Carotid Artery Longitudinal Displacement Predicts 1-Year Cardiovascular Outcome in Patients With Suspected Coronary Artery Disease

Sara Svedlund, Charlotte Eklund, Per Robertsson, Milan Lomsky, Li-Ming Gan

Objective—Total longitudinal displacement (tLoD) of the common carotid artery can be measured using the ultrasound-based velocity vector imaging (VVI) technique. This study aimed to investigate clinical correlates and the possible predictive value of tLoD for cardiovascular outcome.

Methods and Results—Four hundred forty-one patients referred for myocardial perfusion scintigraphy examination for suspected coronary artery disease were recruited and underwent VVI-assisted tLoD measurement. Patients were followed up with regard to major adverse cardiovascular event (MACE) 1 year later. Low tLoD (≤0.055 mm) was associated with greater clinically determined myocardial ischemia (P<0.01). During a median follow-up time of 372 days, 61 MACEs occurred. In a Kaplan–Meier survival analysis, high tLoD (>0.055 mm) predicted 1-year event-free survival (P<0.01, highest versus lowest tertile odds ratio [OR]=1.9). In a Cox regression model adjusting for age, gender, intima-media thickness, radial strain, pulse pressure, and percentage reversibility mass of myocardium, low tLoD remained a significant independent predictor of MACE (P=0.03). Finally, low tLoD provided additional predictive value in subjects with increased intima-media thickness.

Conclusion—VVI-derived tLoD seems to reflect cardiovascular status and predicts short-term event-free survival in medium- to high-risk patients. Finally, tLoD per se or in combination with intima-media thickness measurement may be a novel cardiovascular surrogate biomarker. (Arterioscler Thromb Vasc Biol. 2011;31:1668-1674.)

Key Words: carotid arteries ▪ coronary artery disease ▪ risk factors ▪ ultrasonic diagnosis

Large artery stiffness, most commonly defined as increased stiffness in the aorta and its major branches, is accepted as an independent risk factor for cardiovascular (CV) morbidity and mortality and is therefore an important variable in risk assessment.1 The most extensively studied method to analyze large artery stiffness is pulse wave velocity. Increases in large artery stiffness values measured by pulse wave velocity have been shown to be prognostic for future CV events in various patient categories, as well as in a general population.2-11

Because arterial stiffness is a descriptive term,12 no single definition is possible because of the complexity of the arterial tree. Several different approaches to quantify the assessment of large artery stiffness are being used to investigate regional stiffness and local stiffness; these different approaches include a variety of methods, such as ultrasound measurements and the use of pressure tonometers.13 The methods used to assess local arterial stiffness are based principally on the vessel wall radial movement (change in the vessel diameter) during the cardiac cycle. However, the longitudinal vessel wall movement that occurs along the length of the common carotid artery (CCA), in the cranio-caudal direction (ie, at right angles to the radial wall motion), has gained less attention and has previously been considered to be of minor clinical importance.

Recent advances in ultrasound software technology have made it possible to investigate cardiac wall motion with velocity vector imaging (VVI). This image analysis software is based on multiple M-mode evaluations. Tissue speckle tracking enables angle-independent measurement of ultrasound images in both radial and longitudinal directions during cardiac cycles. In the context of echocardiographic image analysis, VVI has been used to evaluate ventricular dyssynchrony.14 The feasibility and reproducibility of this technique to study the CCA longitudinal wall motion by calculation of the total longitudinal displacement (tLoD) during a cardiac cycle has been investigated previously by our research group.15 Our measuring concept includes assessment of the peak systolic and diastolic longitudinal CCA displacements.

In the present study, we investigated potential predictive values of tLoD for future CV events in a population with...
clinically suspected coronary artery disease (CAD). We also studied possible relationships between VVI-derived variables and CV correlates.

Methods

Patients and Study Design
Four hundred forty-one consecutive patients with clinically suspected CAD (referred for investigation of chest pain) were recruited for study participation at the Department of Clinical Physiology, Sahlgrenska University Hospital, Gothenburg, Sweden, from 2006 to 2008. All patients underwent standard myocardial perfusion scintigraphy (MPS) for detection of clinically meaningful myocardial ischemia. All patients were investigated on a second occasion, within 1 month of the MPS examination, with a complete ultrasound examination of the carotid arteries. Blood sampling was performed following overnight fasting. VVI measurements were processed later at a workstation. The study was approved by the local ethics committee in Gothenburg. All subjects gave written informed consent to participate in the study.

Ultrasound Examination of the Carotid Arteries
Carotid artery ultrasound was conducted by experienced sonographers, blinded to the result of the MPS examination, according to a standard protocol. The Acuson Sequoia 512 ultrasound system was used (Siemens Medical Solutions Inc) with an 8 MHz transducer (Sequoia 8L5C). CINE-looped images of the distal CCA, carotid bulb, and proximal internal carotid artery were stored for offline analysis. B-mode real-time ultrasound was used to evaluate the arterial wall intima-media thickness (IMT) of the CCA. IMT was defined as the distance from the lumen-intimal interface to the medial-adventitial border.16 Presence of stenosis was defined as a 50% lumen narrowing and diagnosed as an elevated peak systolic velocity of >1.2 m/s in the internal carotid artery, external carotid artery or CCA.17 The presence of plaques was evaluated in short-axis view of the carotid bifurcation by manual delineation. Conventional CCA radial strain was calculated as the radial (systolic diameter-diastolic diameter)/diastolic diameter, and the stiffness index β was calculated according to Kawasaki et al as ln(systolic blood pressure/diastolic blood pressure)/diastolic diameter/(systolic diameter−diastolic diameter), where ln is the natural logarithm.18

Velocity Vector Ultrasound Imaging Measurements
Our concept for measuring the tLoD of the CCA has been described in detail elsewhere.15 Briefly, VVI software (Research Arena 2, TomTec imaging systems GmbH, Unterschleissheim, Germany) was used to derive the CCA vessel wall displacement in the longitudinal and radial directions of the right CCA far wall. Measurements were performed offline at a workstation using the leading-to-leading edge principle; edges were outlined manually approximately 1 cm distal to the carotid bifurcation in the right CCA. Five guiding points were distributed evenly within a 1-cm segment in both the near and far walls (Figure 1). VVI measurements were all conducted to display peak values in systole and diastole during 1 cardiac cycle. tLoD, ie, the magnitude of the vessel motion during 1 cardiac cycle, was calculated as the sum of the peak displacement in systole and diastole in CCA. The tracking ability of the VVI technique has previously been validated with good accuracy.19 Figure 1 also illustrates the output of the software.

MPS
MPS was performed according to the standard clinical protocol. Briefly, the gated-SPECT studies were performed using a 2-day nongated stress/gated rest 99m Tc-sestamibi protocol. Patients un-
The apolipoprotein A1 and B concentrations were measured with No. 2016630, Roche Diagnostics GMBH, Mannheim, Germany). Triglycerides and cholesterol in serum were measured using reagent systems from Roche (triglycerides/GB kit No. 12146029216, cholesterol kit No. 2016630, Roche Diagnostics GMBH, Mannheim, Germany). The apolipoprotein A1 and B concentrations were measured with turbidimetric technique, using polyclonal rabbit anti-human antibodies (Q 0496 and Q 0497, Dako Cytomation, Glostrup, Denmark). C-reactive protein was measured with a high-sensitivity reagent kit (CP 3847, Randox Laboratories Ltd, Crumlin, United Kingdom).

Definitions of Outcome Measures
Patients were followed up by telephone interviews and by medical records at 1 year. Study end point was set to major adverse CV events (MACEs), defined as the incidence of death from any cause, stroke, myocardial infarction, and coronary arterial revascularizations (as either coronary artery bypass grafting or percutaneous intervention). The definition of stroke was focal or global neurologic deficits lasting for more than 24 hours and verified by either a neurologist or computed tomography brain scan. Definition of myocardial infarction was clinically driven and confirmed by elevation of troponin above upper normal limit in at least 2 consecutive samples.

Statistical Analysis
Analyses were made using SPSS statistical software, version 17.0 for Windows (SPSS Inc, Chicago, IL). Data are expressed as mean±SD. A 2-tailed probability value of less than 0.05 was considered significant. Student t test and ANOVA were used to determine
differences between groups. The Bonferroni correction was used for multiple comparisons between groups. Kaplan–Meier survival analysis was used to explore prospective predictive value of tLoD. For tests of linear trend significance of tLoD tertiles, a $\chi^2$ test was used. Cox regression analysis was used to analyze the impact of various parameters on MACEs using dichotomized variables. The $\chi^2$ test was used to determine the incremental value of tLoD above IMT.

**Results**

**Baseline Characteristics**
The study population consisted of 441 patients aged 62.0±9.0 years (range, 35 to 84 years). The range of tLoD was 0.002 to 2.129 mm. For the statistical analysis, tLoD were divided into tertiles (lowest tertile, ≤0.055 mm; middle tertile, 0.056 to 0.144 mm; highest tertile, ≥0.145 mm). As can be seen in Table 1, patients with lower compared with higher tLoD did not display any differences in age or gender. Patients with low tLoD had a greater body mass index compared with patients with middle tertile of tLoD ($P=0.03$). Systolic and diastolic blood pressure components did not differ between the groups, nor was there a difference in pulse pressure. Furthermore, tLoD did not relate to the presence of diabetes mellitus, hypertension, or smoking habit. Medical treatments at baseline are displayed in Table 1. Although no relationship to CCA plaque area in short-axis view could be seen, low tLoD had the greatest IMT, with a significant linear trend toward higher tLoD having the thinnest IMT ($P=0.04$). There was no difference in the tLoD tertiles with regards to presence of stenosis. Manually calculated radial carotid strain was lower in the lowest tertile compared with the highest tertile of tLoD, in addition to a significant linear association. The interrelationship of the VVI-generated variables was highly associated: low tLoD showed the lowest radial displacement, lowest longitudinal velocity, lowest longitudinal strain, and lowest strain rate ($P<0.001$).

**Relationship of tLoD, Laboratory Analysis, and Cardiac Performance**
No obvious relationship between tLoD tertiles and reported plasma markers was seen. Patients exhibiting lower compared with higher tLoD showed a greater clinically scored MPS ischemia area and ischemia severity. Automatically generated MPS ischemia severity was also higher in the lowest tertile compared with the highest. A summary of MPS data in the different tLoD groups can be seen in Table 2.

**Relationship Between tLoD and CV Outcome**
Median follow-up time was 372 days. A total number of 61 MACEs occurred, including death, myocardial infarction, stroke, and coronary arterial revascularization (percutaneous intervention, $n=43$; coronary artery bypass grafting, $n=9$). In a Kaplan–Meier survival analysis, lower tLoD predicted 1-year event rate with an OR of 1.9 when comparing the highest and lowest tertiles ($\chi^2 P<0.01$, Figure 2A). In a Cox regression model including gender, age, CCA IMT, radial strain, pulse pressure, and percentage reversibility mass of myocardium, low tLoD remained a significant independent predictor of MACEs ($P=0.03$) alongside gender and percentage reversibility mass of myocardium (Table 3). The distributions of MACEs are shown in Table 4. In a separate survival analysis including patients with IMT above and below the median value of 0.06 cm, lower tLoD provided a significantly greater event rate compared with higher tLoD and IMT in the lower median. Thus, as shown in Figure 2B, tLoD provides an incremental value above IMT in prediction of event-free survival.

**Discussion**
In the present study, we investigated longitudinal CCA wall displacement with VVI technique and the possible relationship to clinical variables and CV prognosis in a population with suspected CAD. In this initial study, we demonstrated that patients presenting with a lower longitudinal VVI-assessed wall displacement of the CCAs have a greater clinically scored MPS ischemia area and score and automatically generated ischemia severity. Patients presenting with a greater IMT in the CCA exhibited the lowest tLoD. Divided in tertiles, higher tLoD was associated with a better CV prognosis at 1-year follow-up. VVI-derived tLoD seems to reflect both vessel wall morphology characteristics and myocardial ischemia in a population with suspected CAD.

The longitudinal vessel wall movement has previously been observed to be very small when assessed invasively by
external electromechanical devices attached to the aorta in dogs.\textsuperscript{20,21} However, with modern ultrasound techniques, Persson et al have developed a method with the ability to measure simultaneously the magnitude of the longitudinal and radial wall motion at different depths of the arterial wall.\textsuperscript{22} Their initial in vivo trial of this method revealed a greater longitudinal movement of the intima-media complex compared with the tunica adventitia. In the study mentioned, the movements of the anterior and posterior CCA walls were reported to be of equal size.

Male gender is known to be associated with increased arterial stiffness and CAD. Also, hypertension is well known to be 1 of the most important determinants of arterial stiffness. Surprisingly, tLoD does not seem to be related to gender, blood pressure, or diabetes mellitus diagnosis. Unlike conventional arterial stiffness measurements, the lack of association with known risk factors may indicate that tLoD is reflecting other aspects of arterial wall function or, alternatively, is a result of this specific patient cohort.

Our study shows lower tLoD is associated with increasing IMT but that there is no significant relationship to plaque area. This may indicate that tLoD is reflecting local vascular properties. Both the occurrence of plaque in the carotid bifurcation and the IMT have been shown to reflect CV status. The occurrence of plaque in carotid bifurcations is dependent not only on systemic atherogenic risk factors but also on the local hemodynamic environment. To avoid potential local mechanical influence from the carotid bifurcation, tLoD was measured 1 cm proximal to the bulb, with the intention to reflect mechanical properties of a systemic atherosclerotic disease. In analogy with this finding, we suggest that tLoD be measured preferentially approximately 1 cm proximal to the carotid bulb to avoid local influence of plaque occurrence.

Interestingly, few studies have shown prospective values for future CV events with local stiffness measurements in the radial direction.\textsuperscript{23–27} In the current study, local radial strain was not associated with CV outcome. As suggested by Humphrey et al, studying mechanical forces acting on vessel walls following vascular wall thickening due to various CV risk factors, the axial stress is decreased to a larger extent than the circumferential stress, which may imply that the longitudinal wall motion might be an earlier and more sensitive measure of vascular wall remodeling compared with traditional local radial diameter measurements.\textsuperscript{28} Indeed, the

Table 3. Cox Regression Model Predicting MACE

<table>
<thead>
<tr>
<th></th>
<th>B</th>
<th>Significance</th>
<th>OR</th>
<th>Lower</th>
<th>Upper</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td>0.88</td>
<td>0.016</td>
<td>2.41</td>
<td>1.18</td>
<td>4.92</td>
</tr>
<tr>
<td>Age</td>
<td>0.03</td>
<td>0.116</td>
<td>1.04</td>
<td>0.99</td>
<td>1.08</td>
</tr>
<tr>
<td>Radial strain medians</td>
<td>0.01</td>
<td>0.993</td>
<td>1.01</td>
<td>0.548</td>
<td>1.83</td>
</tr>
<tr>
<td>Pulse pressure</td>
<td>0.01</td>
<td>0.628</td>
<td>1.01</td>
<td>0.99</td>
<td>1.02</td>
</tr>
<tr>
<td>CCA IMT medians</td>
<td>0.38</td>
<td>0.299</td>
<td>1.47</td>
<td>0.71</td>
<td>3.03</td>
</tr>
<tr>
<td>Reversibility mass of myocardium</td>
<td>0.09</td>
<td>&lt;0.001</td>
<td>1.10</td>
<td>1.07</td>
<td>1.12</td>
</tr>
<tr>
<td>tLoD medians</td>
<td>−0.72</td>
<td>0.030</td>
<td>0.488</td>
<td>0.25</td>
<td>0.94</td>
</tr>
</tbody>
</table>

CCA indicates common carotid artery; IMT, intima-media thickness.

Table 4. Distribution of MACEs in the Different tLoD Groups

<table>
<thead>
<tr>
<th>MACEs</th>
<th>Lowest Tertile (n=148)</th>
<th>Middle Tertile (n=147)</th>
<th>Highest Tertile (n=147)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>MI, death, stroke</td>
<td>4</td>
<td>5</td>
<td>4</td>
<td>NS</td>
</tr>
<tr>
<td>Coronary arterial revascularization*</td>
<td>28</td>
<td>13</td>
<td>11</td>
<td>0.005</td>
</tr>
<tr>
<td>Total MACEs</td>
<td>32</td>
<td>16</td>
<td>13</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Total MACEs refers to the most severe event. MI indicates myocardial infarction; NS, not significant.

* Percutaneous intervention and coronary artery bypass grafting.
correlation between tLoD tertiles and IMT may partially support this presumption.

Furthermore, the magnitude of the CCA longitudinal movement is closely related to the presence of cardiac ischemia, both clinically and automatically determined by MPS. It has been shown previously that the presence of ischemia is strongly related to extent and severity of CAD as verified by coronary angiogram.29,30 Also, carotid IMT has been shown to correlate with extent of CAD as verified by coronary angiogram.31 Although no direct correlation has been provided between tLoD and angio-verified CAD severity, the fact that tLoD correlates with both carotid IMT and presence of ischemia suggests that tLoD reflects the extent of CAD in this population. Whether tLoD is under the influence of cardiac performance, ie, contractility, merits further investigation.

CCA vessel wall displacement has been shown to be multiphasic, at least in healthy volunteers.32 Even though the VVI software generates robust measurements of peak and reversed peak values, in its current version, the software does not seem to be suitable for evaluation of this multiphasic aspect. However, future software development may shed light on the clinical importance of this reported phenomenon.

In CV risk stratification, it is of great importance to view both cardiac and vessel status. VVI-derived tLoD of the CCA is a simple, highly feasible, noninvasive method and can be a possible future approach in local arterial stiffness determination, with the advantage of being an integrative method reflecting both vessel and cardiac functions.

**Study Limitations**

In the present study, we defined MACEs as a composite measure of death, stroke, acute myocardial infarction, and coronary arterial revascularization, including percutaneous intervention and coronary artery bypass grafting. Because of the short follow-up time and relatively low number of events, the difference in events in the various tLoD groups was mainly driven by arterial revascularization. However, in this clinical setting, with patients undergoing MPS to diagnose presence of ischemia for potential intervention, the ability of tLoD to predict this clinical outcome is considered relevant. Indeed, it has been shown that MPS-verified ischemia is a great predictor of future hard MACEs,33 and medical and surgical intervention leading to reduction in ischemia saves lives.34 Future long-term follow-up may address its potential ability to predict spontaneous cardiac events in terms of cardiac death and nonfatal myocardial infarction. Also, because only a subset of the patients underwent coronary angiogram, we cannot provide a direct correlation between tLoD and the extent and severity of the atherosclerosis-related morphological changes in the coronary arteries. This topic will hopefully be addressed in an ongoing study involving patients after percutaneous intervention.

In this patient cohort, tLoD seems to be associated with both local vessel structure and presence of cardiac ischemia. Despite this, tLoD appears to be an independent predictor of 1-year event-free survival, and more mechanistic studies are required to deepen our understanding of this interesting vascular mechanical property. Furthermore, whether tLoD will be a prognostic factor in a general population other than patients with suspected CAD needs to be investigated further.

In this study, no evaluation of pulse wave analysis was performed. Consequently, the potential relationship between tLoD and central blood pressures could not be directly evaluated, and this matter remains to be investigated.

**Conclusions**

Several ultrasound-based arterial stiffness methods are in use in addition to cardiac examinations in investigations of patients with suspected CAD. Our results suggest that VVI-derived tLoD of CCA is an integrative variable combining assessment of both vessel and cardiac status. Furthermore, tLoD predicts ischemia and predicts that those patients with a low tLoD could potentially be considered for coronary angiography to evaluate need for revascularization. Finally, tLoD seems to provide additional prognostic value on top of morphological characteristics of the CCA.

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**Disclosures**

Dr Gan is employed by AstraZeneca R&D.

**References**


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경동맥 종축 변위는 심혈관계환 환자의 1년째 임상 결과를 예측한다.

배 장 호 교수
건양대학교병원 순환기내과

Summary

목적
초음파를 이용한 VVI (velocity vector imaging)으로 총경동맥의 종축 변위(longitudinal displacement)를 측정할 수 있다. 본 연구는 총경동맥의 종축 변위가 임상 인자와의 관련성 및 심혈관계 사건에 대한 예측을 할 수 있는지 확인하고자 하였다.

방법 및 결과
심혈관계환의 의심되어 심근관류 조영을 받는 441명의 환자를 대상으로 VVI를 이용한 총경동맥의 종축 변위를 측정하였다. 대상 환자에서 1년 동안 심혈관계 사건에 대해 추적 조사를 하였다. 총경동맥의 종축 변위가 높은 경우(≤0.055mm) 임상적 심근 허혈이 흔히 관찰되었다($P<0.01$). 372일간 추적 시 61건의 심혈관계 사건이 발생했다. 연령, 성별, 내중막 두께, 횡측 strain, 맥압, 심근의 가역성 허혈 정도를 보정한 Cox regression 분석 후에도 낮은 총경동맥 종축 변위는 심혈관계 사건의 독립적인 예측인자였다($P=0.03$). 총경동맥 종축 변위가 낮은 것은 경동맥 내중막 두께가 증가된 환자에서 부가적인 예측인자가 될 수 있었다.

결론
VVI를 이용한 총경동맥의 종축 변위는 심혈관계 상태를 반영하며, 중등도 이상의 위험도를 가진 환자에서 단기 임상 결과를 예측한다. 결론적으로, 총경동맥 종축 변위 자체 혹은 경동맥 내중막 두께를 같이 고려하는 것은 중요한 심혈관계 표지로서 활용될 수 있다.
경동맥 내중막 두께, 동맥 경직도, 동맥 탄성도와 내피세포 기능 등은 심혈관질환의 지표로 많이 사용되고 있으며, 예후와도 관련이 있음이 잘 알려져 있다. 총경동맥의 종축 움직임에 대해서는 잘 알려지지 않았으나, 심실 dyssynchrony 연구에 사용되는 VVI를 이용하여 총경동맥의 종축 변위를 측정하는데, 심실과 달리 비교적 움직임이 덜한 총경동맥에서의 측정은 측정의 정확도가 더 높을 수 있다.

본 연구에서, 총경동맥의 종축 변위가 낮은 경우 내중막 두께도 두꺼웠으며 심근 허혈이 더 심한 것과도 관련이 있었다. 총경동맥의 종축 움직임이 낮은 것은 동맥 경직도와 관련이 있을 것으로 유추되지만, 본 연구에서는 동맥 경직도를 측정하지 않았으므로 심근 허혈과의 관련성을 내중막 두께와의 관련성을 보이는 기전에 대해서 명확히 설명할 수는 없는 상태이다.

동맥 경화의 지표로서 총경동맥의 종축 변위의 임상적 의미에 대한 연구로서 본 논문의 의미를 찾을 수 있었다.

REFERENCES
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Key Words: carotid arteries • coronary artery disease • risk factors • ultrasonic diagnosis

Large artery stiffness, most commonly defined as increased stiffness in the aorta and its major branches, is accepted as an independent risk factor for cardiovascular (CV) morbidity and mortality and is therefore an important variable in risk assessment. The most extensively studied method to analyze large artery stiffness is pulse wave velocity. Increases in large artery stiffness values measured by pulse wave velocity have been shown to be prognostic for future CV events and mortality in various patient categories, as well as in a general population.

Because arterial stiffness is a descriptive term, no single definition is possible because of the complexity of the arterial tree. Several different approaches to quantify the assessment of large artery stiffness are being used to investigate regional stiffness and local stiffness; these different approaches include a variety of methods, such as ultrasound measurements and the use of pressure tonometers. The methods used to assess local arterial stiffness are based principally on the vessel wall movement (change in the vessel diameter) during the cardiac cycle. However, the longitudinal vessel wall movement that occurs along the length of the common carotid artery (CCA), in the cranio-caudal direction (ie, at right angles to the radial wall motion), has gained less attention and has previously been considered to be of minor clinical importance.

Recent advances in ultrasound software technology have made it possible to investigate cardiac wall motion with velocity vector imaging (VVI). This image analysis software is based on multiple M-mode evaluations. Tissue speckle tracking enables angle-independent measurement of ultrasound images in both radial and longitudinal directions during cardiac cycles. In the context of echocardiographic image analysis, VVI has been used to evaluate ventricular dyssynchrony. The feasibility and reproducibility of this technique to study the CCA longitudinal wall motion by calculation of the total longitudinal displacement (tLoD) during a cardiac cycle has been investigated previously by our research group. Our measuring concept includes assessment of the peak systolic and diastolic longitudinal CCA displacements.

In the present study, we investigated potential predictive values of tLoD for future CV events in a population with...
clinically suspected coronary artery disease (CAD). We also studied possible relationships between VVI-derived variables and CV correlates.

Methods

Patients and Study Design

Four hundred forty-one consecutive patients with clinically suspected CAD (referred for investigation of chest pain) were recruited for study participation at the Department of Clinical Physiology, Sahlgrenska University Hospital, Gothenburg, Sweden, from 2006 to 2008. All patients underwent standard myocardial perfusion scintigraphy (MPS) for detection of clinically meaningful myocardial ischemia. All patients were investigated on a second occasion, within 1 month of the MPS examination, with a complete ultrasound examination of the carotid arteries. Blood sampling was performed following overnight fasting. VVI measurements were processed later at a workstation. The study was approved by the local ethics committee in Gothenburg. All subjects gave written informed consent to participate in the study.

Ultrasound Examination of the Carotid Arteries

Carotid artery ultrasound was conducted by experienced sonographers, blinded to the result of the MPS examination, according to a standard protocol. The Acuson Sequoia 512 ultrasound system was used (Siemens Medical Solutions Inc) with an 8 MHz transducer (Sequoia 8L5C). CINE-looped images of the distal CCA, carotid bulb, and proximal internal carotid artery were stored for offline analysis. B-mode real-time ultrasound was used to evaluate the arterial wall intima-media thickness (IMT) of the CCA. IMT was defined as the distance from the lumen-intimal interface to the medial-adventitial border. Presence of stenosis was defined as a 50% lumen narrowing and diagnosed as an elevated peak systolic velocity of >1.2 m/s in the internal carotid artery, external carotid artery or CCA. The presence of plaques was evaluated in short-axis view of the carotid bifurcation by manual delineation. Conventional CCA radial strain was calculated as the radial (systolic diameter-diastolic diameter)/diastolic diameter, and the stiffness index β was calculated according to Kawasaki et al as ln(systolic blood pressure/diastolic blood pressure)×diastolic diameter(systolic diameter–diastolic diameter), where ln is the natural logarithm.

Velocity Vector Ultrasound Imaging Measurements

Our concept for measuring the tLoD of the CCA has been described in detail elsewhere. Briefly, VVI software (Research Arena 2, TomTec imaging systems GmbH, Unterschleissheim, Germany) was used to derive the CCA vessel wall displacement in the longitudinal and radial directions of the right CCA far wall. Measurements were performed offline at a workstation using the leading-to-leading edge principle; edges were outlined manually approximately 1 cm distal to the carotid bifurcation in the right CCA. Five guiding points were distributed evenly within a 1-cm segment in both the near and far walls (Figure 1). VVI measurements were all conducted to display peak values in systole and diastole during 1 cardiac cycle. tLoD, ie, the magnitude of the vessel motion during 1 cardiac cycle, was calculated as the sum of the peak displacement in systole and diastole as absolute values. All results on tLoD values represent the total movement of the right CCA far wall. The inter- and intraobserver variabilities of tLoD measurements are 9.1% and 10.5%, respectively. The tracking ability of the VVI technique has previously been validated with good accuracy. Figure 1 also illustrates the output of the software.

MPS

MPS was performed according to the standard clinical protocol. Briefly, the gated-SPECT studies were performed using a 2-day nongated stress/gated rest 99m Tc-sestamibi protocol. Patients un-
The apolipoprotein A1 and B concentrations were measured with laboratory analyses.

The interrelationship of the VVI-generated variables was highly associated: low tLoD showed the lowest radial displacement, tLoD, CCA stiffness index, and lowest strain rate (1/s) in tertiles, with regards to trend toward higher tLoD having the thinnest IMT (P<0.001). There was no difference in the tLoD tertiles with regards to gender. Patients with low tLoD had a greater body mass index compared with patients with middle tertile of tLoD (P<0.012). No obvious relationship between tLoD tertiles and reported smoking, BMI, use of beta blockers, or C-reactive protein was observed. Table 1. Clinical Characteristics of the Study tLoD Groups.

<table>
<thead>
<tr>
<th>Clinical Variables</th>
<th>Lowest Tertile (n=148)</th>
<th>Middle Tertile (n=147)</th>
<th>Highest Tertile (n=147)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>tLoD (mm)</td>
<td>≤0.055</td>
<td>0.056 to 0.144</td>
<td>≥0.145</td>
<td></td>
</tr>
<tr>
<td>Age (y)</td>
<td>62.35±9.29</td>
<td>62.37±8.90</td>
<td>62.05±8.95</td>
<td>NS</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>26.85±3.89</td>
<td>25.70±3.57</td>
<td>26.16±4.02</td>
<td>0.03*</td>
</tr>
<tr>
<td>Sex (% male)</td>
<td>50.0</td>
<td>40.1</td>
<td>47.6</td>
<td>NS</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>13.2</td>
<td>14.4</td>
<td>13.0</td>
<td>NS</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>54.4</td>
<td>42.9</td>
<td>51.4</td>
<td>NS</td>
</tr>
<tr>
<td>Smoking (%)</td>
<td>12.5</td>
<td>12.1</td>
<td>11.6</td>
<td>NS</td>
</tr>
<tr>
<td>SBP (mm Hg)</td>
<td>147.3±23.4</td>
<td>144.9±24.3</td>
<td>144.3±23.0</td>
<td>NS</td>
</tr>
<tr>
<td>DBP (mm Hg)</td>
<td>86.2±10.4</td>
<td>84.9±11.7</td>
<td>83.5±12.0</td>
<td>NS</td>
</tr>
<tr>
<td>Aspirin (%)</td>
<td>52.7</td>
<td>39.7</td>
<td>54.4</td>
<td>0.02†</td>
</tr>
<tr>
<td>Beta blockers (%)</td>
<td>45.2</td>
<td>43.2</td>
<td>55.8</td>
<td>NS</td>
</tr>
<tr>
<td>ACE inhibitors (%)</td>
<td>25.3</td>
<td>21.9</td>
<td>21.1</td>
<td>NS</td>
</tr>
<tr>
<td>Clopidogrel (%)</td>
<td>6.8</td>
<td>8.2</td>
<td>6.1</td>
<td>NS</td>
</tr>
<tr>
<td>Statins (%)</td>
<td>44.5</td>
<td>35.6</td>
<td>47.6</td>
<td>NS</td>
</tr>
<tr>
<td>CCA IMT (cm)</td>
<td>0.065±0.028</td>
<td>0.061±0.016</td>
<td>0.060±0.015</td>
<td>0.04‡</td>
</tr>
<tr>
<td>Plaque area (cm²)</td>
<td>0.083±0.099</td>
<td>0.080±0.127</td>
<td>0.078±0.077</td>
<td>NS</td>
</tr>
<tr>
<td>CCA manual strain (%)</td>
<td>0.079±0.031</td>
<td>0.084±0.032</td>
<td>0.093±0.039</td>
<td>0.003‡</td>
</tr>
<tr>
<td>CCA stiffness index β</td>
<td>3.17±0.46</td>
<td>3.08±0.45</td>
<td>3.03±0.59</td>
<td>NS</td>
</tr>
<tr>
<td>Stenosis presence, n (%)</td>
<td>6 (4.1)</td>
<td>4 (2.7)</td>
<td>11 (7.5)</td>
<td>NS</td>
</tr>
<tr>
<td>tRaeD (mm)</td>
<td>0.088±0.080</td>
<td>0.134±0.126</td>
<td>0.344±1.049</td>
<td>0.01†</td>
</tr>
<tr>
<td>Long velocity S (cm/s)</td>
<td>0.015±0.013</td>
<td>0.042±0.018</td>
<td>0.134±0.126</td>
<td>&lt;0.0001‡</td>
</tr>
<tr>
<td>Long velocity D (cm/s)</td>
<td>0.012±0.009</td>
<td>0.044±0.044</td>
<td>0.108±0.098</td>
<td>&lt;0.0001‡</td>
</tr>
<tr>
<td>Long strain S (%)</td>
<td>0.633±0.661</td>
<td>1.589±1.879</td>
<td>3.996±4.970</td>
<td>&lt;0.0001‡</td>
</tr>
<tr>
<td>Long strain D (%)</td>
<td>0.189±0.280</td>
<td>1.101±8.315</td>
<td>1.239±1.981</td>
<td>NS</td>
</tr>
<tr>
<td>Long strain rate S (1/s)</td>
<td>0.033±0.026</td>
<td>0.170±1.064</td>
<td>0.214±0.248</td>
<td>0.04‡</td>
</tr>
<tr>
<td>Long strain rate D (1/s)</td>
<td>0.029±0.024</td>
<td>0.071±0.045</td>
<td>0.185±0.215</td>
<td>&lt;0.0001‡</td>
</tr>
</tbody>
</table>

Values are means±SD or percentages. NS indicates not significant; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; ACE, angiotensin-converting enzyme; tRaeD, total radial displacement; long, longitudinal; S, systole; D, diastole.

*Significance between group 1 and 2.
†Significance between group 2 and 3.
‡Significant as linear-by-linear association.

**Laboratory Analyses**

The biochemical analyses were performed using commercially available kits according to the manufacturers’ protocols. Triglycerides and cholesterol in serum were measured using reagent systems from Roche (triglycerides/GB kit No. 12146029216, cholesterol kit No. 2016630, Roche Diagnostics GmbH, Mannheim, Germany). The apolipoprotein A1 and B concentrations were measured with turbidimetric technique, using polyclonal rabbit anti-human antibodies (Q 0496 and Q 0497, Dako Cytomation, Glostrup, Denmark). C-reactive protein was measured with a high-sensitivity reagent kit (CP 3847, Randox Laboratories Ltd, Crumlin, United Kingdom).

**Definitions of Outcome Measures**

Patients were followed up by telephone interviews and by medical records at 1 year. Study end point was set to major adverse CV events (MACEs), defined as the incidence of death from any cause, stroke, myocardial infarction, and coronary arterial revascularization (as either coronary artery bypass grafting or percutaneous intervention). The definition of stroke was focal or global neurological deficits lasting for more than 24 hours and verified by either a neurologist or computed tomography brain scan. Definition of myocardial infarction was clinically driven and confirmed by elevation of troponin above upper normal limit in at least 2 consecutive samples.

**Statistical Analysis**

Analyses were made using SPSS statistical software, version 17.0 for Windows (SPSS Inc, Chicago, IL). Data are expressed as mean±SD. A 2-tailed probability value of less than 0.05 was considered significant. Student t test and ANOVA were used to determine
differences between groups. The Bonferroni correction was used for multiple comparisons between groups. Kaplan-Meier survival analysis was used to explore prospective predictive value of tLoD. For tests of linear trend significance of tLoD tertiles, a χ² test was used. Cox regression analysis was used to analyze the impact of various parameters on MACEs using dichotomized variables. The χ² test was used to determine the incremental value of tLoD above IMT.

Results

Baseline Characteristics
The study population consisted of 441 patients aged 62.0±9.0 years (range, 35 to 84 years). The range of tLoD was 0.002 to 2.129 mm. For the statistical analysis, tLoD were divided into tertiles (lowest tertile, ≤0.055 mm; middle tertile, 0.056 to 0.144 mm; highest tertile, ≥0.145 mm). As can be seen in Table 1, patients with lower compared with higher tLoD did not display any differences in age or in gender. Patients with low tLoD had a greater body mass index compared with patients with middle tertile of tLoD (P=0.03). Systolic and diastolic blood pressure components did not differ between the groups, nor was there a difference in pulse pressure. Furthermore, tLoD did not relate to the presence of diabetes mellitus, hypertension, or smoking habit. Medical treatments at baseline are displayed in Table 1. Although no relationship to CCA plaque area in short-axis view could be seen, low tLoD had the greatest IMT, with a significant linear trend toward higher tLoD having the thinnest IMT (P=0.04). There was no difference in the tLoD tertiles with regards to presence of stenosis. Manually calculated radial carotid strain was lower in the lowest tertile compared with the highest tertile of tLoD, in addition to a significant linear association. The interrelationship of the VVI-generated variables was highly associated: low tLoD showed the lowest radial displacement, lowest longitudinal velocity, lowest longitudinal strain, and lowest strain rate (P<0.001).

Relationship of tLoD, Laboratory Analysis, and Cardiac Performance
No obvious relationship between tLoD tertiles and reported plasma markers was seen. Patients exhibiting lower compared with higher tLoD showed a greater clinically scored MPS ischemia area and ischemia severity. A manually calculated MPS ischemia severity was also higher in the lowest tertile compared with the highest. A summary of MPS data in the different tLoD groups can be seen in Table 2.

Relationship Between tLoD and CV Outcome
Median follow-up time was 372 days. A total number of 61 MACEs occurred, including death, myocardial infarction, stroke, and coronary arterial revascularization (percutaneous intervention, n=43; coronary artery bypass grafting, n=9). In a Kaplan-Meier survival analysis, lower tLoD predicted 1-year event rate with an OR of 1.9 when comparing the highest and lowest tertiles (χ² P<0.01, Figure 2A). In a Cox regression model including gender, age, CCA IMT, radial strain, pulse pressure, and percentage reversibility mass of myocardium, low tLoD remained a significant independent predictor of MACEs (P=0.03) alongside gender and percentage reversibility mass of myocardium (Table 3). The distributions of MACEs are shown in Table 4. In a separate survival analysis including patients with IMT above and below the median value of 0.06 cm, lower tLoD provided a significantly greater event rate compared with higher tLoD and IMT in the lower median. Thus, as shown in Figure 2B, tLoD provides an incremental value above IMT in prediction of event-free survival.

Discussion
In the present study, we investigated longitudinal CCA wall displacement with VVI technique and the possible relationship to clinical variables and CV prognosis in a population with suspected CAD. In this initial study, we demonstrated that patients presenting with a lower longitudinal VVI-assessed wall displacement of the CCA’s have a greater clinically scored MPS ischemia area and score and automatically generated ischemia severity. Patients presenting with a greater IMT in the CCA exhibited the lowest tLoD. Divided in tertiles, higher tLoD was associated with a better CV prognosis at 1-year follow-up. VVI-derived tLoD seems to reflect both vessel wall morphology characteristics and myocardial ischemia in a population with suspected CAD.

The longitudinal vessel wall movement has previously been observed to be very small when assessed invasively by
external electromechanical devices attached to the aorta in dogs. However, with modern ultrasound techniques, Persson et al have developed a method with the ability to measure simultaneously the magnitude of the longitudinal and radial wall motion at different depths of the arterial wall. Their initial in vivo trial of this method revealed a greater longitudinal movement of the intima-media complex compared with the tunica adventitia. In the study mentioned, the movements of the anterior and posterior CCA walls were reported to be of equal size.

Male gender is known to be associated with increased arterial stiffness and CAD. Also, hypertension is well known to be 1 of the most important determinants of arterial stiffness. Surprisingly, tLoD does not seem to be related to gender, blood pressure, or diabetes mellitus diagnosis. Unlike conventional arterial stiffness measurements, the lack of association with known risk factors may indicate that tLoD is reflecting other aspects of arterial wall function or, alternatively, is a result of this specific patient cohort.

Our study shows lower tLoD is associated with increasing IMT but that there is no significant relationship to plaque area. This may indicate that tLoD is reflecting local vascular properties. Both the occurrence of plaque in the carotid bifurcation and the IMT have been shown to reflect CV status. The occurrence of plaque in carotid bifurcations is dependent not only on systemic atherogenic risk factors but also on the local hemodynamic environment. To avoid potential local mechanical influence from the carotid bifurcation, tLoD was measured 1 cm proximal to the bulb, with the intention to reflect mechanical properties of a systemic atherosclerotic disease. In analogy with this finding, we suggest that tLoD be measured preferentially approximately 1 cm proximal to the carotid bulb to avoid local influence of plaque occurrence.

Interestingly, few studies have shown prospective values for future CV events with local stiffness measurements in the radial direction. In the current study, local radial strain was not associated with CV outcome. As suggested by Humphrey et al, studying mechanical forces acting on vessel walls following vascular wall thickening due to various CV risk factors, the axial stress is decreased to a larger extent than the circumferential stress, which may imply that the longitudinal wall motion might be an earlier and more sensitive measure of vascular wall remodeling compared with traditional local radial diameter measurements. Indeed, the

Table 3. Cox Regression Model Predicting MACE

<table>
<thead>
<tr>
<th></th>
<th>B</th>
<th>Significance</th>
<th>OR</th>
<th>Lower</th>
<th>Upper</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td>0.88</td>
<td>0.016</td>
<td>2.41</td>
<td>1.18</td>
<td>4.92</td>
</tr>
<tr>
<td>Age</td>
<td>0.03</td>
<td>0.116</td>
<td>1.04</td>
<td>0.99</td>
<td>1.08</td>
</tr>
<tr>
<td>Radial strain</td>
<td>0.01</td>
<td>0.993</td>
<td>1.01</td>
<td>0.548</td>
<td>1.83</td>
</tr>
<tr>
<td>Pulse pressure</td>
<td>0.01</td>
<td>0.628</td>
<td>1.01</td>
<td>0.99</td>
<td>1.02</td>
</tr>
<tr>
<td>CCA IMT median</td>
<td>0.38</td>
<td>0.299</td>
<td>1.47</td>
<td>0.71</td>
<td>3.03</td>
</tr>
<tr>
<td>Reversibility</td>
<td>0.09</td>
<td>&lt;0.001</td>
<td>1.10</td>
<td>1.07</td>
<td>1.12</td>
</tr>
<tr>
<td>tLoD median</td>
<td>-0.72</td>
<td>0.030</td>
<td>0.488</td>
<td>0.25</td>
<td>0.94</td>
</tr>
</tbody>
</table>

CCA indicates common carotid artery; IMT, intima-media thickness.

Table 4. Distribution of MACEs in the Different tLoD Groups

<table>
<thead>
<tr>
<th>MACEs</th>
<th>Lowest Tertile (n=148)</th>
<th>Middle Tertile (n=147)</th>
<th>Highest Tertile (n=147)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>MI, death, stroke</td>
<td>4</td>
<td>5</td>
<td>4</td>
<td>NS</td>
</tr>
<tr>
<td>Coronary arterial revascularization*</td>
<td>28</td>
<td>13</td>
<td>11</td>
<td>0.005</td>
</tr>
<tr>
<td>Total MACEs</td>
<td>32</td>
<td>16</td>
<td>13</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Total MACEs refers to the most severe event. MI indicates myocardial infarction; NS, not significant.

*Percutaneous intervention and coronary artery bypass grafting.
correlation between tLoD tertiles and IMT may partially support this presumption.

Furthermore, the magnitude of the CCA longitudinal movement is closely related to the presence of cardiac ischemia, both clinically and automatically determined by MPS. It has been shown previously that the presence of ischemia is strongly related to extent and severity of CAD as verified by coronary angiogram.29,30 Also, carotid IMT has been shown to correlate with extent of CAD as verified by coronary angiogram.31 Although no direct correlation has been provided between tLoD and angio-verified CAD severity, the fact that tLoD correlates with both carotid IMT and presence of ischemia suggests that tLoD reflects the extent of CAD in this population. Whether tLoD is under the influence of cardiac performance, ie, contractility, merits further investigation.

CCA vessel wall displacement has been shown to be multiphasic, at least in healthy volunteers.32 Even though the VVI software generates robust measurements of peak and reversed peak values, in its current version, the software does not seem to be suitable for evaluation of this multiphasic aspect. However, future software development may shed light on the clinical importance of this reported phenomenon.

In CV risk stratification, it is of great importance to view both cardiac and vessel status. VVI-derived tLoD of the CCA is a simple, highly feasible, noninvasive method and can be a possible future approach in local arterial stiffness determination, with the advantage of being an integrative method reflecting both vessel and cardiac functions.

Study Limitations

In the present study, we defined MACES as a composite measure of death, stroke, acute myocardial infarction, and coronary arterial revascularization, including percutaneous intervention and coronary artery bypass grafting. Because of the short follow-up time and relatively low number of events, the difference in events in the various tLoD groups was mainly driven by arterial revascularization. However, in this clinical setting, with patients undergoing MPS to diagnose presence of ischemia for potential intervention, the ability of tLoD to predict this clinical outcome is considered relevant. Indeed, it has been shown that MPS-verified ischemia is a great predictor of future hard MACES,33 and medical and surgical intervention leading to reduction in ischemia saves lives.34 Future long-term follow-up may address its potential ability to predict spontaneous cardiac events in terms of cardiac death and nonfatal myocardial infarction. Also, because only a subset of the patients underwent coronary angiogram, we cannot provide a direct correlation between tLoD and the extent and severity of the atherosclerosis-related morphological changes in the coronary arteries. This topic will hopefully be addressed in an ongoing study involving patients after percutaneous intervention.

In this patient cohort, tLoD seems to be associated with both local vessel structure and presence of cardiac ischemia. Despite this, tLoD appears to be an independent predictor of 1-year event-free survival, and more mechanistic studies are required to deepen our understanding of this interesting vascular mechanical property. Furthermore, whether tLoD will be a prognostic factor in a general population other than patients with suspected CAD needs to be investigated further.

In this study, no evaluation of pulse wave analysis was performed. Consequently, the potential relationship between tLoD and central blood pressures could not be directly evaluated, and this matter remains to be investigated.

Conclusions

Several ultrasound-based arterial stiffness methods are in use in addition to cardiac examinations in investigations of patients with suspected CAD. Our results suggest that VVI-derived tLoD of CCA is an integrative variable combining assessment of both vessel and cardiac status. Furthermore, tLoD predicts ischemia and predicts that those patients with a low tLoD could potentially be considered for coronary angiography to evaluate need for revascularization. Finally, tLoD seems to provide additional prognostic value on top of morphological characteristics of the CCA.

Sources of Funding

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Disclosures

Dr Gan is employed by AstraZeneca R&D.

References
