Relation Between Number of Cardiovascular Risk Factors/Events and Noninvasive Doppler Ultrasound Assessments of Aortic Compliance


Abstract—The aim of this study was to establish the relation between noninvasive Doppler ultrasound assessments of aortic compliance, based on “foot-to-foot” aortic pulse wave velocity measurements, and presumed atherosclerotic load in patients with vascular disease and/or diabetes mellitus. One hundred ten patients with vascular disease and/or diabetes mellitus (arteriopaths) underwent measurement of in vivo aortic compliance using Doppler ultrasound. Demographic data on these subjects were recorded along with details of cardiovascular risk factors and events. Aortic compliance values were compared with data from 51 age-matched healthy, asymptomatic subjects putatively free of vascular disease (controls). Data are expressed as mean±SD. Arteriopaths were aged 64.1±8.4 years and had total cholesterol levels of 5.9±1.1 mmol/L and aortic compliance of 0.78±0.42%/10 mm Hg [1.33 kPa]. Most arteriopaths had 2 or more cardiovascular risk factors and events: diabetes (n=41), hypertension (n=45), smoking (n=86), cerebrovascular/transient ischemic event (n=13), myocardial infarction (n=44), angina (n=51), and/or peripheral vascular disease (n=33). Controls were aged 64.3±12.1 years with total cholesterol of 6.1±1.1 mmol/L and aortic compliance of 1.14±0.46%/10 mm Hg [1.33 kPa] (P<0.002 versus arteriopaths). Subset analysis revealed that patients with the greatest number of cardiovascular risk factors and events (n=5) had the stiffest aortas (aortic compliance, 0.58±0.15%/10 mm Hg [1.33 kPa]) compared with those patients with the median and mean (n=2) number of risk factors and events (aortic compliance, 0.80±0.50%/10 mm Hg [1.33 kPa]; P<0.02). The data suggest that a significant inverse relation exists between presumed atherosclerotic load (as assessed by the number of cardiovascular risk factors and events) and aortic compliance determined noninvasively based on aortic pulse wave velocity measurements. If these findings are confirmed by prospective, longitudinal follow-up studies, such measurements may prove useful as a noninvasive marker of vascular risk. (Hypertension. 1998;32:565-569.)

Key Words: aorta ■ pulse wave velocity ■ atherosclerosis ■ risk factors ■ cardiovascular diseases ■ myocardial infarction

Adult patients with cardiovascular risk factors and events such as hypertension, diabetes mellitus, familial hypercholesterolemia, growth hormone deficiency, obesity, renal failure, ischemic heart disease, myocardial infarction, cerebrovascular disease, and stroke are well recognized to have less compliant (stiffer) aortas than putatively normal healthy control subjects.1–15 However, in most studies, highly selected groups of patients, generally with only a single cardiovascular risk factor, have been investigated. In clinical practice, such patients often have multiple cardiovascular risk factors. We therefore set out to investigate whether in patients with vascular disease and/or diabetes mellitus a significant relationship can be found between noninvasive assessments of aortic biophysical properties and presumed atherosclerotic load as assessed by the number of cardiovascular risk factors and events.

Of vital importance for the widespread application of any measurement technique in clinical studies is the reproducibility of the method.16–24 Such reproducibility data need to be obtained not only for young, fit normal healthy subjects but also in the elderly and for patients with vascular disease (in whom many clinical studies using such biophysical measurement techniques are performed). Therefore, a secondary purpose of this study was to document the reproducibility of the noninvasive aortic compliance measurement technique in elderly patients with vascular disease and/or diabetes mellitus.

Methods

Subjects
The study was approved by the local hospital ethics committee. Patients were recruited after being invited for eligibility screening as
part of a large UK multicenter study investigating the secondary prevention of vascular events in patients already known to have vascular disease and/or diabetes mellitus. One hundred ten patients were studied (arteriopath cohort); 51 putatively normal healthy subjects of similar ages who were asymptomatic for cardiovascular disease and had been previously studied provided control data (control cohort).

Demographic data were recorded via a standardized history taken at the time of the compliance measurements, along with details of cardiovascular risk factors and events. Presumed atherosclerotic load was assessed on the basis of a cumulative total vascular risk score (TVRS), with 1 point being given for each of the following risk factors/events: diabetes mellitus, hypertension (requiring medication), current or ex-smoker, cerebrovascular event (CVA) or transient ischemic attack (TIA), myocardial infarction (MI), angina, and peripheral vascular disease (PVD).

Measurement Technique

Aortic compliance was assessed noninvasively on the basis of Doppler ultrasound measurements of the pulse wave velocity (PWV) along the descending thoracoabdominal aorta. Briefly, the measurement protocol is as follows. Each subject is required to rest supine for at least 10 minutes, and the examination is begun once the blood pressure has stabilized. One continuous-wave Doppler ultrasound transducer is placed in the left supravacuicular fossa pointing medially to insonate close to the root of the left subclavian artery just as it comes off the aortic arch. The other transducer insonates the abdominal aorta at the level of the umbilicus just proximal to the aorto-iliac bifurcation. Doppler-shifted signals from the 2 transducers are spectrally analyzed and processed in real time on a heartbeat-by-heartbeat basis. The processing results in recognition of the “foot” of the systolic upstroke in the sonogram flow-velocity waveforms recorded by each transducer (Figure 1). This permits the determination of the aortic transit time of the flow pulse in real time for each heartbeat. These transit time values are then averaged over 40 consecutive cardiac cycles.

The patient’s resting supine brachial blood pressure is measured with a standard sphygmomanometer at the beginning and end of this procedure. A random zero length measurement technique is then used to determine the distance from the sternal notch to the position of the transducer on the surface of the abdomen. Cadaver studies have shown this distance to be within 5% of the effective aortic path length. Thereafter, 9 successive sets of measurements are performed, each set consisting of data from 40 consecutive cardiac cycles. In each case, a value for aortic compliance (AC) per 10 mm Hg (1.33 kPa) pulse pressure is automatically calculated by the computer, based on the mean transit time (T), mean path length (L), and the density of blood (ρ) where

\[ AC = \frac{T(L/2)^2}{2L} \]

On completion of the 9 sets of readings, a mean value of AC is computed, which is used in all further analyses.

Measurement Reproducibility

The reproducibility of this technique has been previously documented in vivo to be better than 10% in normal, healthy young adult subjects. In elderly normal, healthy subjects, coefficients of variation at 1 and 3 months of follow-up were 13.7% and 14.4%, respectively. The validity of the methodology has also been established in vitro with electromagnetic flowmeter comparison studies.

To document the reproducibility of the technique in elderly patients with vascular disease and/or diabetes mellitus, a subset of 39 patients in the arteriopath cohort had their AC remeasured approximately 4 weeks after their original eligibility screening visit (but before any therapeutic interventions). The observers were not aware on the repeated measurement occasion of the original measurement results.

Data Analysis

Statistical analyses were performed using the NCSS statistical system (Dr J. Hintze, Kaysville, Utah). Repeated measurement reproducibility data were analyzed using linear regression analysis and a Bland-Altman plot. The relationship between AC and demographic details and the cumulative TVRS was assessed using logistic regression analysis. Comparisons between different TVRS subgroups were done using unpaired t tests. Unpaired t tests were also used to compare AC values between controls, patients who had only cardiovascular risk factors (diabetes mellitus, hypertension [requiring treatment], smoking, and angina), and patients with cardiovascular risk factors plus events (MI, CVA/TIA, and PVD). Multivariate stepwise regression analysis was performed with AC as the dependent variable and age, gender, systolic blood pressure, diastolic blood pressure, body mass index, MI, CVA/TIA, angina, PVD, diabetes mellitus, antihypertensive therapy, smoking status, and total cholesterol as independent variables. The significance level was set at P<0.05.

Clinical Details of Patients and Control Subjects

<table>
<thead>
<tr>
<th>Clinical Details</th>
<th>Patients</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>64.1±8.4</td>
<td>64.3±12.1</td>
</tr>
<tr>
<td>Gender, M/F</td>
<td>80/30</td>
<td>9/42</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>41</td>
<td>0</td>
</tr>
<tr>
<td>Hypertension</td>
<td>45</td>
<td>5</td>
</tr>
<tr>
<td>Smoker</td>
<td>86</td>
<td>0</td>
</tr>
<tr>
<td>CVA/TIA</td>
<td>13</td>
<td>0</td>
</tr>
<tr>
<td>MI</td>
<td>44</td>
<td>0</td>
</tr>
<tr>
<td>Angina</td>
<td>51</td>
<td>0</td>
</tr>
<tr>
<td>PVD</td>
<td>33</td>
<td>0</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>26.7±3.6</td>
<td>24.6±3.9</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>146±23</td>
<td>129±21†</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>82±12</td>
<td>72±9†</td>
</tr>
<tr>
<td>Total cholesterol, mmol/L</td>
<td>5.9±1.1</td>
<td>6.1±1.1</td>
</tr>
<tr>
<td>PWV, m/s</td>
<td>10.4±3.1</td>
<td>8.2±2.1*</td>
</tr>
<tr>
<td>AC, %/10 mm Hg [1.33 kPa]</td>
<td>0.78±0.42</td>
<td>1.14±0.46*</td>
</tr>
</tbody>
</table>

Data are number or mean±SD.

*P<0.002, †P<0.01.
Clinical details for patients and control subjects are shown in the Table. There was no significant difference between the cohorts with regard to age, although there was a preponderance of postmenopausal female subjects in the control cohort. Blood pressure was significantly higher in the arteriopath patient cohort than in the asymptomatic, putatively normal, healthy control subjects.

Most of the arteriopath patient cohort had at least 2 cardiovascular risk factors and events (mean and median TVRS = 2). Seven patients had a TVRS = 1, 46 patients had a TVRS = 2, 35 patients had a TVRS = 3, 17 patients had a TVRS = 4, and 5 patients had a TVRS = 5. In total, 38 patients had only cardiovascular risk factors, whereas 72 patients had symptomatic cardiovascular events. Five of the control subjects were taking antihypertensive medication at the time of their compliance measurement (TVRS = 1). The remaining control subjects did not have any vascular risk factors or events (TVRS = 0).

As shown in the Table, the arteriopath patients had substantially less compliant (stiffer) aortas than the controls (P < 0.002). However, even within the arteriopath cohort, subset analysis revealed that patients with the greatest number of cardiovascular risk factors and events (TVRS = 5) had the stiffest aortas (AC, 0.58 ± 0.15%/10 mm Hg [1.33 kPa]) compared with those patients with fewer risk factors and events (eg, patients with TVRS = 2; AC, 0.80 ± 0.50%/10 mm Hg [1.33 kPa]; P < 0.02) (Figure 2). There was no difference in systolic, mean, or diastolic blood pressures between the TVRS = 2 and TVRS = 5 groups (mean blood pressure, 100 ± 12 versus 106 ± 17 mm Hg; P = 0.37, NS). Furthermore, on logistic regression analysis, a significant inverse association was observed between AC and the TVRS (number of cardiovascular risk factors and events), with the regression equation being AC = −0.12 × TVRS + 1.1 (r = −0.38, P < 0.0001).

Reproducibility
The 39 patients who had repeated AC measurements performed approximately 4 weeks after their original eligibility screening visit measurements were representative of the arteriopathy patient cohort as a whole. The mean ± SD age of the subset reproducibility cohort was 62.9 ± 8.6 years (26 men, 13 women), average TVRS = 2. Figure 3 shows the AC values from the first visit plotted against those for the second visit (r = 0.87). The coefficient of variation for these repeat measurements was 16.7%. A Bland-Altman plot 32 (Figure 4) revealed no significant bias between the 2 measurement occasions.

Discussion
The data suggest that a significant inverse relation exists between presumed atherosclerotic load (as assessed by the number of cardiovascular risk factors and events [TVRS]) and AC determined noninvasively on the basis of aortic PWV measurements. This observation is not reliant on the data from the control cohort, which is provided only to offer a comparison with asymptomatic, putatively normal, healthy subjects of similar ages. In this respect, we cannot be certain that some of our control subjects did not have cardiovascular
disease. Indeed, in western countries, advanced atherosclerosis is almost ubiquitous by the third decade of life; therefore, it is highly probable that some of the control cohort did indeed have some asymptomatic vascular disease. However, such “misclassification” of the controls would only serve to obscure differences between the 2 groups and contribute to an overlap between the cohorts, rather than create differences.

Furthermore, even though age, the most important determinant of arterial biophysical properties, was well controlled for, there was a preponderance of female subjects in the control cohort. However, as shown in Figure 5 for data from a previous study of over 600 normal healthy subjects, by 64 years of age there are no measurable differences between AC values for men and women. In the present study, no significant differences could be found in AC values between men and women.

Another potential confounding variable that needs to be considered in these analyses is blood pressure. As shown in the Table, the control cohort had lower blood pressures than the arteriopath cohort. While at higher blood pressures the aorta will be stiffer, accounting for some of the difference in AC values observed between the 2 groups, the simple passive effect of a higher blood pressure in the arteriopath cohort cannot provide the entire explanation as to why the patients with vascular disease and/or diabetes mellitus have stiffer aortas. For example, within the arteriopath cohort itself, the group with a TVRS of 5 had substantially stiffer aortas than the group with a TVRS of 2 ($P<0.02$). However, systolic, mean, and diastolic blood pressures were not significantly different between these 2 groups of patients. Furthermore, on multivariate regression analysis, in addition to age and blood pressure, previous MI was observed to be a significant independent correlate of AC, providing additional evidence that blood pressure alone does not explain all the observations arising from Figure 2.

As would be expected, patients with cardiovascular events also had risk factors. Therefore, it was not possible to identify any significant difference in AC values between patients with risk factors alone compared with patients with risk factors and cardiovascular events. However, patients with cardiovascular risk factors (but no symptomatic events) did have significantly stiffer aortas than control subjects without risk factors. Patients with symptomatic cardiovascular events (MI, CVA/TIA, and PVD) had even stiffer aortas.

In animal and human studies, the atherosclerotic involvement of vessels at postmortem has been closely correlated with arterial stiffness assessed noninvasively just before death. In humans, Hira et al have also shown strong associations between aortic stiffness and the degree of coronary artery disease assessed at coronary angiography. Furthermore, an international cooperative study of the distribution of coronary and aortic atherosclerosis at autopsy has shown that the different arterial segments develop similar degrees of atherosclerosis, with the correlation coefficients of the rankings between segments of the coronary arteries and the abdominal aorta being $>0.85$. Collectively, these data support a possible role for arterial stiffness measurement as a noninvasive marker of atherosclerotic load or coronary vascular risk. This is especially the case because aortic stiffness is an important determinant of both left ventricular function and coronary blood flow. For example, in humans, Bouthe et al and Dahan et al have shown aortic PWV to correlate significantly with the left ventricular mass/volume and wall thickness-to-radius ratio in both hypertensive and normotensive subjects. In animals, Watanabe et al have shown that increasing aortic stiffness aggravates myocardial ischemia when coronary blood flow is impaired, possibly by decreasing the inverse pressure gradient responsible for coronary filling, especially in the presence of coronary flow–limiting lesions. Therefore, in addition to AC measurement offering the possibility of a marker of vascular change in the coronary vessels, AC may also be an important determinant of coronary perfusion, becoming even more clinically significant in the presence of coronary artery disease. This may explain why in the present study, a previous MI is a significant independent correlate of AC, more so than any other cardiovascular risk factor or event.

However, because the data presented here are only observational they clearly cannot be used to prove a causal...
relationship between AC and cardiovascular events. In this respect, it is expected that longitudinal follow-up studies, such as are currently ongoing, should help to establish whether AC measurements can provide independent predictions of vascular morbidity and mortality and perhaps offer useful surrogate end points for clinical trials.

Summary

We found less compliant (stiffer) aortas in patients with cardiovascular risk factors and clinically evident atherosclerotic vascular disease. Furthermore, the contribution of multiple cardiovascular risk factors or events appears to be additive, with patients with more risk factors/events having substantially stiffer aortas than patients with fewer risk factors/events. Of all the risk factors/events studied, the incidence of MI appears to correlate most significantly with the presence of aortic stiffness.

Acknowledgment

This study was supported by the British Diabetic Association.

References

Relation Between Number of Cardiovascular Risk Factors/Events and Noninvasive Doppler Ultrasound Assessments of Aortic Compliance


Hypertension. 1998;32:565-569
doi: 10.1161/01.HYP.32.3.565

Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1998 American Heart Association, Inc. All rights reserved.
Print ISSN: 0194-911X. Online ISSN: 1524-4563

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://hyper.ahajournals.org/content/32/3/565

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Hypertension can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Hypertension is online at:
http://hyper.ahajournals.org//subscriptions/