Comparison of Arterial Assessments in Low and High Vascular Disease Risk Groups

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Background: An increasing number of arterial function assessments are available, including small and large arterial elasticity (SAE/C2, LAE/C1), endothelial function as measured by flow mediated dilation (FMD), carotid intima–medial thickness (IMT), ankle brachial index (ABI), pulse pressure (PP), and pulse wave velocity (PWV). We have consecutively performed these measures in subjects with low and high vascular disease risks to assess the interrelationships.

Methods and Results: Twenty healthy subjects (HS) and 20 older subjects with type 2 diabetes mellitus (DM) were studied with all techniques at a single sitting by a single operator. In HS, C2 correlated with FMD ($R = 0.577, P = .008$), PWV ($R = 0.522, P = .046$), and ABI ($R = 0.463, P = .04$). There was no significant correlation of C1 and FMD or blood pressure (BP) measurements. In DM, C2 correlated with FMD ($R = 0.443, P = .05$), systolic BP ($R = -0.553, P = .01$), PP ($R = -0.601, P = .005$), and systemic vascular resistance ($R = -0.577, P = .008$). There was no significant correlation between anthropometric measures and arterial function measures in either group. The IMT was not correlated with any measure of arterial function in either group.

Conclusions: C2 assessed by pulse wave analysis correlated with endothelial function measured by FMD in young apparently healthy subjects and older subjects with type 2 diabetes. Systolic BP and PP correlated with C2 and FMD in older diabetic subjects but not healthy subjects. The interrelationships between arterial function measures are different in high and low risk populations. This variability needs to be considered when applying these techniques to individuals in different populations.

Key Words: Endothelium, arterial function, arterial compliance, pulse wave analysis.

Arterial function can be assessed noninvasively, and is abnormal in subjects with or at high risk of developing vascular disease. Measures have been applied to population screening, case control and prospective cohort studies and can be abnormal before overt cardiovascular disease develops, enabling targeted early intervention.

Pulsatile arterial function, compliance from pulse wave analysis, endothelial function (ie, flow-mediated dilation), pulse wave velocity (PWV), total systemic arterial compliance, and augmentation index can be assessed.

Brachial artery flow-mediated dilation (FMD) measures dilation of the vessel in response to altered flow, is mediated by endothelial nitric oxide (NO) release, and has been used to measure endothelial function. The FMD is abnormal in type 1 and type 2 diabetes, hypertension, hypercholesterolemia, and hyperhomocysteinemia. The FMD can be improved by hydroxymethylglutaryl coenzyme A reductase inhibitors (statins), fish oil, folate, and antioxidants. The FMD is demanding to perform, requiring a steady state environment and a trained ultrasonographer. Although FMD is a valuable research tool, its place in assessing large numbers of subjects in less controlled settings is less certain.

Capacitive arterial compliance/large artery elasticity (C1), oscillatory/reflective compliance/small artery elasticity (C2), and systemic vascular resistance (SVR) can be measured using the HDI/pulse wave CR-2000 research system (Hypertension Diagnostic Inc., Egan, MN) using a radial arterial transducer to assess the arterial waveform and calculate arterial elasticity based on a modified Windkessel model. This measure has been shown to be abnormal in patients with increased vascular risk and to be predictive of vascular events. In the Atherosclerosis Risk In Communities (ARIC) study, a 1 SD decrease in arterial...
elastocidity was associated with 15% greater risk for developing hypertension, independent of other risk factors for hypertension and baseline blood pressure (BP). There appears to be a link between pulsatile arterial function and NO-mediated arterial tone, but the extent to which measures with this technique are related to other assessments, particularly FMD, has not been studied in detail.20

For the assessment of arterial structure, measurement of carotid intimal-medial thickness (IMT) by B-mode ultrasound21,22 and, ankle brachial index (ABI), the ratio of leg to arm BP, measured with Doppler ultrasound, can be used. The ABI has been associated with prevalent atherosclerosis and with risk of stroke in elderly men.23

There have been very few studies comparing different arterial assessment techniques in the same subjects.24,25 We have addressed this question in two sets of subjects, healthy young subjects with no apparent vascular disease and older subjects with type 2 diabetes mellitus, a condition associated with a two to four times increased risk of vascular disease.26

Methods

Study Population

Twenty healthy volunteers (15 men and 5 women, mean age 29 years) and 20 subjects with type 2 diabetes (10 men and 10 women, mean age 54 years; mean duration of diabetes, 10 years) participated. These groups represent two distinct vascular risk groups (low and high). Healthy volunteers responded to a call for subjects and gave no history of vascular risk factors and were not on medications. Diabetic subjects were recruited from the Diabetes Clinic at St. Vincent’s Hospital. Subjects then underwent a full cardiovascular history and examination. The study was approved by the St. Vincent’s Hospital Ethics Committee. All subjects gave written informed consent. Measurements were performed consecutively by a single operator (AW).

Procedures

All studies commenced at 8 AM in a quiet room with subjects resting supine. Subjects were fasting and had not consumed alcohol, caffeine, or tobacco for at least 12 h before the studies. Waist-to-hip ratio (WHR: defined as the minimal abdominal circumference between the xiphoid process and iliac crests [waist] divided by the circumference over the femoral heads [hips] and body mass index [kg/m²]) were calculated.

Brachial Artery FMD

Left brachial artery diameter was assessed with a linear array ultrasound probe (10 MHz) and a Vingmed Vivid 5 (General Electric Medical, Waukesha, Wisconsin). Images were digitally recorded and archived for offline assessment. Assessments were performed blinded to subject details. The arm was splinted with a prothetic splint and secured with straps above and below the elbow. The brachial artery was scanned 1 to 5 cm above the medial epicondyle. Measurements were taken from the anterior to the posterior arterial wall incident with the R wave and the T wave on electrocardiograph. A BP cuff was placed on the forearm. When a clear image was obtained, the probe was held in place with a clamp to ensure no probe movement. Resting scans were taken and the cuff was inflated to 300 mm Hg for 5 min and deflated. Measurements were recorded after deflation for 90 sec. Brachial FMD was determined as the percentage change from baseline to 60 sec after deflation.

Pulse Wave Analysis

Radial artery pulse waveform analysis was performed using the HDI/ Pulse wave CR-2000 (Hypertension Diagnostic Inc.) system. The right wrist was splinted and a pressure sensor was placed over the maximal radial impulse and positioned to obtain a stable waveform with maximal sensitivity. A BP cuff was placed over the left upper arm and inflated concurrently with the pulse waveform for recording for calibration. Three measurements were taken and averaged. Systolic BP, diastolic BP, mean BP, and pulse pressure (PP) were recorded. Measurements of C2, C1, and SVR were calculated by the device. Elasticity indices are represented in units of milliliters per mm Hg (× 100 for C2 and × 10 for C1).

Carotid Intimal-Medial Thickness

Imaging of the left common carotid artery was performed using high-resolution ultrasound (Vingmed Vivid 5, General Electric Medical). A linear array transducer (7 to 8 MHz) scanned a region 1 cm proximal to the origin of the carotid bulb as previously described.3 Three averaged readings were taken. Measurements were taken between the leading edges of two lines that represent the luminal–medial and medial–adventitial lines.

Ankle Brachial Index

A Doppler probe (Hayashi Denki, Kawasaki, Japan) was used. In a supine position brachial artery systolic blood pressure was taken. Measurements were also made at the posterior tibial and dorsalis pedis. The higher of these values was divided by the brachial pressure to obtain the ABI.

Pulse Wave Velocity

The PWV was determined between a point 1 cm distal to the bifurcation of the left common femoral artery and the midpoint of the popliteal artery after placing the ultrasound probe at these two sites and images were recorded digitally and stored for offline assessment. The external distance in meters was measured with a tape. The interval in seconds between the peak of the R wave (which coincides with ventricular contraction) on a simultaneously recorded electrocardiographic trace and the upstroke of the
measured pulse wave measured by Doppler probe recorded at the two points and the time difference between these points calculated by subtraction. The PWV was calculated as the time difference divided by the measured distance in meters per second.

**Statistical Analysis and Reproducibility**

Coefficients of variation (CV) were calculated as CV = standard deviation/mean. Intraobserver variability was assessed by analyzing 10 subjects a second time 2 to 4 weeks later. The CVs were calculated for 10 repeated measurements on the same subject on the same day for SAE (9.8%), LAE (10.2%), IMT (2.8%), ABI (5.1%), PWV (9.5%), and FMD (6.0%). Data were analyzed with Microsoft Excel 2000 (Microsoft, Redmond, WA) and Minitab version 13.20 (e-academy Inc., Ottawa, Ontario, Canada). Relationships of arterial assessment measures were examined using Pearson bivariate correlation coefficients.

**Results**

Diabetic subjects were older and had greater mean BMI, WHR, and BP measures and were receiving a range of medications (Table 1) compared with healthy subjects. All measures of arterial function were worse in diabetic subjects (Table 2).

**Relationships Between Arterial Assessments**

Table 3 shows bivariate correlations of arterial assessments in the HS group. The C2 was correlated with FMD, PWV, and ABI but not BP. The C1 was not significantly correlated with other variables in healthy subjects. The

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**Table 1.** Subject characteristics

<table>
<thead>
<tr>
<th></th>
<th>Healthy Subjects</th>
<th>Type 2 DM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)*</td>
<td>29 (24–34)</td>
<td>54 (34–72)</td>
</tr>
<tr>
<td>Weight (kg)*</td>
<td>78 (50–105)</td>
<td>91 (58–127)</td>
</tr>
<tr>
<td>BMI*</td>
<td>25 (18–31)</td>
<td>32 (24–45)</td>
</tr>
<tr>
<td>WHR*</td>
<td>0.80 (0.68–1.04)</td>
<td>0.95 (0.88–1.15)</td>
</tr>
<tr>
<td>SBP (mm Hg)*</td>
<td>116 (96–143)</td>
<td>140 (110–199)</td>
</tr>
<tr>
<td>DBP (mm Hg)*</td>
<td>65 (52–78)</td>
<td>76 (63–101)</td>
</tr>
<tr>
<td>PP (mm Hg)*</td>
<td>51 (41–65)</td>
<td>64 (43–97)</td>
</tr>
</tbody>
</table>

BMI = body mass index; DBP = diastolic blood pressure; DM = diabetes mellitus; PP = pulse pressure; SBP = systolic blood pressure; WHR = waist-to-hip ratio.

* Difference presented as mean and range.

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**Table 2.** Arterial function measurements

<table>
<thead>
<tr>
<th></th>
<th>Healthy Subjects</th>
<th>Diabetic Subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean ± SEM</td>
<td>Range</td>
</tr>
<tr>
<td>IMT/(mm)*</td>
<td>0.40 ± 0.02</td>
<td>0.27–0.60</td>
</tr>
<tr>
<td>ABI*</td>
<td>1.17 ± 0.02</td>
<td>1.05–1.30</td>
</tr>
<tr>
<td>FMD (%)*</td>
<td>7.9 ± 0.5</td>
<td>4.2–13.1</td>
</tr>
<tr>
<td>PWV (m/sec)*</td>
<td>7.9 ± 0.6</td>
<td>3.4–11.9</td>
</tr>
<tr>
<td>SAE (mL/mm Hg × 100)*</td>
<td>10.1 ± 0.6</td>
<td>6.1–15.1</td>
</tr>
<tr>
<td>LAE (mL/mm Hg × 10)*</td>
<td>21.0 ± 1.1</td>
<td>11.4–28.7</td>
</tr>
<tr>
<td>SVR (dyne · sec · cm⁻⁵)*</td>
<td>1101 ± 33</td>
<td>846–1400</td>
</tr>
</tbody>
</table>

ABI = ankle brachial index; FMD = flow-mediated dilation; HS = healthy subjects; IMT = intimal-medial thickness; LAE = large arterial elasticity; PWV = pulse wave velocity; SAE = small arterial elasticity; SVR = systemic vascular resistance; other abbreviations as in Table 1.

Data presented as mean and range.

* Difference between HS and DM group significant, $P < .01$. 
have recently demonstrated a relationship between re-

**Table 3.** Interrelationships of assessments of vascular function in healthy subjects

<table>
<thead>
<tr>
<th></th>
<th>FMD</th>
<th>SAE</th>
<th>LAE</th>
<th>ABI</th>
<th>PWV</th>
<th>SBP</th>
<th>DBP</th>
<th>PP</th>
<th>SVR</th>
</tr>
</thead>
<tbody>
<tr>
<td>SAE</td>
<td>0.577†</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LAE</td>
<td>0.213</td>
<td>0.310</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ABI</td>
<td>0.587*</td>
<td>0.463*</td>
<td>0.092</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PWV</td>
<td>-0.641†</td>
<td>-0.522*</td>
<td>-0.324</td>
<td>-0.524*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SBP</td>
<td>-0.060</td>
<td>0.135</td>
<td>-0.008</td>
<td>0.060</td>
<td>0.000</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DBP</td>
<td>-0.232</td>
<td>-0.005</td>
<td>-0.120</td>
<td>0.066</td>
<td>-0.066</td>
<td>0.820†</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PP</td>
<td>0.158</td>
<td>0.234</td>
<td>0.122</td>
<td>0.029</td>
<td>0.066</td>
<td>0.786†</td>
<td>0.291</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SVR</td>
<td>0.507*</td>
<td>-0.241</td>
<td>-0.257</td>
<td>-0.163</td>
<td>-0.255</td>
<td>0.413*</td>
<td>0.455*</td>
<td>0.198</td>
<td></td>
</tr>
<tr>
<td>IMT</td>
<td>0.192</td>
<td>0.026</td>
<td>0.074</td>
<td>0.177</td>
<td>0.278</td>
<td>0.398</td>
<td>0.143</td>
<td>0.508</td>
<td>-0.199</td>
</tr>
</tbody>
</table>

Bold indicates statistical significance; * P < .05; † P < .01.
Abbreviations as in Tables 1 and 2.

FMD, C2, PWV, and ABI were strongly intercorrelated and FMD correlated with SVR.

The correlation of systolic BP with SVR approached significance. Diastolic BP was significantly correlated with SVR. There was no significant association between IMT and other vascular function assessments in this group.

In subjects with type 2 diabetes (Table 4), C2 was correlated with FMD; however, there was no significant correlation between C2 and ABI or PWV. Strong correlation was observed between C2 and all BP measures and SVR. In contrast to the findings in healthy subjects, C1 correlated with FMD and BP. Endothelial function as measured by FMD correlated with C2, C1, and inversely with BP. The ABI was inversely correlated with BP.

### Discussion

Arteries become less elastic with age. Cigarette smoking or disease states such as hypertension, diabetes, chronic renal failure, or dyslipidemia accelerate this process. Agents implicated in this arterial damage include deposition of lipoproteins including LDL, advanced glycation end product formation, calcification and increased oxidative stress, and inflammation.27 These agents also cause small arterial damage and endothelial dysfunction.28 We have recently demonstrated a relationship between reduced C2 and C1 and measures of inflammation (high sensitivity CRP and adhesion molecules) in rheumatoid arthritis, another high vascular disease risk group.29 With a range of arterial assessments assessed individually in cross-sectional studies, it is increasingly important to be aware of the inter-relationships (if any) in individual subjects. We have compared multiple techniques of arterial assessment in low- and high-risk groups, and report the correlations or lack thereof. These groups represent two distinct populations in whom arterial assessment may be targeted. This information is particularly relevant to low risk cohorts who may be assessed as part of a screening approach and in high risk groups where various studies may be used to monitor interventions.

### Relationship Between Endothelial Function and Arterial Elasticity

In both healthy subjects and those with diabetes, a significant correlation was observed between C2 derived from pulse waveform analysis and FMD, a well-established measure of endothelial function. This correlation supports a link between arterial elasticity and endothelial function, most likely relating to the endothelial release of nitric oxide.30,31

Significant changes in the arterial waveform have been...
ARGININE METHYL ESTER (L-NAME), a specific inhibitor, such as where PWV was measured. Specifically more with age and diabetes than peripheral arteries, and may reduce in nitric oxide donors. This response is ablated by NO synthesis and restored with L-arginine, supporting a key role of NO in the regulation of arterial pulsatile function and the regulation of arterial stiffness. It is known that the propagation of the arterial pulse wave velocity by B mode ultrasound (PWV).

In HS, C1 inversely correlated with a measure of femoral arterial elasticity (SAE) in healthy subjects and diabetic subjects (pooled data).

![FIG. 1. Regression plot of flow mediated dilation (FMD) versus small arterial elasticity (SAE) in healthy subjects and diabetic subjects (pooled data).](image)

The ABI is simple to measure with Doppler ultrasound, and in this study, correlated with C2 in healthy subjects. As expected, healthy subjects in this study had ABI measurements in the normal range (1.05 to 1.30), but there was still correlation with C2 and FMD. In subjects with diabetes, no correlation was found between ABI and C2 or FMD. The ABI does not consider diastolic or PP. As the arterial tree ages, especially in the presence of diabetes, regional differences in arterial structure and function, particularly between the arm and leg, may develop leading to a reduction in ABI; however, the reason for the differential relationships between ABI and other measures in the groups studied is not clear.

**Arterial Structure**

The IMT did not correlate with other measures that assess arterial function at a point in time. The mean IMT in the diabetic subjects was relatively normal at 0.63. In published studies increased risk was particularly found in much higher levels (ie, IMT >1 mm), suggesting the relationship between IMT and risk may not be linear, particularly below 1 mm. Increase in IMT is age related and is not acutely influenced by other variables, which may vary arterial tone and function such as sympathetic activity and circulating vasomotor agents (such as NO and endothelin-1) that influence BP, arterial reactivity, and probably elasticity. Many of the diabetic subjects were taking medications that improve vascular health such as statins and angiotensin-converting enzyme inhibitors. These may have improved vascular function, but they would not be expected to acutely alter IMT. Some patients with demonstrated coronary artery disease with normal IMT have been shown to have abnormal FMD. This result suggests that structural and functional characteristics, which are measured in a point in time, can be dissociated. Serial measurements may give more accurate information in this context. This dissociation is more likely to occur in younger patients before significant permanent structural changes occur.

**Pulse Pressure**

In the Framingham study, PP was shown to be an important risk predictor in normotensive and untreated hypertensive middle aged and elderly subjects. Other studies have underlined the significance of PP as an independent risk factor. Pulse pressure is determined by ventricular contraction, elastic properties of the large elastic arteries, and pulse wave reflection, which impact on pulse wave augmentation. As such, PP is a surrogate measure of arterial stiffness. This amplification has been extensively studied and shown to vary with age, pulse rate, exercise, and the administration of nitrates, among other factors. In the Framingham study in younger patients, however, elevated diastolic BP appeared to be a more important marker of risk. This may be due to pressure amplification in
young subjects leading to an underestimation of the central effect of diastolic BP. In older subjects with diabetes, PP, systolic and diastolic BP were strongly correlated with measures of pulsatile arterial function and endothelial function measured by different techniques. This was not the case in young healthy subjects.

The Use of Arterial Function Assessment in Clinical Practice

Arterial function is different in high and low risk subjects. Pulse pressure is a marker of vascular function in older, diabetic subjects but not in healthy young subjects. In young, healthy subjects other surrogate markers of vascular function such as PP, systolic and diastolic BP, IMT, and anthropometric measures did not correlate with elasticity or brachial reactivity.

Test reproducibility can be achieved with arterial elasticity assessment but this requires operator training and a controlled environment. Because FMD and PWV are affected by vasoactive medications, exercise, and ingestion of meals, it would be expected that similar changes might be seen in C2 and C1.

In conclusion, arterial elasticity (C2) assessed by radial pulse wave analysis significantly correlated with flow-mediated dilation in young healthy subjects and older subjects with type 2 diabetes mellitus. Systolic BP and PP were correlated with arterial elasticity and flow-mediated dilation in diabetic subjects but not in younger healthy subjects. The inter-relationships between measures of arterial function appear different in high and low risk populations and these relationships may vary over time in the same individual. This needs to be considered when applying these techniques in different populations, particularly in intervention studies and interpreting overall population data. Information on the relative values of these assessments in predicting risk is limited and longitudinal studies using multiple techniques in the same subjects would be highly useful in clarifying this issue.

Acknowledgment

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References