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Defining the Role of Duplex Ultrasound Assessment to Determine Severity of Arterial Calcification: An Analysis of the Superficial Femoral Artery

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Abstract

Lower limb arterial calcification associates with poor cardiovascular outcomes. The gold standard method of assessment is via computed tomography, yet duplex is our primary imaging modality. Currently, there is no standardized objective assessment of lower limb arterial calcification using duplex. We aimed to define the role of duplex in the assessment of lower limb arterial calcification. Initial consensus was achieved between a cohort of vascular scientists on objective imaging specific markers of lower limb arterial calcification severity using duplex. This resulted in objective descriptions to grade calcification from 0 to 3 (no calcification through to severe calcification) which formed the duplex lower limb arterial calcification score. Reproducibility of the duplex lower limb arterial calcification score was assessed and further validation was undertaken by comparing the duplex lower limb arterial calcification with computed tomography–based assessment in a separate cohort of 44 patients investigated with both modalities. The intra- and inter-class correlation coefficient were > 0.87 . The Spearman rank correlation coefficient between the duplex and CT based arterial calcium measurements was ($\rho = 0.644$, $P < .001$). The duplex lower limb arterial calcification score provides a standardized and reproducible modality for assessment of lower limb arterial calcification and may aid with risk stratification in patients with peripheral arterial disease.

Keywords

arterial calcification, peripheral arterial disease, ultrasound, duplex, computed tomography angiogram

Introduction

Lower limb peripheral arterial disease (PAD) is a prevalent condition associated with significant risk of cardiovascular morbidity and mortality.[1] Patients suffering from PAD commonly present with symptoms ranging from intermittent claudication to critical limb ischemia which may ultimately result in amputation.[1]

Safe and reliable imaging methods are critical in assessment of patients with PAD. They are used for planning vascular interventions as well as prediction of future limb and overall patient outcomes.

In recent years, atherosclerotic plaque calcification across multiple vascular beds has been linked with poor outcomes, including mortality, major adverse cardiovascular events, and failure of interventions in both low-risk and high-risk patients.[2-5]

The current gold standard for assessing arterial calcium burden is axial computed tomography (CT) imaging using the Agatston scoring.[6,7] This method was originally developed to assess calcification in coronary arteries and is routinely used in clinical practice to risk stratify patients with coronary heart disease.[8] More recently, CT-based studies have shown that extensive lower limb arterial calcification (LLAC) is associated with an increased severity of ischemia, reduced technical success of angioplasty, increased incidence of amputation, and increased cardiac morbidity and mortality.[5,8,9]

Despite its advantages, CT imaging is rarely used as a first-line imaging modality in vascular patients. It delivers high-dose ionizing radiation and often requires use of contrast media, which are major issues in patients suffering from multiple comorbidities including renal impairment. For these reasons, duplex ultrasound scanning (DUS) has been adopted as the routine first-line diagnostic tool in vascular surgery. Although it is a cheap and simple investigation with no known side effects, traditional Color DUS often struggles with assessment of near-occluded and calcified blood vessels due to artifacts. Recent

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Table 1. Ultrasound-based Lower Limb Arterial Calcium Score Developed Based on the Results of Initial Questionnaire Sent to Vascular Scientists (VS).

	No calcification	Mild calcification	Significant calcification	Severe calcification
Wall echogenicity	Normal arterial wall with low echogenicity	Intermittent segments of white/echogenic wall	Walls are mostly echogenic throughout	Continuous echogenic walls throughout
Acoustic shadowing	No acoustic shadowing	No acoustic shadowing	Acoustic shadowing in segments, but can still see color flow in large segments of lumen	Severe acoustic shadowing resulting in poor views in multiple segments
Diagnostic impact	Color flow is clearly seen	Color flow is clearly seen	Can still come to a diagnostic conclusion	Affects diagnostic capability of image and you cannot come to a confident conclusion

developments in ultrasound (US) scanning, such as B-flow mode, help to enhance the US image quality, thus reducing its limitations.[10,11]

Given the technological advancements in US scanning methods, we believe that it is a viable alternative to CT imaging for routine assessment of arterial calcification and thus use as a risk stratification tool for patients suffering from PAD. The aims of this study were to determine current methods used to assess and grade arterial calcification within PAD and to develop and validate a DUS-based calcification scoring system for arterial calcification focusing on assessment of the superficial femoral artery (SFA).

Methods

Development of Scoring System

A written questionnaire developed by an expert group consisting of vascular surgeons and vascular scientists was sent to 15 accredited vascular sonographers (VSs) across 7 vascular centers in the United Kingdom. The results of this questionnaire were used to establish current practice in DUS-based arterial calcification assessment. The authors used the results of this questionnaire and then developed a standardized scoring system (Table 1) to define the degree of PAD calcification using DUS—the duplex lower limb arterial calcification (DULLAC) score.

Scoring System Validation

The reproducibility of the DULLAC score was assessed. Duplex ultrasound scanning of the SFA of 6 patients were selected at random from the lower limb arterial duplex case load of the Vascular Studies Unit (VSU) at Cambridge University Hospitals during a 2-week period. All DUS were performed by accredited VSs and the scans were carried out as part of routine patient care. In keeping with local protocol, images from each scan were stored on the US machine used to perform the scan. From each lower limb arterial DUS, images of 4 arterial segments were assessed: common femoral artery (CFA), proximal superficial femoral artery (P SFA), distal superficial femoral artery (D SFA), and popliteal artery (PopA). For each segment, 2 anonymized longitudinal images (1 B-mode and 1 color Doppler) and 1 cross-sectional image (B-mode) were analyzed.

Interobserver variability of the scoring system was determined using images of the femoro-popliteal region (CFA, P SFA, D SFA, PopA) independently assessed by 5 VSs using the scoring system. Intra-observer variability was determined by repeated image scoring by each of the 5 vascular scientists with a 1-month interval. At the time of the repeated image scoring, the order of images was randomly changed to reduce any potential effect of confounding.

Validation Against Computed Tomography Scanning

Further validation was then undertaken. The DULLAC score was compared with CT-based assessment of arterial calcification. Pre-intervention images from patients recruited from a molecular imaging study were used.[12] The methodology has been detailed elsewhere.[12] In brief, consecutive patients were recruited as part of the CIRLA study, a study evaluating the role of Vascular Positron Emission Tomography to predict Restenosis in Symptomatic Peripheral Arterial Disease. As part of this study, a consecutive series of 50 patients underwent both CT and DUS evaluation of the SFA.

Lower limb CT images were acquired using General Electronics (GE) Healthcare Discovery 690 Scanner using standard protocols. Unenhanced CT imaging of the SFA was used in assessment of arterial macrocalcification. The proximal end of SFA was defined at the CFA bifurcation while the distal end at the adductor hiatus. Raw CT data were reformed at slices of 3-mm thickness and assessed for arterial macrocalcification by an experienced observer (M.M.C.) using Agatston scoring which was previously validated[6] and linked to risk factors and mortality in vascular surgery patients.5 Within each CT slice, regions of interest (ROIs) $\geq$ 1 mm^2 with radiological density of $\geq$130 Houndsfield Units (HU) were determined. Each slice was then graded based on the peak HU density within its borders (1: 130-199; 2: 200-299; 3: 300-399; 4: $>$400) and multiplied by the area of the region to give the Agatston score per slice. Following that, the cumulative score for SFA was determined by summing the scores from each slice. The observer assessing the CT images was blinded to the calcification scores derived from the US scanning. Image analysis was carried out using open-source DICOM Viewer (OsiriX Imaging Software, Pixeo SARL) on an Apple Macintosh computer (Apple Inc, Cupertino, CA, USA).

Ultrasound scanning and calcium load assessment. Images of SFA were assessed using DUS. The entire length of SFA was scanned in 4-cm probe lengths from which the image of SFA with atherosclerotic lesions was reconstructed. Images were stored and then the calcification burden of each 4-cm probe length of artery was then assessed and scored by an experienced VS (CT) using the DULLAC score. The additive cumulative arterial calcium score was then determined for the whole SFA by adding each probe length DULLAC score. In images, where US-based calcium load could not be assessed using the scoring matrix, the score was extrapolated from neighboring segments (by taking average value of their calcium load). A limb was eliminated from further analysis if 2 or more adjacent probe lengths could not be assessed or the imaging revealed a stent in situ.

The vascular scientist assessing US scans for calcification was blinded to the CT-based arterial calcium scores derived using the Agatston method.

Data Analysis and Statistical Tests

Variables are presented as mean ± standard deviation or 95% confidence interval (CI) boundaries, median (interquartile range), or n (%), as appropriate. Intra-observer and interobserver variabilities were measured by intraclass correlation coefficients (ICCs). Intraclass correlation coefficient value of >0.75 was taken as an indicator of good reliability of the scoring system.[13]

To allow comparison of the DULLAC with CT-based calcium scoring, we compared cumulative scores for the whole SFA to allow for correlation between the 2 imaging modalities thus removing the issues of co-registration of a particular length of the SFA between CT and US scan. The normality of US- and CT- based calcium load scores was tested using Kolmogorov–Smirnov test. Although this showed that US-based scores could be assumed to be normally distributed ($P = .2$), this assumption does not hold for the CT-based scores ($P < .001$). Given that there are no data to suggest an exact linear relationship between the variables, we analyzed the data using Spearman rank correlation coefficient. All statistical analyses were carried out using SPSS software (version 25, IBM, Armonk, NY, USA).

Results

Development of Scoring System

Out of 15 vascular scientists initially invited to complete the initial questionnaire, 10 responses were received. Seventy percent of respondents indicated that they would routinely classify calcification as part of their scan report; however there was heterogeneity regarding the descriptors used to quantify the burden of arterial calcification. The vascular scientists would often use qualitative statements, such as mild/minor, moderate, severe/heavy; however, there was a lack of uniformity in how such statements were defined. Calcification severity is frequently based on presence of acoustic shadowing, visibility of color flow, wall echogenicity, and whether diagnostic conclusions on vessel stenosis could be made from the DUS images. Given that these factors were the most frequently used in the assessment of calcium load, we have been incorporated into a scoring system for objectively grading arterial calcification (Table 1).

Study Population

Assessment of the reliability of the DULLAC scoring system was performed using imaging from 6 randomly selected patients. The images acquired from the femoro-popliteal arterial segments of 6 patients were assessed independently by 5 vascular scientists. The ICC was 0.791 (95% CI, 0.657-0.895). Four of the 5 vascular scientists then re-evaluated the images 1 week later with an ICC value of 0.875 (95% CI, 0.775-0.941). Intra-observer variability analysis showed an ICC value of 0.899 (95% CI, 0.761-0.958).

Validation of Ultrasound-based Arterial Calcification Assessment Against Computed Tomography Imaging

In all, 44 individuals were included in the study. The mean total SFA Agatston score based on CT imaging was 5363.09 (95% CI, 3599.93-7126.25). The mean total DULLAC score was 17 (95% CI, 15-18). Figure 1 presents the relationship between CT and US-based calcium score in the test population. The Spearman rank correlation coefficient for this dataset shows a significant correlation ($\rho = 0.644$, $P < .001$).

Discussion

This study is the first attempt to develop and validate a standardized and reproducible method for scoring peripheral arterial calcification assessment using duplex US. While an assessment of arterial calcification is often performed, there is recognized heterogeneity in the assessment of severity. We have unified those features of arterial calcification commonly reported to develop a scoring matrix, the DULLAC score. We then proceed to validate the DULLAC score providing evidence of strong internal validity with good intra-observer and interobserver agreement. Finally, we have shown that the DULLAC score shows strong correlation with CT-based Agatston scoring, the recognized gold standard for assessment of arterial calcification.

Duplex ultrasonography is now the first-line imaging modality in regular clinical practice. The advance of imaging

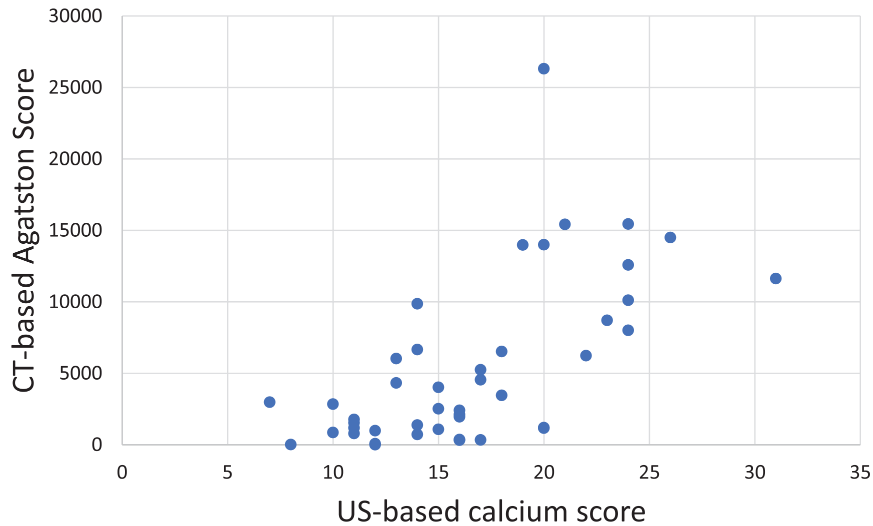

Figure 1. Scatterplot of the CT-based arterial calcium load scores against corresponding US-based total calcium scores.
Note. CT = computed tomography; US = ultrasound.

technology allows duplex to provide detailed anatomical information to guide intervention in a cheap and non-invasive way. Yet it is still user dependent. The presence of arterial calcification does provide challenges with duplex in the lower limb arterial tree predominantly within the crural vessel.

Attempts at correlating US-based arterial calcification with CT imaging have been limited, focused primarily on the carotid arteries and with a lack of a formalized scoring method developed.[14] Others have assessed total calcification burden in multiple arterial beds (carotid arteries, common femoral arteries, popliteal arteries, posterior tibial arteries, and anterior tibial arteries bilaterally alongside the infrarenal abdominal aorta).[15] Although this provides a comprehensive assessment of the vascular calcium load, it necessitates more extensive scanning protocols, increasing their cost and duration, and thus makes opportunistic assessment of calcium burden more cumbersome.

We prove that our method of assessing arterial calcification can provide similar information to a more traditional CT-based scoring, while reducing the cost and radiation exposure of the imaging.

Why is the assessment of LLAC important? Lower limb PAD is becoming increasingly prevalent in part due to the epidemic of cases of diabetes mellitus. Lower limb arterial calcification is a recognized predictor of poor outcomes for such patients. Duplex US is a potentially portable imaging modality that could be performed within primary care and will become increasingly used in the assessment of patients with symptomatic PAD. As such assessment of LLAC has the potential to provide additive value to identify those patients at risk of poorer outcomes which would allow further optimization of cardiovascular risk in such patients.

There are recognized limitations with this study. While we demonstrated that there is a good observer agreement on assessing pre-acquired images, the VSs assessed images that were previously stored. Variation may be more marked if the sonographer had to capture the images independently for the same patient. This study is a single-center study; to make this system widely applicable, validation would need to be extended across multiple centers within and outside of the United Kingdom. Given the increasing incidence of diabetes mellitus and the associated infrapopliteal atherosclerosis and medial calcification, further work is needed to determine how accurate this score is within the infrapopliteal circulation. Last, further validation is needed to determine whether increased burden of LLAC as determined by DUS does equate to poorer long-term patient-related outcomes.

Conclusions

We have developed a DUS-specific scoring system for LLAC which shows strong validity. Further studies are required to further validate its use for routine assessment of patients with lower limb PAD.

Declaration of Conflicting Interests

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