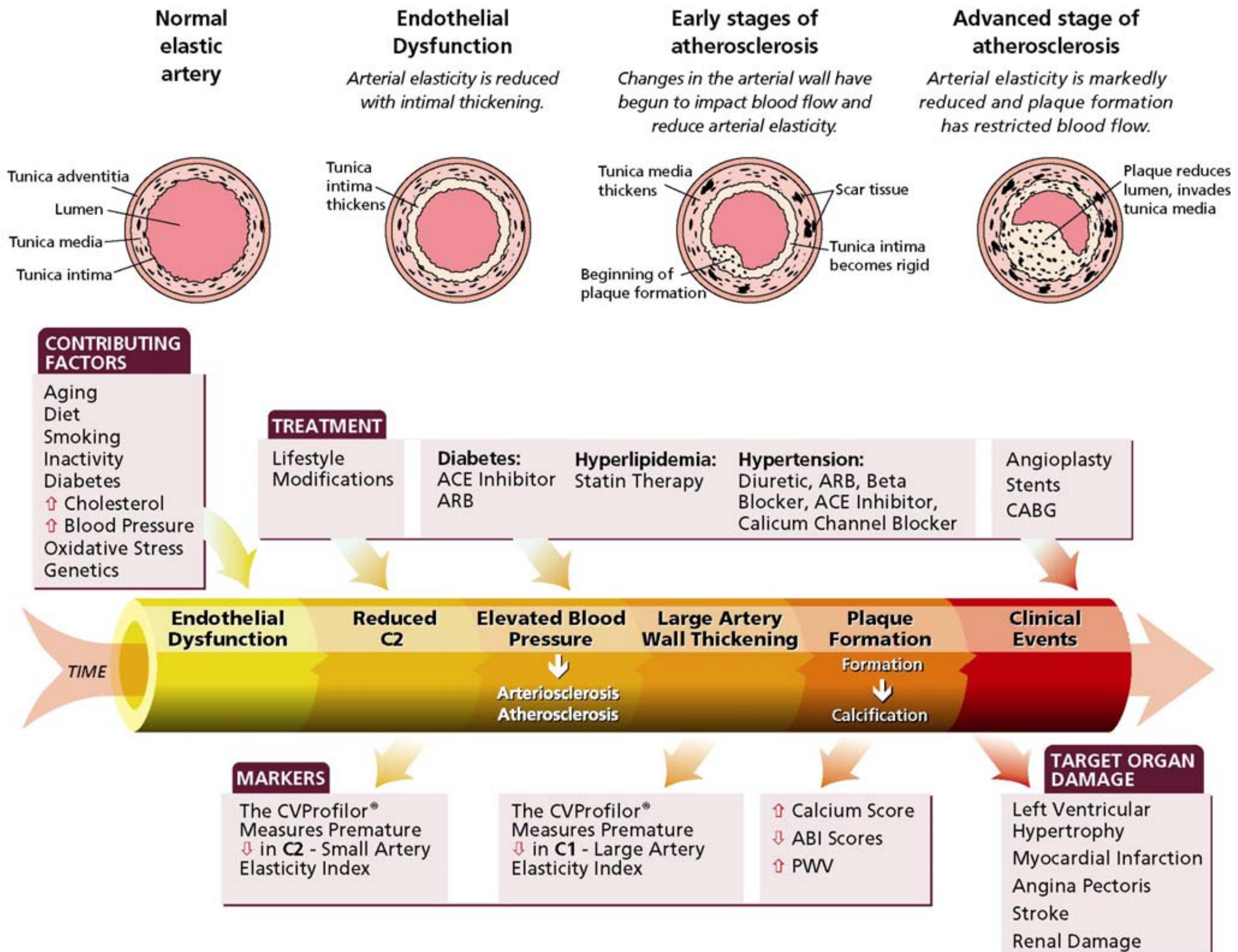


Stiffened or hardened arteries do not distend with each heart beat – blood pressure may increase

Introduction

A major gap in current health care is the inability to detect advancing vascular and cardiac disease before symptoms and clinical signs develop. Indeed, myocardial infarction and sudden death often occur in individuals with no previous diagnosis of cardiovascular disease. Physicians routinely measure blood pressure and frequently measure cholesterol levels to identify individuals at higher risk for cardiovascular disease, but there are no magical cutoff values for normal and abnormal. Recent clinical research data suggest a continuous relationship between blood pressure and cholesterol levels and cardiovascular event risk, yet more than half the cardiovascular morbid events occur in individuals with normal levels of blood pressure and/or normal levels of total cholesterol.

The Pathogenesis of Vascular Disease



- **Vascular disease is initiated by one (or more) contributing factors (see left side of chart) which cause a dysfunction of the endothelial lining of small arteries and arterioles – this early change may be detected as a "premature loss of arterial elasticity" (*i.e.* low C2 based on patient's age and gender).**
- **C2-Small Artery Elasticity Index continues to decrease as vascular disease progresses and typically precedes a fall in C1-Large Artery Elasticity Index – decreasing C2 leads to elevated blood pressure and "hardening of the arteries" (the most common form of which in the U.S. is atherosclerosis).**
- **It is at this stage of vascular disease that a patient may first be diagnosed with diabetes, high blood pressure and/or hyperlipidemia – proper treatment may slow or even arrest disease progression – if not, large arteries are affected (C1 begins to fall) and end-stage cardiovascular disease occurs.**
- **It is important to note that atherosclerosis only occurs in the presence of endothelial dysfunction that can be detected by a reduction in the C2-Small Artery Elasticity Index.**

Tests are available to "screen" individuals for disease, but these are predominantly tests of late-stage cardiovascular disease, not early disease. Stress testing is designed to detect coronary flow-limiting atherosclerotic plaques, but considerable atherosclerosis that places the patient at risk for a myocardial infarction may exist in the absence of such flow-limiting stenosis. Similarly, the ankle/brachial index is measured to detect advanced plaque formation in the peripheral arteries. Rapid CT or spiral CT for coronary calcium scoring provides a gross measure of the degree of infiltration of an inflammatory process in the coronary arteries, but it too is only a guide to advanced disease in the large arteries, and it cannot, and should not, by itself, provide guidance to therapy.

What the CVProfilor® measures

In contrast, the CVProfilor® is designed to detect very early vascular disease that may precede by years the build-up of plaque or calcium in the coronary and other large arteries. The C2-Small Artery Elasticity Index identifies the presence of endothelial dysfunction in the microvascular circulation. This dysfunction of the endothelium occurs in the entire arterial system but is easier to detect in the very small arteries and arterioles. In fact, reduced endothelial function is an obligatory first step in the development of atherosclerosis. A reduction in the C2 Index may be genetically pre-determined, since it has a high prevalence in individuals with a strong family history of cardiovascular events. Such a genetic predilection may be manifested by an individual having an abnormally low C2 Index in the absence of any other clinical signs or symptoms of cardiovascular disease. C2 is also reduced in tobacco smokers, diabetics and other individuals with increased risk for cardiovascular disease.

The C1-Large Artery Elasticity Index is a measure of the elastic behavior of the aorta and large arteries. The walls of these large arteries thicken and become stiffer with age and with athero-sclerotic disease. Thus a falling C1 Index is observed in patients with a wide pulse pressure and those exhibiting systolic hypertension, conditions associated with stiffening or reduced compliance or elasticity of the aorta and large arteries.

The C1 and C2 Indices as determined by the CVProfilor® are, therefore, valuable for assessing the state or clinical condition of both the large and the very small arteries, respectively. The values provide a continuum of health of the arteries, and the arterial elasticity indices are both age-dependent, which means that individuals' arteries stiffen and become somewhat less healthy as they age (part of the "normal aging process"), and gender-dependent, with females generally exhibiting somewhat lower values than males. But aging of the vasculature is not uniform; some individuals exhibit changes at a young age (for example, diabetics and hypertensives) and others retain healthy artery function into their 60's and 70's. Preliminary data indicate that the former are at high risk and the latter at relatively low risk for adverse cardiovascular events. Individuals that show "premature stiffening or hardening" of their arteries (that is, those who have reduced C1 and/or C2 Elasticity Indices based on their age and gender) most likely have underlying vascular disease and therefore are at a higher risk. Such patients may require a more extensive diagnostic evaluation by the physician and are potential candidates for early and aggressive therapy.

Variability of measurements

Just like any other physiologic test, such as measuring blood pressure, arterial elasticity may vary throughout the day and will be influenced by stress, drugs and other environmental factors (for example, drinking beverages with caffeine, smoking tobacco products and/or eating high-fat meals). In general, however, any variability around an arterial elasticity value will still identify the individual's cardiovascular risk. Typically, abnormal values differ from normal by 2-3 fold, so even modest variability does not limit the clinical benefit of measuring the arterial elasticity indices.

If an individual is scheduled to have a CVProfilor® test, it is good practice to remind him/her to avoid environmental factors which might influence test results. If possible, the individual to be tested should fast overnight and should refrain from smoking, drinking caffeinated or alcoholic beverages, and eating meals (especially fatty foods) for at least 2-3 hours prior to being tested. It is also important to be aware of any medication that the individual is taking, especially if such is intended to modify the cardiovascular system. Certain antihypertensive and vasodilator drugs may directly affect the C1 and/or C2 Arterial Elasticity Indices. For example, angiotensin-converting enzyme (ACE) inhibitors, angiotensin

receptor blockers (ARBs), statins, nitroglycerin and calcium antagonists (at appropriate dosages and for sufficient duration) all tend to improve or enhance arterial elasticity, while beta blockers and diuretics have minimal or no influence on arterial elasticity.

C1 and C2 Indices appear to follow the same diurnal pattern as blood pressure, with elasticity somewhat lower when blood pressure is higher (early morning) and with elasticity somewhat higher when blood pressure is lowest (at night).

Patient Selection Criteria

An initial cardiovascular profile using the CVProfilor® may be an appropriate test for many individuals at potential risk for developing cardiovascular disease. Certainly, those patients who have signs of high blood pressure, diabetes, heart failure, hypercholesterolemia and dyslipidemia should be evaluated to establish the status or condition of their arterial vasculature. Individuals who smoke tobacco products, who are obese and/or sedentary, who have a family history of cardiovascular disease, and/or who may have other life style concerns potentially related to the arterial system should also be considered for testing. Patients being treated with medication and/or with life style modification therapy for their cardiovascular conditions as well as peri- and post-menopausal women are candidates for having a CVProfile™ test in that it may be beneficial to measure the impact on the arterial system. As an aide to determining whether or not individuals with borderline hypertension or white coat hypertension have underlying vascular disease, testing with the CVProfilor® should be undertaken. Those individuals with either borderline or abnormal C1 and/or C2 Indices should be considered for additional diagnostic evaluation and/or therapy as indicated.

How to Use the CVProfilor® in Practice

There is now considerable persuasive clinical evidence that interventions can alter the progression of atherosclerosis. Statins, ACE inhibitors, ARBs and other antihypertensive drugs have been shown to reduce morbidity and mortality from progressive cardiovascular disease. Other interventions including estrogens, exercise conditioning, antidiabetic agents, antioxidants, potassium and dietary alteration may also be effective in selective patient populations. Identification of patients with early vascular disease provides a clinical rationale for aggressive and early therapeutic intervention. The absence of such vascular disease provides a rationale for withholding such aggressive therapy. In the clinical setting of endothelial dysfunction with a low C2 Index, it may be appropriate to treat patients with near-normal or even normal levels of LDL or of blood pressure since such treatment appears to slow the progression of the cardiovascular disease.

An intervention(s) may be undertaken for a patient based on additional diagnostic tests in response to the initial finding of reduced arterial elasticity as shown on a CVProfile™ Report. Whether such intervention(s) involved changes in life styles and/or medication and/or some other therapy, or a combination of these, it would be appropriate to re-test the patient at an interval of about 6 to 8 weeks depending upon the severity of the findings from the additional diagnostic tests, the interventions undertaken, and taking the best interests of the patient into consideration. A CVProfilor® re-test provides clinical information as to whether or not the intervention(s) has enhanced the patient's arterial elasticity.

How to interpret elasticity measurements

The C1 and C2 Arterial Elasticity Indices provide measurements of function and structure of the large and very small arteries, respectively. The higher the values, the more elasticity and the healthier the state of the arteries. Young people normally have more flexible and elastic arteries than older people, and therefore higher C1 and C2 Indices. In men and in larger individuals, the elasticity indices are somewhat higher than in women and smaller individuals. In general, C1 Index will vary inversely with blood pressure to some degree, since pressure is itself a minor determinant of large artery elasticity. The C2 Index, however, is much more dependent on arterial endothelial function than on blood pressure.

As a general guide, a C1 Index above 15 to 17 and a C2 Index above 6 to 8 are indicative of healthy and elastic arteries, almost regardless of age or gender. Since an individual's values tend to fall with age, a C1 Index at or above 10 and a C2 Index at or above 4 in individuals over age 60

could be considered a normal consequence of aging. However, these same indices for a person just 20 years of age would be indicative of "premature arterial stiffening" and would suggest a potential for underlying vascular disease (for example, atherosclerosis) worthy of more specific diagnostic evaluation. Regarding individuals from age 40 to 50, a C1 Index between 7 and 10 might suggest some aging of the large arteries, and a C2 Index between 5 and 6 could be consistent with borderline arterial endothelial dysfunction. Arterial elasticity indices below these levels (that is, C1 below 10 and/or C2 below 4), regardless of age or gender, are clearly abnormal.

Shown below are two guideline tables, one for each gender, which provide C1 and C2 Arterial Elasticity Index ranges in relationship to cardiovascular risk stratification. These tables take into account the loss of elasticity with age as well as the difference in arterial elasticity indices observed between men and women. In order to obtain an impression of an individual's cardiovascular risk, simply identify the range in the table for the CVProfile™ Report C1 and C2 Indices across from and in the same row as the appropriate gender and age range. For example, if a 47 year old male patient showed a C1 Index of 14.8 and a C2 Index of 5.1 on his CVProfile™ Report, then by referring to the Male Arterial Elasticity Guideline Table it can be determined that his large arteries show normal elasticity, but his small arteries are prematurely stiff and near the bottom of the borderline range.

Arterial Elasticity Guideline Tables

MALE	**C1 – Large Artery** Elasticity Index Range			**C2 – Small Artery** Elasticity Index Range		
Age Range	**Abnormal**	**Borderline**	**Normal**	**Abnormal**	**Borderline**	**Normal**
15 - 19	< 10	10 – 17	> 17	< 6	6 – 9	> 9
20 - 29	< 9	9 – 16	> 16	< 6	6 – 8	> 8
30 - 39	< 8	8 – 14	> 14	< 6	6 – 8	> 8
40 - 49	< 7	7 – 12	> 12	< 5	5 – 7	> 7
50 - 59	< 6	6 – 11	> 11	< 5	5 – 7	> 7
60 - 69	< 5	5 – 10	> 10	< 4	4 – 6	> 6
> 70	< 5	5 – 9	> 9	< 4	4 – 5	> 5

FEMALE	**C1 – Large Artery** Elasticity Index Range			**C2 – Small Artery** Elasticity Index Range		
Age Range	**Abnormal**	**Borderline**	**Normal**	**Abnormal**	**Borderline**	**Normal**
15 - 19	< 9	9 – 15	> 15	< 6	6 – 8	> 8
20 - 29	< 8	8 – 14	> 14	< 5	5 – 7	> 7
30 - 39	< 7	7 – 12	> 12	< 4	4 – 6	> 6
40 - 49	< 6	6 – 10	> 10	< 4	4 – 6	> 6
50 - 59	< 5	5 – 10	> 10	< 3	3 – 5	> 5
60 - 69	< 4	4 – 9	> 9	< 3	3 – 5	> 5
> 70	< 4	4 – 8	> 8	< 2	2 – 4	> 4

In general, the C2 Index is the more sensitive and clinically significant of the two indices, and often shows a loss of arterial elasticity before, and to a somewhat greater degree, than the C1 Index. If the C1 and C2 Indices present different results, then the one with the greatest risk to the patient should be considered. For example, if a 34 year old female had a C1 Index of 15.3 (normal from the guideline table) and a C2 Index of 4.9 (in the borderline range from the guideline table), then she should be considered to have a potential for having a moderate amount of progressive small artery disease placing her at a moderate risk for cardiovascular disease. Such an individual has a potential for underlying vascular disease and is a candidate for more specific diagnostic evaluation by her physician.

It is important to remember that CVProfilor® System test results as presented on the CVProfile™ Report should always be interpreted by a licensed physician or other health care provider in light of physical examination, lab tests and/or other clinical findings.

Clinical Research References

During the past decade, there have been many scientific abstracts and articles published in peer-reviewed medical journals which have employed the pulse contour or blood pressure waveform analysis technology that is incorporated in the CVProfilor® System. In fact, a bibliography of all such abstracts and articles to date (listing more than 200 references) is available upon request by contacting Hypertension Diagnostics, Inc. in Eagan, MN (Phone: 651-687-9999; Toll-Free: 1-888-785-7392) or by visiting the HDI website at www.cvprofilor.com. Presented herein after are citations for some of the more recent publications which the reader might wish to review.

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