Review Article

Current status of carotid ultrasound in atherosclerosis

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Abstract: Cardiovascular disease (CVD) primarily caused by atherosclerosis is a major cause of death and disability in developed countries. Sonographic carotid intima-media thickness (CIMT) is widely studied as a surrogate marker for detecting subclinical atherosclerosis for risk prediction and disease progress to guide medical intervention. However, there is no standardized CIMT measurement methodology in clinical studies resulting in inconsistent findings, thereby undermining the clinical value of CIMT. Increasing evidences show that CIMT alone has weak predictive value for CVD while CIMT including plaque presence consistently improves the predictive power. Quantification of plaque burden further enhances the predictive power beyond plaque presence. Sonographic carotid plaque characteristics have been found to be predictive of cerebral ischaemic events. With advances in ultrasound technology, enhanced assessment of carotid plaques is feasible to detect high-risk/vulnerable plaques, and provide risk assessment for ischemic stroke beyond measurement of luminal stenosis.

Keywords: Atherosclerosis; carotid artery; intima media thickness; ultrasound

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Atherosclerosis is a leading cause for cardiovascular disease (CVD) (1), of which including stroke remains a major cause of death and disability in developed countries (2). Current guidelines and primary prevention of asymptomatic CVD are mainly based on the use of calculated risk scores e.g., Framingham risk score that utilize a few standard risk factors to stratify future risk and guide treatment. Although intensive control of traditional CVD risk factors based on these guidelines has led to marked reduction in the mortality rate of atherosclerotic CVD (3), there are well-documented limitations (4). Firstly, the guidelines based on the estimated scores are primarily used to predict population risk. They may not be applicable in some individuals. Secondly, some relevant risk factors such as family history of premature coronary heart disease, previous risk factor treatment and the variability in blood pressure are not included in the estimation. Thirdly, the use of 'one-time' measures of traditional modifiable risk scores may significantly underestimate risks in some individuals leading to under-treatment (4).

The advantage of imaging technique is its ability to monitor the disease process. Ultrasound as a cheap, non-invasive and non-ionizing imaging technique, is an ideal tool for long-term CVD risk assessment for the asymptomatic patients, helping refine the risk score stratification and guiding intervention to the patients (5-7). With recent advances in ultrasound technology, enhanced assessment of carotid atherosclerotic lesions is possible in subclinical stages (8-10). This article reviews the literature on the current status of carotid ultrasound in the risk assessment and primary prevention of CVD.

Atherosclerosis

Atherosclerosis is a chronic inflammatory disease (1). The earliest atherosclerotic lesion (the fatty streak) may occur in infancy or childhood because maternal hypercholesterolemia predisposes fatty streak formation in a fetus (11). In the presence of an unopposed and excessive amount of fatty streak formation, the artery undergoes progressive atherosclerotic changes from endothelial dysfunction, remodeling of the

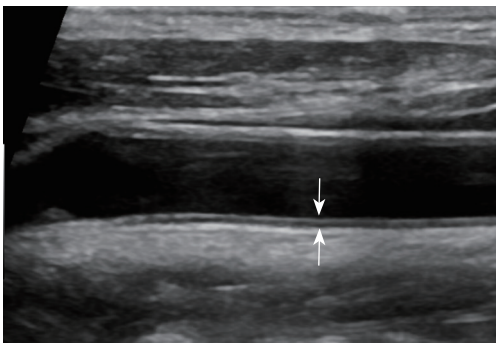

Figure 1 Longitudinal view of CCA shows IMT (arrows) as the distance between two echogenic lines at the far wall representing the lumen-intima interface and media-adventitia interface. CCA, common carotid artery; IMT, intima-media thickness.

artery with wall thickening and arterial dilatation to vessel wall damage resulting in complicated stenotic lesion (12). Nonetheless, in the initial stages of atherosclerosis, the lesions are usually asymptomatic. Neurological symptoms are usually associated with advanced lesions with plaque rupture and thrombosis as complications (1).

Imaging of carotid intima-media thickness (CIMT)

CIMT is widely studied as a surrogate marker for detecting subclinical atherosclerosis for risk assessment and monitoring the progress of atherosclerosis for medical intervention (13-16). On ultrasound, CIMT is the distance between two echogenic lines representing the lumen-intima interface and the media-adventitia interface of the carotid arterial wall (*Figure 1*). This finding has been histologically validated with better correlation of CIMT at the far wall than at the near wall (17).

Although a number of clinical studies have demonstrated that thickened CIMT independently predicts CVD risk or events (13,14,16,18), conflicting results are obtained by others (19-21) (*Table 1*). The inconsistent predictive value of CIMT is likely attributed to the variability of CIMT measurement methodology such as image acquisition, CIMT reading and processing methods, apart from differences in study end-points, cardiovascular risk and factor profiles of the studied population and operator errors (25,26).

CIMT image acquisition

CIMT image acquisition differs in the number of segments, sides and angles between studies. Some studies examined CIMT at one segment predominantly the distal common carotid artery (CCA) because it is easily accessible (18,20,21,23). The success rate of acquiring IMT at the near and far wall of CCA had been reported to be >98% and 100% respectively while those at the bulb were >98% and >99% and those at the internal carotid artery (ICA) were >86% and >98% (27). Other studies examined CIMT at two segments (CCA and ICA) (19,24) or three segments (CCA, carotid bulb and ICA) (22). Imaging of IMT varies between unilateral and bilateral capturing in different studies (13,20,23). If it is imaged unilaterally, the right CCA is usually captured (21,23).

Number of imaging angles is another aspect of discrepancy in CIMT acquisition. Some studies captured the CIMT antero-obliquely at an insonation angle around 45 degrees (22) while others acquired the CIMT from three angles in anterior, lateral and posterior approaches (28) or five angles at an increment of 30 degrees bilaterally (29). These approaches have been used in epidemiological and interventional studies (16,21,30).

CIMT reading and processing methods

Varying CIMT reading methods exist between studies. Some studies read the CIMT measurement at the far wall of the CCA because the far wall measures reflect the true wall thickness and are more accurate than the near-wall measures (13,17,31). Others took CIMT measurements from both near and far walls (20) because a combination of the near and far wall measures is more reproducible than the far-wall measures alone presumably due to reduced random error after averaging the measures (32). However, there is no evidence showing that the combined measures are superior to the far wall measures for CVD prediction (33).

Quantification of the CIMT measures is inconsistent in the studies. The mean or maximum of a single segment (16,23); mean of the mean or mean of the maximum of two or more segments; or composite measures from both sides and different arterial sites have been reported (13,19,21). Among different types of CIMT measures, mean of mean values averaged multiple points along the traced segment is more reproducible, but is less sensitive to change. Mean of maximum values is more sensitive to change, but less reproducible because it is derived from a single point measurement along the 1-cm region (34). However, composite scores including both plaque and IMT are not recommended (35).

Table 1 Variation of CIMT measurement in nine community based studies

Study, N = sample size	Segments studied	Plaque included	Measurement methods	Findings
ARIC (13); N=12,841; age: 45–64 yrs	3 segments: CCA, bulb, ICA (bilateral, far wall)	Yes	CIMT = mean of 6 mean; by manual tracing; non-ECG gated IMT acquisition	CIMT is an independent predictor of future CHD incidence, in particular at higher IMT
CAPS (22); N=5,056; age: 19–90 yrs	3 segments: mid-distal CCA, bulb, ICA (bilateral, far wall)	No	CIMT = mean of 6 mean; by automatic tracing; acquired IMT at systole	CIMT independently predicts future vascular events
CHS (19); N=5,020; age: 72.6±5.5 yrs	2 segments: CCA, ICA (bilateral, near and far wall); one longitudinal CCA & three longitudinal ICA	Yes	CIMT = composite of CCA and ICA IMT mean of maximum; by manual tracing; non-ECG gated IMT acquisition	CIMT or carotid plaque is only a modest independent predictor for CVD
FOS (16); N=2,965; age: 58±10 yrs	2 segments: CCA, ICA (bilateral, far wall)	No	CCA-IMT = mean of 2 mean; maximum ICA-IMT; by manual tracing; acquired IMT at end diastole	Maximum ICA-IMT and mean CCA-IMT both predict CVD outcomes, but only the former significantly improves risk classification
MESA (23); N=5,028; age: 45–84 yrs	1 segment: right CCA (far wall)	No	Mean CIMT; by manual tracing; acquired IMT at end diastole	Right CIMT progression is associated with incident stroke
MESA (21); N=6,814; age: 45–84 yrs	1 segment: right CCA (far wall)	No	CIMT = mean of maximum; by manual tracing; acquired IMT at end diastole	CIMT was not independent predictor of incident CHD/CVD in intermediate-risk individuals
RS (18); N=6,389; age: 69.3±9.2 yrs	1 segment: CCA (bilateral, near and far wall)	Not specified	CIMT = mean of maximum; by manual tracing; acquired IMT at end diastole	CIMT and carotid plaque are strong predictors for myocardial infarction
TS (24); N=6,226; age: 25–84 yrs	2 segments: right CCA (near and far wall) & right bulb (far wall); total 3 locations	Yes	CIMT = mean of 3 mean; by automated tracing; non-ECG gated IMT acquisition	Carotid plaque was a stronger predictor of first-ever myocardial infarction than was IMT
TCS (20); N=5,895; age: 65–85 yrs	1 segment: CCA (bilateral, near and far wall)	No	CIMT = mean of 4 mean; by automated tracing; acquired IMT at end diastole	Plaque-free CIMT was not an independent predictor of CHD in older adults

CIMT, carotid intima-media thickness; ARIC, Atherosclerosis Risk in Communities; CCA, common carotid artery; ICA, internal carotid artery; CHD, coronary disease; IMT, intima-media thickness; CAPS, Carotid Atherosclerosis Progression Study; CHS, CV Health Study; CVD, cardiovascular disease; FOS, Framingham Offspring Study; MESA, Framingham Offspring Study; RS, Rotterdam Study; TS, Tromso Study; TCS, Three Cities Study.

Two tracing methods are commonly used in the CIMT studies, viz manual tracing and automated edge-detection. Some studies traced CIMT manually by electronic calipers while others used automated/semi-automated edge-detection system (23,27). Although it is generally agreed that automated edge detection method is more reproducible than the manual tracing, recent evidences show that both methods result in high reproducibility and similar associations with CVD risk factors, outcomes, rate of change and treatment effects (30,36,37). Therefore, choices between automated/semi-automated and manual reading software for CIMT studies should be based on logistical considerations and cost implication rather than differences in expected data quality (38).

Recording IMT values at different phases of cardiac cycle is also a cause of discrepancy (13,21,22). Of note, the CIMT values vary in different phases of cardiac cycle with the peak-systolic IMT slightly thinner than the end-diastolic IMT by an average of 0.041 mm (39). Despite both types of IMT values are similarly associated with CVD risk factors; the end-diastolic IMT is preferred in most studies. It is because peak-systolic IMT tends to give a higher CVD risk for the asymptomatic subjects than would be expected for diastolic IMT (39).

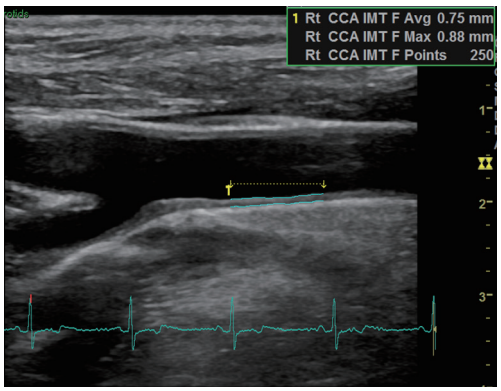

Figure 2 Longitudinal view of CCA shows CIMT measurement at the far wall on an R-wave gated still frame. Note the measurement is made on a 1-cm segment at least 5 mm caudal to the divergence of near and far walls indicating the end of CCA at an imaging depth of 4 cm. CCA, common carotid artery; CIMT, carotid intima-media thickness.

Standardization of CIMT measurement methods

In spite of the extensive use of CIMT measures, there is no widely accepted ultrasound protocol for CIMT measurement in epidemiological and interventional studies. Two consensus reports, the Mannheim CIMT Consensus Report (35) and the American Society of Echocardiography (ASE) Consensus Statement (34) were released attempting to address the issues of standardization.

The Mannheim CIMT Consensus Report was first published in 2004 and updated in 2006 and 2011. This report emphasizes the importance of standardizing CIMT measurement method and distinguishing IMT thickening from early plaque formation. Only when these aspects have been addressed, consistent data collection/analysis, improved power of randomized clinical trials and matching of large databases for meta-analyses can be possible (35). Standardized CIMT measurement is suggested to be performed on the far wall of distal 1-cm segment of CCA at least 5 mm away from its bifurcation within a region free of plaque (*Figure 2*). Plaque-free IMT should be measured at the carotid bulb and proximal ICA and on a shorter length in case of vessel tortuosity, but these values must be recorded separately. It is mentioned that imaging of distal CCA segment has the advantages of increased accuracy and reproducibility of the measures; allowing automated-edge detection for IMT measurement; and producing data that could be compared to a majority of reference data within large epidemiological studies (35). Plaques should be distinguished from thickened IMT because they are distinct phenotypes with different localization, natural history, risk factors and predictive value for CVD events. A plaque is defined as a focal structure encroaching into the arterial lumen of at least 0.5 mm or 50% of the surrounding IMT value, or demonstrating an IMT thicker than 1.5 mm. Furthermore, CIMT and plaque presence are recommended for the initial investigation of CVD risk in asymptomatic patients (35).

Similarly, a detailed CIMT measurement method is proposed in the ASE Consensus Statement based on large epidemiologic studies (34). In this Statement, the CIMT measurement is limited to the far wall of the distal 1-cm CCA and supplemented by documenting the carotid plaque in the near and far walls of CCA, bulb and ICA segments so as to increase sensitivity for detecting subclinical CVD. The CIMT should be obtained in the longitudinal planes from three imaging angles (anterior, lateral and posterior) with clear depiction of double lines on near and far walls. The imaging depth is adjusted at a depth of 4 cm to avoid slice thickness artifacts. Use of zoomed images is not recommended. The CIMT measurement should be made at end-diastole on an R-wave gated still frame with inclusion of the plaque if detected (*Figure 2*). A semi-automated edge detection program with validated accuracy is preferred to manual tracing using electronic calipers for the former tends to improve reproducibility and reduce reading time. Simple point-to-point measurements of CIMT are not accepted. Plaque defined by the ASE task force is basically same as that defined in the Mannheim report, except with the omission of a focal structure encroaching into the arterial lumen of at least 0.5 mm" (34). Lastly, the Consensus Statement stresses on the importance of measuring CIMT by appropriately trained sonographers and readers who could carefully adhere to predefined scanning protocol so that measurement error can be minimized.

Extensive or restrictive ultrasound protocols

Debate continues for adoption of extensive (multiple angles, walls and segments) or restrictive (one single-angle far wall CIMT) protocols for CIMT measurement in clinical studies. Proponents for extensive ultrasound protocols maintain that although extensive protocols increase examination time, length of training of sonographers and cost of the procedure, it enhances the reproducibility, magnitude and precision of progression of CIMT over time and treatment

effect (32). The best protocols suggested are mean common CIMT protocols in which both the near and far walls are measured at multiple angles (32,40) because these protocols could produce data of the highest precision to observe a treatment effect and to fully reflect the asymmetric nature of atherosclerotic burden (30). The opponents to the extensive protocols argue that extensive protocols using multiple angles and multiple projections have been shown to produce similar variability for determining IMT change as those derived from restriction of analyses to only one segment and to only one projection (41). In addition, the long examination time of around three hours for an extensive three-segment, five-angle protocol is clinically impracticable as compared to a half-an-hour restrictive CIMT protocol. More importantly, since IMT progression rates vary with the carotid artery segment, a global measurement of IMT progression as done in extensive protocols might underrate the association between specific segment IMT progression and outcome (41).

Recommendations for appropriate use of CIMT screening

With the inconsistent results of the predictive power of CIMT measures for CVD risk, it is not surprising to find the recommendations for use of CIMT are variable. European Guidelines on CVD prevention in clinical practice (version 2012) support CIMT screening in asymptomatic individuals at moderate risk (5). Likewise, Canadian Cardiovascular Society guidelines for the prevention of CVD recommend CIMT measurements as a means to enhance risk assessment provided the test is restricted to centers with specific expertise (6). On the contrary, the Mannheim report does not recommend serial monitoring of CIMT in individual patients (35). While the ASE Consensus Statement affirms the value of CIMT measures including plaque presence for re-stratifying CVD risk in patients at intermediate risk, CIMT testing is not warranted unless the results would be expected to alter therapy and serial IMT studies are not recommended for use in clinical practice. Similarly, the 2013 American College of Cardiology/American Heart Association guidelines on cardiovascular risk assessment and cholesterol treatment do not advocate routine measurement of CIMT in clinical practice because of the concerns about the quality and standardization of CIMT measurement (7). It is apparent that the use of CIMT as a marker for risk assessment and the use of CIMT progression to guide intervention are controversial. Only when consistent results are yielded in the studies with improved quality through standardization of the measurement methodology, the sonographic CIMT measurement as a screening marker for CVD risk assessment and a guide for intervention will be generally accepted in clinical practice.

Imaging of carotid plaque

Screening of plaque presence

Even though CIMT measures have been widely used for risk prediction in the past decades, increasing evidences show that IMT adds little value to risk prediction and progression of IMT does not predict CVD events (42-44). Nonetheless, inclusion of plaque to CIMT measurement has been consistently shown to improve the predictive power for CVD and coronary events (42,45-47). Compared with traditional risk factors, carotid plaque presence also improves prediction of stroke/transient ischemic attacks (28).

The improved predictive power of plaque presence can be accounted for by the potential pathological differences between CIMT and plaque, and the geometrical configuration and flow properties of the carotid bifurcation. It should be noted that increased sonographic CIMT is not necessarily indicative of atherosclerosis and can occur in patients without atherosclerosis. It is because atherosclerosis exclusively involves the intimal layer whereas thickened CIMT may be due to medial hypertrophy as a result of adaptive arterial wall remodeling (48) or aging with thickening of both the intimal and medial layers (8). In contrast, carotid plaque is characteristic of advanced atherosclerosis (1) with prevalence at the region where the wall shear stress is low such as the outer wall of proximal ICA and carotid bulb (49). However, these segments are usually excluded from the standard CIMT measurements explaining why the measures are less sensitive to predict CVD risks or events. In ASE Consensus Statement, screening of plaque for its presence in CIMT measurement should cover bilateral CCA, carotid bulb and ICA (34).

Measurement of plaque burden

To enhance the predictive power of plaque screening for CVD events beyond plaque presence, quantifying the carotid plaque burden has been developed as a promising alternative to CIMT measurement. Carotid plaque burden can be measured either as total plaque area (TPA) by 2-dimensional (2D) ultrasound (*Figure 3*) or total plaque volume (TPV) by 3-dimensional (3D) ultrasound (*Figure 4*).

TPA is the total cross-sectional area of all detected plaques on longitudinal views. When comparing the usefulness of TPA and TPV, progression of TPV strongly predicts CVD events while that of TPA only does it weakly (50).

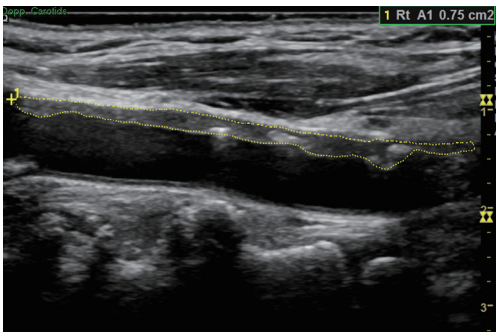

Figure 3 TPA measurement of a long CCA plaque with foci of calcifications. It is made longitudinally in the plane where the plaque is maximum by tracing the perimeter of whole cross section. Note TPA is the total cross-sectional area of all detected plaques on longitudinal views. TPA, total plaque area; CCA, common carotid artery.

Quantification of plaque burden is superior to CIMT because the plaque burden measures and their progression have been shown to strongly predict CVD events and can identify high risk patients (50,51). In contrast, CIMT without plaque thickness is a weak predictor of CVD risk (42) and its change over time neither predicts CVD events (52) nor enables monitoring of medical therapeutic effects in clinically meaningful timeframes because the CIMT change is subtle around 0.15 mm/year (53). For TPA and TPV, the changes are more noticeable around 10 mm^2/year and 50 to 100 mm^3/year respectively (54). It is thus easier to monitor the changes in these parameters for treatment effect with higher sensitivity for TPV than TPA (50). In addition, the easily measurable changes in plaque burden allows smaller sample size and shorter duration of follow-up required to study effects of new therapies (55). More importantly, plaque burden measures can be used in managing patients with asymptomatic carotid stenosis by a strategy called "treating arteries instead of risk factors". With this strategy, more intensive medical therapy can be given to the patients based on plaque measurement resulting in marked reduction in

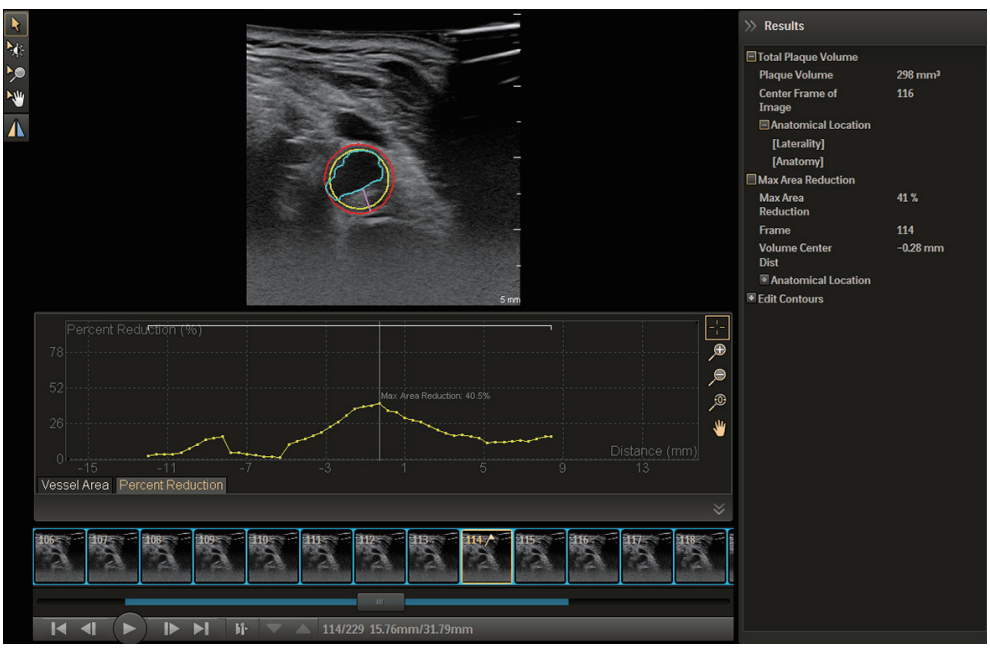

Figure 4 TPV measurement by semi-automated volume quantification software. After volume data acquisition, a series of cross-sectional images covering the arterial segment above and below the plaque are automatically displayed by thumbnails (lower). After manually selecting three image slices from the thumbnails: two showing the start and end of the plaque and one key slide showing the maximal stenosis, plaque volume and maximal area reduction is computed (right upper) and a line graph of the area reduction along the plaque is displayed (middle). On selected image slide, the media/adventitia border (red), the lumen/intima border (yellow) and the residual lumen border (blue) are outlined (top). TPV, total plaque volume.

CVD risks among patients (56,57).

Measurement of plaque burden is also useful in genetic research because it helps genotyping the sampled individuals. Of note, carotid ultrasound phenotypes are biologically distinct implying that genetic factors affecting IMT, plaque burden, stenosis and plaque rupture are different. These distinct ultrasound phenotypes are important with regard to studies of new therapies (54). Making use of plaque burden measures, targeted genotyping of individuals with specific phenotypes and known risk factors is feasible. In this way, the sample size needed for genome-wide association studies can be reduced (58).

Characterization of plaque

Sonographic plaque characteristics are found to be predictive of subsequent cerebral ischemic events (59). Although current guidelines have established degree of carotid stenosis as the primary surrogate for stroke risk and indication of intervention, there is increasing evidence showing that vulnerable carotid plaques are more prone to cerebroembolic events regardless of degree of stenosis (60) and a high proportion of these strokes are likely due to rupture or erosion of non-stenotic, unstable plaques (61). Carotid ultrasound, by means of plaque echogenicity and morphology, provides a clue to differentiate "vulnerable" from "non-vulnerable" plaques and may help in risk stratification and therapy. A recent meta-analysis of the literature demonstrated that several sonographic features of the complex plaques such as intraplaque echolucency, neovascularization and ulceration were found to associate with cerebral ischemic symptoms (59).

Intraplaque echolucency

Plaque echolucency is a strong marker for risk of ischemic stroke (62) and is histologically proven to represent lipid-rich necrotic core (LRNC) or intraplaque hemorrhage (IPH) (63). Ultrasound is sensitive in detecting plaque echolucency with a detection rate up to 90% (64). Detection of the size and site of "juxtaluminal echolucency" which represents either a LRNC or IPH is important because a large LRNC near the lumen is associated with increased risk of stroke and clinical ischemic events (65,66).

Neovascularization

Neovascularization as a source of IPH is associated with plaque progression and vulnerability (67). Contrast-enhanced ultrasound (CEUS) can detect neovascularization and allow quantification of the neovessels in the entire plaque (68) or on the plaque shoulder (69). The latter technique is suggested to be more reliable to predict the risk of plaque rupture and IPH compared to studies evaluating the contrast effects of the entire plaque (Saito K, 2014).

Plaque ulceration

Ultrasound lacks sensitivity for the detection of plaque ulceration with wide variation ranging from 33–75% in sensitivity and 33–92% in specificity (70). The conventional criteria defines plaque ulceration as a recess of the plaque surface measuring at least 2 mm deep and 2 mm long, with a well-defined wall at its base and an area of reversed color Doppler flow within the recess (71). However, a simplified criteria adopted by Muraki *et al.* who simply considered plaque ulceration as a clearly depicted concavity with a less intense border echo at its base resulted in significant improvement in the diagnostic accuracy of plaque ulceration compared to the use of conventional criteria (72). Both CEUS and 3D ultrasound have been suggested to reliably characterize the surface morphology of atherosclerotic carotid plaques and is superior to 2D in detecting ulcers in the plaques (73,74).

Plaque motion

Abnormal plaque motions have been observed with high-resolution ultrasound by Muraki *et al*. on 49 symptomatic carotid stenoses, which were histologically proven to represent high-risk carotid lesions from plaque rupture to ulcer (75). Two types of abnormal plaque motions were detected: a fine trembling motion within the plaque and a systolic retractive motion of the plaque surface. The former motion was reported to have a high sensitivity of 95% of predicting plaque rupture/ulcer while the latter motion was highly associated with soft content within the plaque. Further studies may be required to evaluate the diagnostic accuracy of these observations.

From degree of stenosis to plaque vulnerability

Quantification of carotid artery stenosis is universally adopted for stratifying patients for therapeutic intervention over the past two decades. With current state-of-the-art advances in carotid plaque imaging, patient stratification can be made by identification of vulnerable plaques. Currently, MR angiography and CT angiography with improved resolution are highly sensitive to detect vulnerable plaques. MRI is the gold standard in carotid plaque imaging for identifying IPH, ulceration, LRNC, neovascularization

and inflammation but is limited by its long examination time while CT is reliable to detect ulceration and calcifications but is insensitive to differentiate IPH from LRNC (60). Compared with MRI and CT, ultrasound is inferior to detect ulceration (76,77) but is relatively sensitive for detecting LRNC and IPH which appear as plaque echolucency (78). With the aid of contrast imaging, the sensitivity and specificity of ultrasound for detecting ulceration and neovascularization can be increased (68,74). Therefore carotid ultrasound may be used for risk assessment for ischemic stroke beyond measurement of luminal stenosis.

Conclusions

Despite the extensive use of CIMT measures in recent decades for risk prediction of CVD, CIMT measurement methods are variable in clinical studies leading to conflicting results. It is noteworthy that CIMT measurement alone without plaque presence or plaque burden measures has limited value in risk prediction. Only when consistent results are yielded in the clinical studies with improved quality through standardization of the measurement methodology, CIMT measurement as a screening marker for CVD risk assessment and a guide for medical intervention will be widely accepted in clinical practice. With advances in ultrasound technology, enhanced assessment of carotid plaques is feasible to detect high-risk/vulnerable plaques, and provide risk assessment for ischemic stroke beyond measurement of luminal stenosis.

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None.

Footnote

Conflicts of Interest: The author has no conflicts of interest to declare.

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