Noninvasive evaluation of the health of the vasculature is an increasingly important approach to identifying individuals at risk for cardiovascular morbidity events. Vascular health assessment involves functional and structural examination of the large and small arteries. Endothelial dysfunction, which alters small artery function, is a key contributor to progressive structural vascular changes. Ultrasonography of conduit arteries and aortic pulse-wave velocity provide information limited to structural changes in large arteries. Comprehensive assessment of the large and small arteries is best carried out by pulse-contour analysis. This can provide insight into functional and structural abnormalities in the small as well as the large arteries, and may be useful in monitoring response to therapy.

There has been growing recognition in recent years in the assessment of the health of the arterial wall, which can provide a valuable means of predicting future cardiovascular morbidity events and in evaluating the effectiveness of interventions designed to alter the course of cardiovascular disease [1]. Emphasis on identifying and treating early disease prior to occurrence of symptoms has further increased the need for reliable methods for vascular evaluation that can be applied noninvasively [2]. A variety of techniques have been introduced to provide clinical assessment of vascular health [3]. The purpose of this review is to critically evaluate the various methods and to focus on pulse-contour analysis as a means for comprehensive assessment of an individual’s vascular health.

Structure of the arterial system
The arterial system is composed of a network of tubes of diminishing caliber that transform pulsatile to continuous flow and distribute blood to metabolically active capillary beds that nourish organs and tissues [4]. From a functional standpoint, the arterial vasculature can be compartmentalized into a conductive function residing in the larger arteries and a resistance function at the arteriolar level. Delivery of blood to organs is dependent on the patency of large conduit arteries. The tone of the arteriole determines resistance to blood flow and the arterial pressure for any given cardiac output.

Between the conduit arteries and the arterioles is a large network of branching arteries that are the site of reflected pressure waves or pressure oscillations that are superimposed on the incident pressure wave generated by the left ventricle in its interaction with impedance to left ventricular ejection. These oscillations are influenced predominantly by the tone of the small arteries that constitute these branch points in the circulation. They play a major role in determining the shape of the pressure waveform recorded at any site in the arterial tree [5].

The lumen of the larger conduit arteries receives the majority of attention in cardiology because it is affected by plaque formation, which may chronically and progressively obstruct blood flow, and by clots, which are the usual cause of acute obstruction to blood flow [6]. Coronary arteries are of course examined by angiography and treated by percutaneous intervention or bypass surgery. The resistance vessel caliber is a major determinant of blood pressure and is the focus for efforts to control hypertension. The net caliber of these arteries or systemic vascular resistance can be calculated from pressure and cardiac output.

The small branch arteries are disregarded in most analyses because they may not directly influence either flow or pressure. Nonetheless, this segment of the vasculature is responsive to all the factors that influence conduit and resistance artery function and, therefore, can serve as a valuable window into the function of the arterial system.

The entire arterial vascular network is lined by a single layer of endothelial cells that protect the surface of the artery and its underlying media. Normal endothelial function provides continuous constitutive release of nitric oxide (NO) that maintains low tone of the underlying smooth muscle, prevents blood cell adhesion to the vascular surface, inhibits endothelial infiltration and suppresses vascular smooth muscle growth and remodeling [7]. Endothelial release of NO
serves to slow vascular aging and to inhibit progression of atherosclerosis. It also prevents blood pressure increases by maintaining vasodilation in the arterioles.

**Consequences of endothelial dysfunction**

Suppression of endothelial release of NO is observed in a variety of clinical situations. Aging itself is associated with progressive endothelial dysfunction (ED), but the rate at which this occurs may be genetically determined [8]. ED also appears to be induced by oxidative stress, diabetes, elevated blood pressure, elevated low-density lipoprotein (LDL)-cholesterol, smoking, obesity and fatty foods [9]. Racial and/or geographic differences in ED also suggest a possible genetic determinant [10].

A deficiency of NO bioactivity, whether through decreased release of NO or its rapid destruction by oxidative stress, results in functional and structural vascular changes that critically affect arterial health [11]. Constriction of arterioles will raise blood pressure, whereas constriction of small branching arteries will alter wave propagation through the arterial tree. The smooth muscle tone of the large conduit arteries is not affected as much by constitutive release of endothelial NO because of its rapid inactivation. Nonetheless, ED renders the conduit arteries prone to cholesterol plaque formation, platelet aggregation, vascular smooth muscle growth, infiltration with oxidized LDL, collagen growth and elastic fragmentation. All of these changes are associated with stiffening of the artery wall. ED also leads to structural changes in the arterioles and small arteries with smooth muscle growth and remodelling leading to thickening of the walls and their stiffening.

**Assessment of arterial health**

Noninvasive assessment of the health of the arterial wall is dependent on visualization of the wall in ultrasound-accessible conduit arteries or on functional assessment of the arteries by measurement of their stiffness (compliance) or their influence on the arterial pressure waveform [12]. Caution is required in evaluating the usefulness of any methodology, whether systemic or regional, because the functional and structural abnormalities described above may be remarkably heterogeneous in various vascular beds [13]. Therefore, although aging and atherosclerosis are systemic processes, the manifestations may influence the lumen and walls of some vascular beds more than others. Indeed, the predilection for coronary events in some populations, strokes in others and renal failure in others raises the likelihood of genetic as well as environmental factors in disease progression [14,15].

The carotid artery, a central vessel with conduit function, is the artery most commonly imaged for assessment of intimal-media thickness (IMT) using ultrasound technology [16]. Guidelines for the meticulous measurement of IMT have been published [17]. In addition, functional assessment of the carotid artery can be obtained by monitoring caliber change between systole and diastole. Such assessment requires precise measurements of caliber and would ideally be combined with a simultaneous pressure measurement at the same site in order to calculate carotid arterial compliance [18]. Such pressure measurements are rarely available so that accurate assessment of compliance is not possible. Since conduit artery studies provide no information regarding small artery function or structure we will focus on more comprehensive methods.

**Pulse-wave velocity**

The velocity of propagation of the pulse-wave through the arterial tree is directly related to the stiffness of the arterial system between the sensors detecting the waveform [19,20]. This relationship has served as the basis for measuring pulse-wave velocity (PWV) as a guide to arterial health (Figure 1). Many studies have demonstrated its correlation in a variety of clinical conditions with future atherosclerotic morbidity and mortality events [3,21-24].

Pulse-wave velocity is limited to the assessment of conduit artery stiffness and, similar to ultrasound, does not provide comprehensive vascular evaluation. The most frequent assessment is between the carotid artery, as equivalent to the root of the aorta, and more distal accessible sites such as the femoral, radial or tibial arteries. Methodology requires two or more individuals to position sensors over the desired vessel and operate the recording system in order to define time intervals. Velocity measurement requires an estimate of the linear length of the vasculature between the two sites of measurement. The methodology for measurement of the time delay between the two arterial sites can be controversial. The initial upstroke of the arrival of pressure at the site may be difficult to identify precisely, depending on the methodology used to detect it. Various slope methods are employed in an attempt to uniformly record the time point and these variables may impact on the calculation [25].
Pressure has a powerful influence on arterial stiffness because of the nonlinear relationship between pressure (P) and volume (V) in the vasculature. Therefore, the slope of ΔP/ΔV, or stiffness, rises as the ambient pressure rises. The PWV is thus sensitive to pressure as well as to structural changes in the arterial wall. Therefore, optimally, PWV should be normalized for mean arterial blood pressure.

**Diastolic pulse-contour analysis**

Analysis of the diastolic decay of the arterial pressure waveform allows the assessment of the vascular influence on arterial pressure independent of left ventricular ejection during systole (Figure 1). The diastolic oscillating decay results from the loss of energy as the pressure wave moves down the arterial tree and from the wave reflections at the branching points along the arterial tree. The diastolic decay can be represented mathematically by a waveform consisting of two major components, a single exponential decay beginning at the dicrotic notch and an exponentially decaying oscillation that generally decays to zero before the next systolic upstroke begins [26,27]. This waveform can be represented by this equation describing the time course of diastolic pressure:

\[ p(t) = A_1 \exp(-A_2 t) + A_3 \exp(-A_4 t) \cos(A_5 t + A_6) \]

A parameter estimating algorithm, such as the Gauss–Newton method, can be used to determine the best estimate of the \( A_1, A_2, \ldots, A_6 \) parameters describing the diastolic decay by iteratively comparing the estimated and actual measured arterial pressure waveforms [28]. Early methods used invasive measures of arterial blood pressure waveforms; more recent approaches use noninvasive recordings from the radial artery for pulse-contour analysis [5]. In current methods employing diastolic pulse-contour analysis, each beat in a 30-s time interval is identified using specific landmarks such as peak systole, the dicrotic notch and the beginning of the systolic upstroke; the \( A_i \) parameters are then determined for each of the most highly correlated \( r > 0.95 \) beats within the 30-s interval and the average of each of the \( A_i \) parameters for these beats is determined. These parameters, derived directly from measured arterial pressure waveforms, can be used to assess the condition of the arterial vasculature. However, investigators have found that a more sensitive assessment of the relationship between these diastolic descriptors and potential disease state can be found when the \( A_i \) decay parameters are further defined in terms of the compliance, iner-tance and resistance elements of a modified Windkessel model of the vasculature during diastole. The equations for the pressure waveforms within the model look exactly like the third order equation stated; equating the comparable terms in the analysis of the model with the \( A_i \) parameters in the above equation permit the determination of the Windkessel elements in terms of the measured experimental or clinical waveforms. One interpretation of the modified Windkessel elements considers them to be representative of large and small vessel compliance or
large and small artery elasticity, inerterance related to arterial blood flow dynamics and peripheral resistance [28]. While there has been considerable discussion regarding the physical interpretation of these elements, results from many studies throughout the world have found them to be well correlated with underlying cardiovascular disease [29-34].

The predictive value of large and small artery elasticity in comparison with carotid IMT, coronary calcium score in relation to coronary heart disease events and heart failure was studied in the Multi-Ethnic Study of Atherosclerosis (MESA) [33,34]. MESA investigated the prevalence, correlates and progression of subclinical cardiovascular disease in 6814 men and women who identified themselves as White, African–American, Hispanic and Chinese and were aged 45–84 years, were free of clinically apparent cardiovascular disease and they were recruited from six US communities [35]. The predictive value of small artery elasticity for coronary heart disease events, especially for myocardial infarction, was superior to carotid IMT, but inferior to coronary calcium score after adjusting for several risk factors and anthropometric characteristics. Large and small artery elasticity was very predictive for congestive heart failure beyond blood pressure and other confounders, while carotid IMT and coronary calcium score were not. Moreover, reduced small artery elasticity may indicate earlier vascular disease in African–Americans and Hispanics than other groups [36].

Although the anatomic boundaries of the large and small arteries cannot be defined in this functional construct, the conduit arteries in the model are assumed to have the major effect on the exponential diastolic pressure decay and the small branching arteries to have the major effect on the reflections or oscillations in the waveform.

The assumptions in the modified Windkessel model render the large and small artery elasticity calculated by this technique somewhat hypothetical. However, data from years of measurement in multiple laboratories in a wide variety of patients have confirmed that small artery elasticity as defined by this procedure is sensitive to endothelial function [37], is abnormal in hypertension [38], is inversely related to cardiovascular risk [5] and responds to interventions in predictable fashion [39]. Both small and large artery elasticity are dramatically age-dependent [40].

In many clinical facilities, diastolic pulse-contour analysis is used to supplement blood pressure and other risk or disease markers to aid in further identification of individuals with vascular disease in need of pharmacotherapy [41]. This technique may also be used to monitor the vascular response to therapy.

Systolic pulse-contour analysis
The systolic arterial pressure wave is composed of an initial incident wave generated by the left ventricle and reflected waves from oscillations induced by interaction of the incident wave at branch points in the circulation, similar to the same physical phenomena creating the decaying oscillations during diastole (Figure 1) [5]. The magnitude of these wave reflections is dependent in part on the elasticity characteristics of the small arteries, and the timing of this reflection to be superimposed on the incident wave is dependent in part on PWV.

A second systolic peak or plateau can usually be detected in peripheral arterial waveforms and is assumed to represent these reflected waves. In radial artery waveforms, the second peak may be a pressure bump late in systole or may occur early and even surpass the pressure of the incident wave [5]. The ratio of this second peak pressure to the first peak pressure can be calculated as an augmentation index [42]. Any transducer that records an arterial waveform can be utilized to calculate an augmentation index.

A commercial device designed to calculate augmentation index uses a transfer function to recreate the presumed central arterial waveform from which the augmentation index is computed [43]. The transfer function has been calculated from analysis of peripheral and central waveforms but is not adjusted for different vascular characteristics of individual patients. The transfer function is utilized primarily as a means of calculating central arterial pressure, which may provide a better guide to systemic pressure than the usually measured arm cuff pressure [44]. However, the accuracy of this model-derived calculation has been questioned [45,46].

Augmentation index provides a value that is dependent on both wave reflection and PWV. Therefore, the role of large arteries and small arteries in the calculation can not be independently assessed. Although augmentation index increases with age and is increased in clinical situations associated with cardiovascular disease, there has been some controversy regarding its predictive value for coronary artery disease [3,47].

The age-related structural changes of conduit arteries speed PWV may mask the small artery manifestations of atherosclerosis [48]. Separate
derivation of small and large artery elasticity from diastolic pulse-contour analysis appears to provide greater discriminatory value \[5\].

**Clinical application of arterial vascular assessment**

Evaluation of the health of the arterial vasculature can be a valuable aid in the diagnosis and management of cardiovascular disease (Figure 2). In fact, this may be the only guide to the presence of disease and its need for treatment, especially in the early asymptomatic phase of disease vascular abnormalities. Such evaluation is particularly useful in individuals with other risk factors that may potentially mandate therapy. Thus, in patients with borderline blood pressures, borderline levels of LDL-cholesterol and borderline blood sugars the presence of early disease may justify more aggressive therapy than might be indicated for the risk factor level alone \[1,3,4\]. Similarly, individuals with a strong family history of early cardiovascular disease might be benefited by the recognition of vascular abnormalities indicative of disease likely to progress.

Tracking of vascular abnormalities as an aid to the management of cardiovascular disease has not been subjected to careful study. Since lifestyle alterations and drug therapy have been demonstrated in several studies to favorably affect the measure of vascular health, sequential study of changes induced by therapy might provide an early measure for effectiveness. It must be recognized, however, that population-based observations demonstrating significant correlations between measurements and outcomes do not necessarily imply that these measurements will be useful in individual patients. Further documentation in controlled trials would be necessary before advocating such an approach to management.

Nonetheless, if therapy is instituted in individuals without a traditional risk factor target, vascular evaluation may be the only intermediate surrogate marker for long-term efficacy.

The selection of methodology for clinical application will be dependent on the experience of the clinic or laboratory as well as the goal of the study. Small artery functional changes in response to effective treatment can be detected within days or weeks. Therefore, pulse-contour analysis would be the ideal means of evaluating an early favorable effect on endothelial function or vascular tone. Since long-term favorable effects will depend on halting or reversing structural changes in the vasculature, IMT or PWV might provide a guide to these responses. All of the measurements have been demonstrated to have some predictive value for morbid events, but since all of them are age-dependent, as are events, care must be taken in adjusting for age in any analysis.

The ultimate clinical value of any measurement of vascular health will be dependent on ease of performance, cost and reliability. Some of the techniques lend themselves to large-scale screening with minimally trained technicians, whereas others are more demanding. Costs of any of the procedures will be reduced by improvements in technology and more widespread use.

**Future perspective**

Efforts to prevent cardiovascular morbid events should take priority over management strategies in end-stage disease in the revised healthcare policy over the next decade. Early vascular disease likely to progress can now be identified noninvasively. Efforts to identify those at risk for therapeutic intervention is a key to future reduction of healthcare costs.

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*Figure 2. Measurement of arterial function with different techniques.*

*AIx: Augmentation Index; LAE: Large artery elasticity; PWV: Pulse-wave velocity; SAE: Small artery elasticity.*
Executive summary

- Most cardiovascular morbid events are complications of progressive abnormalities of the arteries.
- Functional and structural disturbances of the small and large arteries can now be identified noninvasively in asymptomatic individuals.
- The most comprehensive assessment involves pulse-contour analysis recorded from the radial artery.
- The clinical value of noninvasive arterial assessment needs to be documented in prospective studies.

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Papers of special note have been highlighted as:
- of interest
- of considerable interest


3. Describes a comprehensive approach to detecting early vascular disease.


6. Describes a comprehensive approach to detecting early vascular disease.


8. Provides details regarding contributors to pulse-wave analysis abnormalities.


12. Mathematical background for the modified Windkessel model used in assessing arterial elasticity.


14. Detailed discussion of endothelial dysfunction, a critical contributor to decreases in arterial compliance.


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