This is the published version of a paper published in *Scandinavian Cardiovascular Journal*.

Citation for the original published paper (version of record):

Carotid IM-GSM is better than IMT for identifying patients with multiple arterial disease
*Scandinavian Cardiovascular Journal*, 52(2): 93-99
https://doi.org/10.1080/14017431.2018.1435903

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To cite this article: Fisnik Jashari, Pranvera Ibrahimi, Elias Johansson, Christer Grönlund, Per Wester & Michael Y. Henein (2018) Carotid IM-GSM is better than IMT for identifying patients with multiple arterial disease, Scandinavian Cardiovascular Journal, 52:2, 93-99, DOI: 10.1080/14017431.2018.1435903

To link to this article: https://doi.org/10.1080/14017431.2018.1435903

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Published online: 06 Feb 2018.

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Carotid IM-GSM is better than IMT for identifying patients with multiple arterial disease

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ABSTRACT

Objective. Atherosclerosis is a systemic inflammatory disease that can affect more than one arterial bed simultaneously. The aim of this study was to determine the relationship between ultrasound markers of atherosclerosis and multiple arterial disease. Design. We have included 87 currently asymptomatic carotid disease patients (mean age 69 ± 6 year, 34% females) in this study. Intima media thickness (IMT) and intima media-grey scale median (IM-GSM) were measured in the common carotid artery (CCA), and correlated with previous and/or current atherosclerotic vascular disease in the coronary, carotid and lower extremities. Patients were divided into three groups: (1) asymptomatic, (2) previous symptoms in one arterial territory and (3) previous symptoms in multiple arterial territories. Results. Patients with previous disease in the coronary arteries had higher IMT (p = 0.034) and lower IM-GSM (p < 0.001), and those with prior stroke had lower IM-GSM (p = 0.007). Neither IMT nor IM-GSM was different between patients with and without previous lower extremity vascular disease. IM-GSM was significantly different between groups, it decreased significantly with increasing number of arterial territories affected (37.7 ± 15.4 vs. 29.3 ± 16.4 vs. 20.7 ± 12.9) p < .001, for asymptomatic, symptoms in one and in multiple arterial systems, respectively. Conventional IMT was not significantly different between groups p = .49. Conclusion. Carotid IMT was higher and IM-GSM lower in patients with symptomatic nearby arterial territories but not in those with peripheral disease. In contrast to conventional IMT, IM-GSM can differentiate between numbers of arterial territories affected by atherosclerosis, suggesting that it is a better surrogate for monitoring multiple arterial territory disease.

Introduction

Atherosclerosis is a systemic inflammatory disease of the arterial wall and is the underlying cause of the majority of cardiovascular events worldwide [1]. Severity of carotid artery stenosis has been traditionally used as the main criterion for predicting future cerebrovascular (CV) symptoms [2] however, other plaque features have recently been reported to have incremental value over and above arterial stenosis [3]. Plaque composition, ulceration and surface irregularities can be easily and reproducibly obtained by duplex ultrasound (US) [4]. In the absence of a carotid plaque, IMT measurements by ultrasound, has been shown to be closely associated with the risk of developing future ischemic heart disease and stroke [5,6]. However, recent evidence refuting any association between IMT progression and CV risk in the general population has contradicted these findings [7,8]. Intima media-grey scale median (IM-GSM) has recently been introduced as an innovative method with additional incremental information over conventional risk factors, with echoluent intima-media complex (low IM-GSM) associated with increased risks for atherosclerosis e.g. dyslipidemia, oxidative stress and inflammation, as well as increased risk of cardiovascular mortality [9,10].

Being a systemic disease, atherosclerosis predominantly affects coronary, carotid and other arterial systems. Patients with detectable disease in the coronary and peripheral arteries carry double the risk of future ischemic events compared to those with only one arterial territory affected by atherosclerosis [1,11]. We aimed in this study to compare carotid artery wall measurements (IMT and IM-GSM) between different patient groups, based on prior vascular symptoms in different arterial territories and number of diseased arteries.

Methods

Patients’ selection

This is a subgroup analysis of the Additional Neurological Symptoms before Surgery of the Carotid Arteries – a Prospective study (ANSYSCAP) [12]. In ANSYSCAP, consecutive patients with a 50–100% internal carotid artery stenosis/occlusion were prospectively included between August 2007 and December 2009. In the main analysis, symptomatic and asymptomatic patients with moderate to severe (50–99%) carotid stenosis who were primarily eligible...
for carotid endarterectomy (CEA) were analysed. Over the course of the original study, the ultrasound imaging storage process was upgraded from analogue to digital. In the current study, we have included only asymptomatic patients whose carotid ultrasound examinations were stored in digital format and could be retrieved for detailed plaque analyses (n = 87), (Figure 1).

Patients with asymptomatic carotid stenosis were defined as those with carotid stenosis without an ipsilateral ischemic CV event within 6 months of the carotid examination. Diseased carotid arteries were identified in several ways: (a) objective bruit during auscultation or subjective bruit (tinnitus), (b) a suspicion of CV symptoms led to a carotid examination, but final assessment was that the symptoms were not CV in origin (e.g. seizure, migraine), (c) follow up of a previously confirmed carotid stenosis, (d) previous CV symptoms more than 6 months ago, (e) detection of calcification in the territory of carotid artery by panorama imaging (a dental procedure), (f) posterior circulation CV symptoms, or (g) during examination of the thyroid gland.

Patients clinical data were prospectively collected to establish; (i) the number and duration of ischemic events; (ii) time of most recent symptom (if any); (iii) risk factors (smoking, diabetes, hypertension and dyslipidemia) and (iv) any surgical information. All clinical data were undertaken during preoperative evaluation or from patients’ medical notes. All patients underwent a thorough clinical examination including neurological assessment. Routine biochemical data were also collected from the patient’s clinical notes including lipid profile and glycated hemoglobin (HbA1c) (Table 1). Biochemical data and medical history were taken at the time of preoperative evaluation. The median delay between preoperative evaluation and carotid ultrasound was 4 (intra quartile range 2–20) days.

**Carotid ultrasound examination**

Carotid Doppler US examination was performed in all patients by experienced vascular sonographers, using a Siemens Acuson Sequoia 512® system with an 8L5 linear transducer. The severity of carotid stenosis was assessed by conventional Doppler US criteria [13]. According to the North American Symptomatic Carotid Endarterectomy Trial (NASCET) criteria, all velocity cut-off values were related to the angiographic evaluation of the carotid stenosis [14]. The ultrasound images were exported in the DICOM format for intima media analyses of IMT and IM-GSM as described below.

**Intima-media complex measurements**

Both IMT and IM-GSM measurements were made in the distal segment of the common carotid artery within 1 cm (± 2 mm) distance starting from the carotid bifurcation at the right and left sides (Figure 2(a)). When a plaque was present in this region, the IM-complex free-of- plaque was selected, and if it was < 0.8 cm long the artery was excluded from the study (n = 8). The average of carotid measurements of both sides was used for analysis. We have used color flow Doppler stored video examinations of carotid arteries and frames when color Doppler was just passed away were used to measure intima-media features.

**Carotid-intima media thickness (IMT)**

IMT was conventionally defined as the distance between the lumen-intima interface and the media-adventitia interface. One cm segments of the far wall carotid arteries were manually measured in three different points on a single frame, and then averaged [15]. The IMT measurement were made using the EchoPac software (General Electric, EchoPac version 8.0.1, Waukesha, WI).

### Table 1. Patients’ data.

<table>
<thead>
<tr>
<th>Description</th>
<th>Mean ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>69 ± 6</td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>30 (35)</td>
</tr>
<tr>
<td>Current smoking, n (%)</td>
<td>18 (21)</td>
</tr>
<tr>
<td>Diabetes, n (%)</td>
<td>25 (29)</td>
</tr>
<tr>
<td>Previous myocardial infarction, n (%)</td>
<td>20 (23)</td>
</tr>
<tr>
<td>Current angina, n (%)</td>
<td>14 (16)</td>
</tr>
<tr>
<td>Previous stroke, n (%)</td>
<td>18 (21)</td>
</tr>
<tr>
<td>Intermittent claudication, n (%)</td>
<td>19 (22)</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg), mean ± SD</td>
<td>145.7 ± 20</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg), mean ± SD</td>
<td>77 ± 12</td>
</tr>
<tr>
<td>Anti-platelet or anti-coagulation therapy, n (%)</td>
<td>84 (97)</td>
</tr>
<tr>
<td>Blood pressure lowering therapy, n (%)</td>
<td>80 (92)</td>
</tr>
<tr>
<td>Lipid lowering therapy, n (%)</td>
<td>78 (90)</td>
</tr>
<tr>
<td>HbA1c (%), mean ± SD</td>
<td>5.2 ± 1.1</td>
</tr>
<tr>
<td>Total cholesterol (mmol/l), mean ± SD</td>
<td>4.7 ± 0.9</td>
</tr>
<tr>
<td>LDL (mmol/l), mean ± SD</td>
<td>2.6 ± 0.9</td>
</tr>
<tr>
<td>HDL (mmol/l), mean ± SD</td>
<td>1.3 ± 0.4</td>
</tr>
</tbody>
</table>

Low density lipoprotein (LDL); high density lipoprotein (HDL); hemoglobin A1c (HbA1c), standard deviation (SD).
Intima-media grey scale median (IM-GSM)

This was calculated as the median of the grey values of all pixels within one cm length cropped and normalized intima-media complex image. An in-house custom developed research software package for IM complex and plaque feature extraction was used for IM-GSM calculation (Department of Biomedical Engineering - R&D, Umeå University Hospital, Umeå, Sweden). The software has been previously described and used in Ibrahimi et al. [4,5], and employs a normalization and standardization of the images which is implemented based on the description in Nicolaides et al. [16]. In short, first image normalization was carried out by manually selecting a region of interest (ROI) within the darkest spot of the vessel lumen avoiding areas of "noise", and another ROI at the brightest part of the adventitia (Figure 2(b)). Then the image pixels were normalized by subtracting the average of pixels in the blood ROI followed by division of the maximum pixels in the adventitia ROI, and multiplying them by 190. In this way, the intensity of the blood was set at 0 and the brightest adventitia at 190. The pixel density was then standardized to 20 pixels/millimeter using bicubic 2d interpolation. Finally, the distal carotid intima-media complex was manually outlined and cropped (Figure 2(c)), and IM-GSM was calculated on this normalized and standardized IM complex (Figure 2(d)).

Statistical analysis

Categorical variables were expressed as numbers and percentages and continuous variables were expressed as mean ± SD (median). Mean values of the IMT and IM-GSM were compared between groups. The significance of the difference between two groups was tested using unpaired Student t test with statistical significance indicated by a p value < .05. The linear increase/decrease IMT and IM-GSM between the three groups (going from asymptomatic to previous symptoms in one and > one arterial systems) was tested using the one-way ANOVA with post-hoc Bonferroni test. ROC curve analysis was used to define the IM-GSM cut-off that best discriminates between patients with one arterial system and multiple arterial systems affected by atherosclerosis. Binary logistic regression was used to determine the association between IM-GSM and number of arterial systems affected by atherosclerosis. IM-GSM with a cut-off < 25 was used as dependent variable, sex, age and IMT were used as covariates. Intra-class correlation coefficient and Bland-Altman test was used to evaluate inter-observer variability and proportional bias, respectively. We used SPSS statistics 22.0 software.

Results

Clinical data

In this study, we have analyzed 166 carotid arteries in 87 asymptomatic carotid patients (mean age 69 ± 6 year, 34.5% females). 23% (n = 20) of patients had previous MI, 16% (n = 14) had angina, 21% (n = 18) had ischemic stroke more than 6 months, and 22% (n = 19) had lower limb atherosclerosis in the form of intermittent claudication (Table 1). 50% (n = 43) of the patients were asymptomatic (with no prior/current symptoms in any vascular territory), 34% (n = 30) had previous disease in one arterial system and 16%
(n = 14) had previous disease in multiple arterial territory disease.

**Intima-media measurements and previous vascular symptoms**

Patients with previous MI had higher IMT (1.06 ± 0.2 vs. 0.95 ± 0.2 mm, p = .034) and lower IM-GSM (21 ± 15 vs. 33 ± 16, p ≥ .001) than those without. Patients with previous stroke had lower IM-GSM (24 ± 12 vs. 33 ± 16, p = .007) (Figure 3), but IMT was not different between those with and without stroke (1.03 ± 02 vs. 0.96 ± 0.2 mm, p = .195). There was no difference in IMT or IM-GSM between patients with and without previous atherosclerosis disease in the lower extremity.

**Intima-media measurements and multi-system atherosclerosis disease**

IM-GSM showed significant difference between groups, it decreased significantly with increasing number of arterial territories affected by symptomatic atherosclerosis disease (37.7 ± 15.4 vs. 29.3 ± 16.4 vs. 20.7 ± 12.9) p < .001, for asymptomatic, symptoms in one and in multi-arterial system disease, respectively. When analyzing IM-GSM measured in the arteries on the side with higher IMT we obtained similar results (Table 2). Conventional IMT was not significantly different between groups (p = .49), showing values of 0.95 ± 0.2 mm vs. 0.98 ± 0.2 mm vs. 1.02 ± 0.02 mm for asymptomatic, symptoms in one and in multi-system arterial disease, respectively (Table 2). A cut-off IM-GSM value of 25 was used to differentiate between echolucent and echo-genic IM- complexes. Out of 25 arteries in the multiple arterial disease group, 16 (64%) had an IM-GSM < 25, having an OR of 3.23 (95%CI 1.33–7.85), p < .01. This association remained significant even after adjusting for sex, age and IMT as a continuous variable with odds ratio (OR) of 2.65 (95%CI 1.56–6.67), p = .03.

**Reproducibility of the measurements**

There was good agreement between the two observers for both IMT and IM-GSM measurements. The interobserver variability for intima-media (IMT and IM-GSM) measurements expressed by intra-class correlation coefficient was 0.977 (95% confidence interval; 0.963–0.988) and 0.934.
Table 2. Common carotid intima-media complex measurements and clinical data comparisons between different groups.

<table>
<thead>
<tr>
<th></th>
<th>Asymptomatic (n = 43)</th>
<th>Previous symptoms in one arterial system (n = 30)</th>
<th>Previous symptoms in more than one arterial system (n = 14)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>IM-GSM(^a), mean ± SD</td>
<td>37.7 ± 15.4</td>
<td>29.3 ± 16.4</td>
<td>20.7 ± 12.9</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>IM-GSM(^b), mean ± SD</td>
<td>35.0 ± 15.7</td>
<td>29.5 ± 18.6</td>
<td>17.4 ± 13.9</td>
<td>.001</td>
</tr>
<tr>
<td>IMT (mm), mean ± SD</td>
<td>0.9 ± 0.2</td>
<td>0.9 ± 0.2</td>
<td>1.0 ± 0.2</td>
<td>.49</td>
</tr>
<tr>
<td>Age, years, mean ± SD</td>
<td>68.7 ± 5.9</td>
<td>69.0 ± 76.3</td>
<td>69.3 ± 4.7</td>
<td>.94</td>
</tr>
<tr>
<td>Female, n (%), mean ± SD</td>
<td>17 (39)</td>
<td>8 (31)</td>
<td>5 (45)</td>
<td>.64</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg), mean ± SD</td>
<td>148.7 ± 23.4</td>
<td>145.7 ± 17.1</td>
<td>136.6 ± 18.9</td>
<td>.26</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg), mean ± SD</td>
<td>77.1 ± 15.1</td>
<td>77.6 ± 9.3</td>
<td>77.4 ± 9.1</td>
<td>.84</td>
</tr>
<tr>
<td>Antiplatelet/anticoagulation therapy, n (%)</td>
<td>42 (97)</td>
<td>30 (100)</td>
<td>14 (100)</td>
<td>.65</td>
</tr>
<tr>
<td>Total cholesterol, mmol/l, mean ± SD</td>
<td>47.5 ± 8.9</td>
<td>43.1 ± 10.0</td>
<td>49.1 ± 7.2</td>
<td>.02</td>
</tr>
<tr>
<td>Blood pressure lowering therapy, n (%)</td>
<td>39 (90)</td>
<td>30 (100)</td>
<td>14 (100)</td>
<td>.10</td>
</tr>
<tr>
<td>Lipid lowering therapy, n (%)</td>
<td>39 (91)</td>
<td>30 (100)</td>
<td>13 (93)</td>
<td>.20</td>
</tr>
<tr>
<td>HbA1c (%), mean ± SD</td>
<td>50.9 ± 19.7</td>
<td>55.2 ± 13.5</td>
<td>51.3 ± 9.9</td>
<td>.29</td>
</tr>
<tr>
<td>LDL (mmol/l), mean ± SD</td>
<td>2.5 ± 0.9</td>
<td>2.4 ± 1.1</td>
<td>2.9 ± 0.6</td>
<td>.34</td>
</tr>
<tr>
<td>HDL (mmol/l), mean ± SD</td>
<td>147.2 ± 40.7</td>
<td>126.5 ± 32.0</td>
<td>126.8 ± 43.0</td>
<td>.06</td>
</tr>
</tbody>
</table>

Intima-media gray scale median (IM-GSM); intima media thickness (IMT); Hemoglobin A1c (HbA1c); low density lipoprotein (LDL); high density lipoprotein (HDL); standard deviation (SD).

\(^a\)IM-GSM means of both the side measurements;

\(^b\)IM-GSM measured on the side with higher IMT.

(95% CI; 0.783–0.980) p < .001. Bland-Altman plot showed no proportional bias for IMT and IM-GSM measurements and it was reported in a previous study analyzing the same patients’ cohort [5].

**Discussion**

**Findings**

The present study demonstrates that common carotid artery measures of subclinical atherosclerosis; IMT and IM-GSM are associated with significant differences in the severity and distribution of other vascular system disease, particularly coronary artery disease and events, but not the lower extremities. IM-GSM, but not IMT was consistently different between patients’ groups according to the number and location of other arterial disease. It was lower in patients with previous symptoms in one vascular system compared to truly asymptomatic patients and even lower in those with atherosclerosis in multi-system arterial disease. The conventionally used IMT in assessing atherosclerosis was less sensitive in showing similar differences between groups.

**Data interpretation**

It is generally accepted that atherosclerosis is an inflammatory disease that affects the arterial tree with its various branches, despite differences in the disease manifestation in individual arterial systems i.e. coronary vs. peripheral vascular disease [1]. Patients with previous stroke have been shown to be at risk of suffering another stroke and even higher risk of suffering a future myocardial infarction (MI) [17]. A study including a cohort of 68,236 patients showed that after one year follow-up the rate of vascular events was increased with the increasing number of symptomatic diseased locations, ranging from 5.31% in asymptomatic patients to 12.58%, 21.41% and 26.27% in patients with 1, 2 and 3 symptomatic arterial disease locations, respectively [18]. Patients with multisite atherosclerosis therefore, can be described as vulnerable in view of the high risk they carry for vascular events. It was only IM-GSM that was able to differentiate such high-risk patients by showing significantly progressive lower values as patients went from asymptomatic to symptomatic single arterial system and finally to symptomatic multi-system disease.

IM-GSM was recently introduced as a possible marker of subclinical atherosclerosis. This could probably differentiate between adaptive intimal thickening, representing a hyper reactivity of the smooth muscle cells in the tunica media, from intimal xanthoma or pathological intimal thickening of the arterial wall, as a sign of early atherosclerosis. IM-GSM and its association with the risk factors for atherosclerosis and increased risk of mortality rate have recently been demonstrated [9,10]. It can add incremental information over conventional risk factors for optimum patient’s risk stratification and it showed good reproducibility even when patients were scanned by different observers on different equipment [10,19]. An echolucent IM-complex (low $9#IM-GSM) was associated with a three-fold greater risk of all-cause mortality and an eight-fold greater risk of cardiovascular mortality [9]. However, only few head-to-head comparisons of these two measures were previously attempted. Furthermore, the difference in the sensitivity between IMT and IM-GSM is of great interest. IMT was related to increased systolic blood pressure and to male gender whereas low values of IM-GSM was related to low levels of HDL-C and increased level of CRP [20]. IMT, itself, has been demonstrated to correlate with the severity of arterial stenosis and plaque irregularity. On the other hand, $9#IM-GSM correlated with plaque textural features at the bifurcation and ICA [5], with echolucent plaques being more vulnerable than the echo dense ones [21]. Prior studies [9,22] have evaluated the echoluency of carotid intima-media, measured by GSM on scale of 0–250. In the present study, a GSM scale range 0–190, values between 191 and 250 were used to represent calcified tissues with higher density than adventitial connective tissue. This is the reason why the values of IM-GSM presented in this study are lower compared to other studies [9,22]. In addition, our study population are...
patients at high risk for ischemic vascular events, with advanced carotid atherosclerosis at bifurcation that also might reflect in the proximal portions of the vessel with an echolucent intima-media complex.

**Clinical implications**

Carotid IM-GSM is a novel technique for identifying vulnerable patients with atherosclerosis who carry significant risk for future ischemic events, particularly those with multi-system disease. Identifying such patients may assist in their better risk control and hence clinical outcome. Such implication can be justified once our results are reproduced prospectively and the reproducibility of the technique is confirmed among a wide range of operators.

**Study limitations**

This is a retrospective study, known for its limitations. Images were captured some time before this study, so ultrasound device settings can be different between subjects and scan sessions. However, we attempted to minimize these limitations through the image normalization procedures. Information on the previous symptoms in different arterial systems was acquired from patients’ medical records, and the lack of additional data for the atherosclerotic plaque imaging features in other systems (coronary and lower extremity arteries) is another limitation. Information on the duration of individual risk factors that could have influenced the results was not available. Assessing plaque/IMT and GSM in other arterial system, particularly the ones related to the developed events, would have been of great interest but was not possible with the retrospective nature of the study. The studied population is composed of subjects with asymptomatic Carotid, but was not possible with the retrospective nature of the studied population. The studied population is composed of subjects with the developed events, would have been of great interest to the developed events, would have been of great interest and hence clinical outcome. Such implication can be justified once our results are reproduced prospectively and the reproducibility of the technique is confirmed among a wide range of operators.

**Conclusions**

Carotid IMT was higher and IM-GSM lower in patients with symptomatic nearby arterial territories but not in those with peripheral atherosclerosis, such as in the lower extremity. In contrast to conventional IMT, IM-GSM can differentiate between the severity of atherosclerotic arterial territories based on the number of systems involved, thus suggesting a better surrogate for monitoring systemic burden of the disease.

**Disclosure statement**

No potential conflict of interest was reported by the authors.

**References**


[3] Nicolaides AN, Kakkos SK, Griffin M, et al. Effect of image normalization on carotid plaque classification and the risk of ipsilateral hemispheric ischemic events: results from the asym-


