Application of Intima-media Thickness and Early Atherosclerosis at Carotid Arteries as a Window for Cardiovascular Diseases in Preventive Cardiology

Ta-Chen Su, Jiann-Shing Jeng, Bao-Show Hwang, Chiau-Suong Liau*

Early detection and management of preclinical atherosclerotic disease is the mainstream strategy in the prevention and treatment of atherosclerotic vascular disease. Increased intima-media thickness (IMT) and presence of atherosclerotic plaque of extracranial carotid artery (ECCA) have been identified as important markers for prediction of cardiovascular morbidity and mortality. The use of carotid ultrasound in noninvasive cardiology also gains much attention because of the advantage of high reproducibility in the measurements of IMT and ECCA atherosclerotic plaque scores. The superior role of carotid IMT as a good index of preclinical atherosclerosis in association with cardiovascular risk factors leads to worldwide application, not only in epidemiologic observations but also in pharmacologic intervention studies. Regarding the measurements of IMT, common carotid artery has been demonstrated to be highly reliable and easily accessible as compared with those measured at other segments in carotid arteries. Considering the nature of noninvasive, repeatability and reliability, we have demonstrated the feasibility of the measurements of carotid atherosclerosis in community-based, occupational and clinical studies in Taiwan. Thus, this review focuses on the rational and practical use of carotid ultrasound as a window for cardiovascular disease.

KEY WORDS — atherosclerosis, carotid arteries

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to associate the cardiovascular risk factors [2–10] and CVD [11–13] in epidemiologic and clinical studies in the past 20 years. Even though some studies still debate over the statement of carotid IMT as atherosclerosis [14,15], carotid IMT has been established as an early predictor for the future cardiovascular events, including acute myocardial infarction (MI) and stroke [16–22]. With its high reliability and reproducibility [23–25] and for the high correlation between measured IMT and the actual pathologic changes [26–27], ultrasound IMT measurement of carotid artery has been widely used in epidemiologic and clinical studies for the detection and evaluation of early preclinical atherosclerosis. The structural changes of the carotid arteries have been considered as a window for cardiovascular risk in apparently healthy individuals [28].

**Measurements of Carotid Atherosclerosis (CA) as Predictors of CVDs**

Why use CA as the window of CVD? Many studies have documented the measurements of IMT as good predictors for MI and stroke [16–22]. Table 1 summarizes some landmark population-based studies that looked for carotid IMT as predicting markers for CVD: the Rotterdam study, the Atherosclerosis Risk in Communities (ARIC) study, and the Cardiovascular Health Study (CHS). All these studies demonstrated that carotid IMT was significantly associated with future CVD events.

To evaluate the usefulness of carotid IMT as a predictor of CVD, the Rotterdam Study applied a nested case-control design among 7,983 subjects with age ≥ 55 years who participated in the original cohort. After mean duration of 2.7 years’ follow-up, a sample of 1,373 subjects who remained free from MI and stroke was studied. Stroke risk increased as common carotid artery (CCA) IMT increased. The odds ratio (95% CI) was 1.43 (1.16–1.78). Based on a short follow-up period, this study provides evidence that an increased CCA IMT is associated with future cerebrovascular accident (CVA) and CVD events [16]. After a mean follow-up of 4.6 years in the Rotterdam study, a case-cohort approach was assessed to associate the IMT at CCA, carotid bifurcation and internal carotid artery (ICA) with the incident MI. The risk ratios (95% CI) for MI associated with mean maximum IMT at CCA, bifurcation, ICA and the combined measurements were 3.18 (1.83–5.54), 4.11 (2.10–8.05), 5.31 (1.77–15.9) and 6.27 (3.27–12.0), respectively, for the comparisons between the highest and the lowest quartiles. The risk ratios (95% CI) for MI per standard deviation increase of CCA, bifurcation, ICA and combined IMT were 1.44 (1.28–1.62), 1.34 (1.17–1.53), 1.12 (0.94–1.33) and 1.47 (1.31–1.65), respectively [17].

In the ARIC study, the relationship of IMT to CHD incidence was assessed over 4–7 years of follow-up (1987–1993) in four United States communities. Participants composed of 7,289 women and 5,552 men with ages 45–64 years who were free of clinical CHD at baseline. In sex-specific Cox proportional hazard models adjusted only for age, race and center, the hazard rate ratio (95% CI) comparing extreme mean IMT (≥ 1 mm) with not extreme (< 1 mm) was 5.07 (3.08–8.36) for women and 1.85 (1.28–2.69) for men [18]. Additionally, the association of mean IMT to stroke incidence was assessed after 6–9 years’ follow-up (1987–1995) among those without stroke at baseline. The hazard rate ratios (95% CI) comparing extreme mean IMT values (≥ 1 mm) with values less than 0.6 mm were 8.5 (3.5–20.7) for women and 3.6 (1.5–9.2) for men [19].

In CHS, O’Leary and colleagues studied the associations between carotid IMT and the incidence of new MI or stroke in 5,858 subjects 65 years of age or older. Of them, 4,476 subjects were without clinical CVD. Over a median follow-up period of 6.2 years, the incidence of cardiovascular events was correlated with measurements of carotid IMT. The relative risk of MI or stroke increased with IMT. The association between cardiovascular events and IMT remained significant after adjustment.
### Table 1. Carotid artery intima-media thickness (IMT) as a predictor for cardiovascular disease (CVD)

<table>
<thead>
<tr>
<th>Study</th>
<th>Site</th>
<th>Characteristics of study subjects</th>
<th>Follow-up, yr</th>
<th>IMT, mm increase</th>
<th>Cardiovascular disease</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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</tr>
<tr>
<td>Rotterdam</td>
<td>CCA</td>
<td>≥ 55 95 stroke, 99 MI, 1,373 controls</td>
<td>2.7</td>
<td>0.163</td>
<td>AMI Stroke</td>
<td>1.43 (1.16–1.78) 1.41 (1.25–1.82)</td>
</tr>
<tr>
<td></td>
<td>CCA</td>
<td>≥ 55 194 MI, 1,879 controls</td>
<td>4.6</td>
<td>0.21 0.60 0.66</td>
<td>MI MI MI</td>
<td>1.44 (1.28–1.62) 1.34 (1.17–1.53) 1.12 (0.94–1.33)</td>
</tr>
<tr>
<td></td>
<td>Bif</td>
<td></td>
<td></td>
<td></td>
<td>Stroke</td>
<td>1.34 (1.17–1.53)</td>
</tr>
<tr>
<td></td>
<td>ICA</td>
<td></td>
<td></td>
<td></td>
<td>MI</td>
<td>1.12 (0.94–1.33)</td>
</tr>
<tr>
<td>ARIC</td>
<td>Mean, 6 carotid sites</td>
<td>45–64 5,552 males, 7,289 females</td>
<td>4–7,* 6–9†</td>
<td>≥1 mm vs. &lt;1 mm</td>
<td>CHD CHD Stroke Stroke Stroke</td>
<td>1.85 (1.28–2.69)* 5.07 (3.08–8.36)† 3.6 (1.5–9.2)* 8.5 (3.5–20.7)†</td>
</tr>
<tr>
<td></td>
<td>CCA</td>
<td>≥ 64 4,476</td>
<td>6.2</td>
<td>0.20</td>
<td>AMI Stroke Combined MI or stroke</td>
<td>1.24 (1.12–1.38) 1.28 (1.16–1.42) 1.27 (1.17–1.38)</td>
</tr>
<tr>
<td></td>
<td>ICA</td>
<td></td>
<td>0.55</td>
<td></td>
<td>AMI Stroke Combined MI or stroke</td>
<td>1.34 (1.20–1.50) 1.25 (1.12–1.39) 1.30 (1.20–1.41)</td>
</tr>
</tbody>
</table>

*In males; †in females. CI = confidence interval; CCA = common carotid artery; MI = myocardial infarction; AMI = acute myocardial infarction; bif = bifurcation; ICA = internal carotid artery; ARIC = Atherosclerosis Risk in Communities; CHD = coronary heart disease; CHS = Cardiovascular Health study.
for traditional risk factors. There was a progressive increase in risk ratios (95% CI) for each quintile of combined IMT, from the second quintile of 1.54 (1.04–2.28), to the fifth of 3.15 (2.19–4.52). The results of separate analysis of MI and stroke paralleled those for the combined end point. This study also provides strong evidence indicating that increases in carotid IMT are directly associated with an increased risk of MI and stroke in older adults without a history of CVD [20].

The Use of CA in Pharmacologic Studies

The high reproducibility of carotid IMT measurements also makes the application of IMT in many observational studies and pharmacologic interventional studies feasible. In Table 2, we summarized the results of recent important clinical trials that use carotid IMT as the surrogate outcome measures in medications for treating the important risk factors of CVDs, such as hyperlipidemia, hypertension and hyperglycemia.

Lipid-lowering (LDL) therapies

In the 1990s, carotid ultrasound was first applied in the evaluation of the cardiovascular protective effects of cholesterol-lowering agents. PLAC II study [29] was the earlier study to test whether the LDL agent, pravastatin, compared with placebo, had a beneficial effect on IMT progression over 3 years in coronary patients. Although pravastatin significantly reduced IMT progression by approximately 35% in the CCA segment, this study did not demonstrate a significant effect of LDL therapy. However, REGRESS study [30] did show that pravastatin, compared with placebo, significantly decreased the progression of IMT in coronary patients. In the Kuopio Atherosclerosis Prevention Study (KAPS), a population-based primary preventive trial, it was found that LDL had beneficial effects on atherosclerotic progression in carotid and femoral arteries [31]. For the carotid artery segments (CCA and bulb), the annual rate of progression in the pravastatin group (0.017 mm/year) was significantly smaller than in the placebo group in which there was progression of 0.031 mm/year at the overall mean baseline IMT of 1.66 mm. This represents a 45% reduction in atherosclerotic progression.

ACAPS study [32] demonstrated that lovastatin, compared with placebo, significantly decreased IMT progression over 3 years in asymptomatic patients. Reduction in carotid arterial wall thickness was also noted in a randomized controlled clinical trial in which lovastatin and dietary therapy were adopted for hyperlipidemic intervention [33]. In two recent trials, ASAP [34] and ARBITER [35] studies, aggressive LDL with high dose atorvastatin (80 mg/day) was compared with the conventional LDL doses of simvastatin or pravastatin, respectively. High dose atorvastatin was proved to be superior in carotid IMT regression compared with moderate LDL by simvastatin (40 mg/day) in patients with familial hypercholesterolemia [34] or pravastatin (40 mg/day) in patients that met National Cholesterol Education Program II criteria for LDL therapy [35].

Anti-hypertensive medications

In randomized clinical trials, the beneficial effects of anti-hypertensive agents in enhancing atherosclerosis regression or decreasing atherosclerosis progression in carotid arteries have also been established. In an ancillary study of the International Nifedipine GITS Study: Intervention as a Goal in Hypertension Treatment (INSIGHT), CCA IMT progression was compared between the treatments with either nifedipine or diuretic for 4 years [36]. IMT progressed in the co-amilozide-treatment group but not in nifedipine-treatment group. This study demonstrated that agents with equal blood pressure lowering effects may show a different efficacy on early carotid IMT progression. The PREVENT study [37] has shown that in coronary patients undergoing treatment for over 3 years, amlodipine significantly decreased IMT progression in comparison with placebo. In the SECURE study [38], a total of 732 patients of ages ≥55 years who had vascular disease or diabetes and at least one other risk factor but did not have heart failure or a low left ventricular ejection fraction were
Table 2. Pharmacologic effects on carotid intima-media thickness (IMT) in randomized clinical trials

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment/parallel or placebo</th>
<th>Carotid IMT</th>
<th>Patients/parallel or control</th>
<th>Duration, yr</th>
<th>Change in IMT, mm/yr</th>
<th>Reference</th>
</tr>
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<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Treatment/parallel or control</td>
<td>p</td>
</tr>
<tr>
<td>(1) Lipid-lowering agents</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PLAC II</td>
<td>Pravastatin Mean 12 walls</td>
<td>75/76</td>
<td>3</td>
<td>0.059</td>
<td>0.068</td>
<td>NS 29</td>
</tr>
<tr>
<td>REGRESS</td>
<td>Pravastatin Mean CA and FE</td>
<td>131/124</td>
<td>2</td>
<td>0.00</td>
<td>0.05</td>
<td>0.008 30</td>
</tr>
<tr>
<td>KAPS</td>
<td>Pravastatin Mean 12 walls</td>
<td>212/212</td>
<td>3</td>
<td>0.017</td>
<td>0.031</td>
<td>0.005 31</td>
</tr>
<tr>
<td>ACAPS</td>
<td>Lovastatin Mean 12 walls</td>
<td>460/459</td>
<td>3</td>
<td>−0.009</td>
<td>0.006</td>
<td>0.001 32</td>
</tr>
<tr>
<td>MARS</td>
<td>Lovastatin Mean CCA</td>
<td>99/89</td>
<td>4</td>
<td>−0.028</td>
<td>0.015</td>
<td>&lt; 0.001 33</td>
</tr>
<tr>
<td>ASAP</td>
<td>Atorvastatin/simvastatin Mean 12 walls</td>
<td>160/165</td>
<td>2</td>
<td>−0.031</td>
<td>0.036</td>
<td>&lt; 0.001 34</td>
</tr>
<tr>
<td>ARBITER</td>
<td>Atorvastatin/pravastatin Mean CCA</td>
<td>79/82</td>
<td>1</td>
<td>−0.034</td>
<td>0.025</td>
<td>0.03 35</td>
</tr>
<tr>
<td>(2) Anti-hypertensive agents</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>INSIGHT</td>
<td>Nifedipine/co-amilozide Mean CCA</td>
<td>115/127</td>
<td>4</td>
<td>−0.0007</td>
<td>0.0077</td>
<td>0.003 36</td>
</tr>
<tr>
<td>PREVENT</td>
<td>Amlodipine Mean 12 walls</td>
<td>373 total</td>
<td>3</td>
<td>−0.0042</td>
<td>0.011</td>
<td>0.007 37</td>
</tr>
<tr>
<td>SECURE</td>
<td>Ramipril Mean 12 walls</td>
<td>1,023/1,012</td>
<td>4.5</td>
<td>0.014</td>
<td>0.022</td>
<td>0.03 38</td>
</tr>
<tr>
<td>ELSA</td>
<td>Lacidipine/atenolol Mean CCA</td>
<td>81/85</td>
<td>2</td>
<td>−0.0445</td>
<td>−0.0325</td>
<td>0.18 40</td>
</tr>
<tr>
<td>(3) Medications for blood glucose</td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Acarbose</td>
<td>Mean CCA</td>
<td>66/66</td>
<td>3.9</td>
<td>0.007</td>
<td>0.013</td>
<td>0.021 41</td>
</tr>
<tr>
<td>Rosiglitazon</td>
<td>Mean CCA</td>
<td>39/41</td>
<td>48 wk</td>
<td>−0.012</td>
<td>0.031</td>
<td>0.03 42</td>
</tr>
<tr>
<td>Pioglitazone/glimepiride</td>
<td>Mean and maximal CCA</td>
<td>175/186</td>
<td>72 wk</td>
<td>−0.001</td>
<td>0.012</td>
<td>0.02/0.008 43</td>
</tr>
<tr>
<td>Met + glib/glib; gliclazide/glib</td>
<td>Mean CCA</td>
<td>87/59</td>
<td>3</td>
<td>0.003</td>
<td>0.064</td>
<td>&lt; 0.0001 44</td>
</tr>
</tbody>
</table>

NS = not significant; CA = carotid atherosclerosis; FE = femoral artery; CCA = common carotid artery; bif = bifurcation; met = metformin; glib = glibenclamide.
randomly assigned to receive either ramipril 2.5 mg/day or 10 mg/day and vitamin E 400 IU/day or their matching placebos. This study showed that long-term treatment with ramipril had a beneficial effect on atherosclerosis progression, while vitamin E was neutral on atherosclerosis progression.

The European Lacidipine Study on Atherosclerosis (ELSA) [39] was a randomized, double-blind trial on 2,334 patients with hypertension. This study intended to compare the effects of a 4-year treatment based on either lacidipine or atenolol on CA, the IMT in CCA and bifurcations. The greater efficacy of lacidipine on carotid IMT progression and number of plaques, despite a smaller ambulatory blood pressure reduction, indicates an antiatherosclerotic action of lacidipine which is independent of its antihypertensive action. The ELVERA trial was designed to compare the effects of the calcium channel blocker amlodipine and the angiotensin-converting enzyme inhibitor lisinopril on IMT in the elderly, previously untreated hypertensive individuals [40]. After a long-term follow-up, amlodipine and lisinopril reduced IMT to a similar extent in newly diagnosed elderly hypertensive patients. These studies demonstrated that the cardio-protection of antihypertensive agents might be mediated through atherosclerosis regression.

**Medications for hyperglycemia**

Medications for diabetes mellitus (DM) or insulin resistance have also been demonstrated to be beneficial for the regression of CA. Acarbose is an α-glucosidase inhibitor that specifically reduces postprandial glucose excursion by delaying the release of glucose from disaccharides and complex carbohydrates in the small intestine. Acarbose treatment was found to be significantly associated with reduced progression of carotid IMT in subjects with impaired glucose tolerance, a high-risk population for diabetes and atherosclerosis. The annual increase of carotid IMT was reduced by approximately 50% in the acarbose group (0.007 mm/year) vs. the placebo group (0.013 mm/year) [41].

Rosiglitazone, an insulin sensitizer, was assessed for the effect on CCA IMT progression in nondiabetic coronary artery disease (CAD) patients. Consecutive subjects (n=92) with clinically stable, angiographically documented CAD and without DM were randomized in a double-blind manner to receive placebo or rosiglitazone for 48 weeks. Rosiglitazone-treated patients showed reduced IMT progression, compared with the placebo group (−0.012 mm vs. +0.031 mm; p=0.03). Rosiglitazone reduced common carotid IMT progression in nondiabetic CAD patients [42]. Another thiazolidinedione, pioglitazone, was compared with glimepiride regarding the inhibitory effect on carotid IMT. At a study period of 72 weeks, the primary end point of progression of mean carotid IMT was less in group with pioglitazone vs. glimepiride (−0.001 mm vs. +0.012 mm). The reduction of carotid IMT correlated with improvement in insulin resistance and was independent of improvement in glycemic control. In an 18-month treatment period in patients with type 2 DM, pioglitazone could slow the progression of carotid IMT, compared with glimepiride [43].

Metformin, in combination with glibenclamide or gliclazide, was associated with significantly reduced progression of carotid IMT (0.003 and 0.032 mm/year, respectively), compared with glibenclamide alone (0.064 mm/year). Multiple regression analysis revealed that use of metformin or gliclazide significantly and independently accounted for inhibition of the progression of carotid IMT [44]. Thus, the medications for controlling blood sugar also clearly demonstrated the cardiovascular protective effects by using the CA as indexes.

**Measurement Issues**

**Instrumentation**

High-resolution B-mode ultrasonography allows for the observation of carotid arterial structures, including IMT and atherosclerotic plaques. Carotid ultrasound studies require a machine equipped with 5- to 12-MHz linear-array transducers. In addition, a software package for vascular ultrasound is also required. In general, duplex scanning refers to
an ultrasound scanning procedure recording both B-mode images of gray scale of interested arteries and Doppler information of velocity or resistance of interested artery segments [45].

Protocol of ultrasound measurements
Carotid ultrasonography is performed by trained physicians or ultrasonographers. The patients are kept supine with the neck extended in mild lateral rotation. The examination should include the observation of longitudinal and transverse views of the extracranial carotid artery (ECCA) bilaterally. A small soft pillow is favored to support the neck in a fixed position while the examination is undertaken. Examinations should be recorded on super-VHS videotape or digitalized memory system for subsequent off-line analysis [8–10,45]. A moving-image clip of the carotid bulb and CCA with a duration of 5 seconds is acquired and stored in digital format for subsequent offline analysis. At analysis, each image of carotid IMT is recalled with magnification and measured.

ECCA ultrasound measurements
Carotid end-organ disease is assessed by mean and maximal IMTs at the CCAs and by ECCA plaque scores. The mean and maximal IMTs on the CCA proximal to the carotid bifurcation are obtained bilaterally. The CCA1 and CCA2 are points located 0 to 1 cm and 1 to 2 cm, respectively, on the CCA distal from the carotid bifurcation. ECCA segments, including the proximal and distal CCA (> 20 mm and 0–20 mm distal to the bulb bifurcation, respectively), bulb, ICA and external carotid artery, are examined bilaterally [8,9].

IMT measurements
Current ultrasonographic technology does not permit reliable separate measurement of the intima and the media; hence, the standard measurement is combined IMT at the far wall. The IMT of the posterior (or far) wall of the distal CCA is measured as the distance from the leading edge of the first echogenic line (lumen-intima interface) to the leading edge of the second line (media-adventitia interface) (Fig. 1) [46]. The measurement of mean and maximal IMT at the CCA 0–20 mm proximal to the carotid bifurcation will be obtained bilaterally; however, which segment or width of measured site will depend on the protocol of different studies (Fig. 1). Carotid plaque is skipped to prevent the overestimation of the real IMT of individuals. It is required to differentiate carotid IMT from atherosclerotic plaque. CCA IMT is a double-line observed by ultrasonography in a longitudinal view. The carotid plaque is a focal structure encroaching the arterial lumen of at least 0.5 mm or 50% of the surrounding IMT, or an intima-media complex thickness > 1.5 mm [47]. Automated measurement, the mean maximal value of 150 measurements on

Fig. 1. (A) The schematic overview of intima-media thickness (IMT) at carotid arteries and the site of measurements. (B) The real measurements of IMT at distal common carotid artery (CCA).
a 10 mm segment of the CCA, is efficient, reliable and less time-consuming than manual measurement. A minimum of 10 mm length of the CCA and a high-quality image acquisition are better for IMT measurement.

Reliability of measurements
A critical component in scientific studies of most biologic variables is the variation or error in measurements. The measurement variability or error of carotid IMT can be decreased by using ultrasound images from both the right and the left carotid arteries and by the use of an automated analyzing system with automated edge detection which greatly simplifies the reading of ultrasound images with sustained low variability [48,49]. For further comparison and application of the measurements of IMT and carotid plaque, the accuracy of measurements and reliability study for the test-retest should be documented, including the interobserver and intraobserver, or inter-reader and intra-reader reliability. In our previous study, the interobserver correlation coefficients were 0.86 to 0.93, and the intraobserver correlation coefficients were 0.70 to 0.87 for both sides of CCA IMT measurements [24]. The detection limit of measurements depends on the duplex ultrasound system and the software for this application.

Where to measure? CCA, ICA or carotid bulb?
CCA is favored as the measurement site over other locations of ECCA, such as ICA and carotid bulb, in most epidemiologic studies [2,45,50,51]. CCA is considered as the segment of choice, possibly because the IMT variability associated with this segment is lower in comparison with other segments. Not only is the reliability of the IMT measurements reported to be higher but also more accessible at the CCA than at the carotid bulb and ICA [50,51]. The far wall of the ECCA is clearer and more homogenous and consistent; therefore, we suggest that IMT at the far wall of the carotid arteries is the favored measurement site.

ECCA atherosclerotic plaque scoring
There are several methods of carotid plaque quantification applied in clinical or epidemiologic studies. A plaque scoring quantifying method, modified from that of Sutton et al, has been described previously [8,13] and is shown in Fig. 2. Briefly, a focal thickening of IMT with over 50% of thickness than the adjacent IMT is considered as an atherosclerotic plaque. A grade is assigned for each chosen segment: grade 0, normal or no observable plaque; grade 1, one small plaque with diameter stenosis of <30%; grade 2, one medium plaque with 30–49% diameter stenosis or multiple small plaques; grade 3, one large plaque with 50–99% diameter stenosis or multiple plaques with at least 1 medium plaque; and grade 4, 100% occlusion. The total plaque score is calculated by adding up the plaque grades at 10 segments of the ECCA. Reproducibility of the ECCA plaque grade scoring also expresses good agreement with a κ value of 0.70 [25].

Fig. 2. (A) The extracranial carotid artery (ECCA) plaque score of 2 at bulb. (B) ECCA score of 2 at bulb and common carotid artery (CCA).
Carotid stenosis and occlusion
Currently, the degree of carotid stenosis is based on conventional angiography of the carotid arteries. Two different methods are widely used: (1) the distal method, also known as “North American Symptomatic Carotid Endarterectomy (NASCET) method” [52], calculating the ratio of the minimal residual diameter of the stenotic segment; (2) the local method, also known as “European Carotid Surgery Trial (ECST) method” [53], calculating the ratio of the minimal residual diameter of the stenotic segment to the presumed former diameter of the same segment. In general, the ECST method leads to 10–20% higher degree of carotid stenosis than the NASCET method. The ultrasonographic measurement of carotid stenosis should be determined against either the ECST or the NASCET method [54].

According to the various validity ultrasound studies, some methods are proven to be highly accurate in quantification of ICA stenosis [55–57]: (1) The ICA peak systolic velocity (PSV) method: the highest PSV on the stenotic site. As the degree of luminal stenosis of the ICA >50%, the PSV increases to >1.25 m/s. In 70–95% stenosis, the PSV reaches to >2.5 m/s. In ICA stenosis higher than 95%, the PSV decreases due to a significant reduction of the blood flow through the stenotic segment. Inability to detect any residual flow signals in the stenotic segment, it suggests ICA occlusion. (2) The ICA/CCA PSV ratio method: dividing the ICA intrastenotic PSV by the PSV derived from the ipsilateral CCA 3 cm proximal to the bifurcation. In ICA stenosis <50%, 50–69%, and 70–99%, the ICA/CCA PSV ratios are <2, 2–4 and >4, respectively. (3) The cross-sectional area reduction method: the degree of luminal stenosis is determined by the cross-sectional area reduction through the transverse view of the stenotic ICA. In ICA stenosis <50%, 50–69%, and 70–99%, the cross-sectional area reduction are <75%, 75–90%, and 90–99%, respectively.

In addition to the aforementioned methods, there are some other methods applied in quantification of ICA stenosis, including mean flow velocity and end-diastolic flow velocity on the stenotic site, spectrum analysis, ICA/CCA mean flow velocity ratio, color-Doppler flow, and indirect methods (supraorbital Doppler flow and ipsilateral intracranial ICA flow).

Previous Studies in Taiwan
Jeng et al first documented the feasibility of carotid ultrasound in cardiovascular research in Taiwan in 1994 [13]. Consecutive 367 ischemic stroke patients were selected from a medical center to study the frequency of carotid stenosis and its risk factors. Severe ECCA stenosis of ≥50% was found in 32% of patients with cortical infarct, 3% with subcortical infarct, 7% with vertebrobasilar artery infarct, 21% with cardioembolism, and 12% of all ischemic stroke patients. The extent and severity of ECCA atherosclerosis were more prominent in patients with cortical infarct than with other types of ischemic stroke. In the following stroke registry study conducted at National Taiwan University Hospital, the frequency of ECCA stenosis remained at 12% of ischemic stroke and 27% of transient ischemic attack patients [58,59].
Pan et al studied the association between vascular risk factors, particularly coagulation profiles, and CA [7]. The odds ratio of the highest tertile to the lowest tertile of factor VIIIc for CA was 3.35. There was a positive correlation between factor VIIIc and the presence of carotid plaques.
Su et al investigated the determinants of ECCA atherosclerosis in patients with hypertension in Taiwan. Hypertensive patients (146 with hypertension and 117 with borderline hypertension) and 270 normotensive adults were recruited from the Chin-Shan Community Cardiovascular Cohort (CCCC). A significant dose-response relationship was found between the status of hypertension and the severity of CA. Compared with the normotensive subjects, the odds ratios (and 95% CIs) for the hypertensive patients to develop CA were 5.0 indexed by maximal CCA IMT ≥75th percentile, 3.7 by ECCA score >6,
and 4.8 by carotid stenosis $\geq 50\%$. This study clearly documented that hypertension strongly influences CA. The findings reinforced the hypothesis that hypertension has a major role in the pathogenesis of atherosclerosis [8]. In the same study, Su et al also found that pulse pressure was strongly associated with CA in patients with hypertension, after taking into account aortic regurgitation. In terms of risk stratification, pulse pressure was more important in hypertensives than in normotensives, which seems to imply that pulsatile hemodynamic component of BP is crucial in the association with atherosclerosis [60].

Since the adoption of vegetarian diets as part of a healthy lifestyle has become popular, the cardiovascular effects of long-term vegetarianism need to be explored. Su et al studied the micronutrient imbalance, including blood levels of vitamin B12, homocysteine and soluble vascular cell adhesion molecule-1, in vegetarians and their associations with CA in 57 healthy postmenopausal vegetarians and 61 age-matched omnivores. They found that there was no significant difference in CA between apparently healthy postmenopausal vegetarians and omnivores. The findings of elevated homocysteine and soluble vascular cell adhesion molecule-1 in vegetarians indicate the importance of avoidance of B12 deficiency [10]. The relationship between time factors of elevated BP and CA is still unclear. The associations between time-weighted average 24 hour ambulatory systolic BP, duration of hypertension in years (hypertension-year), and CA were investigated in a petrochemical company sample of 95 executives and 91 gender- and age-matched non-executive employees. In this work-site related cardiovascular promotion program, we found that both time-weighted average ambulatory systolic BP and hypertension-year were two major determinants for carotid IMT and CA, which seems to imply that both short-term and long-term durations of elevated BP are probably crucial in the pathogenesis of CA [9]. Because of the high prevalence of hepatitis B infection in Taiwan, we tested the hypothesis of chronic infection of hepatitis B virus and preclinical CA. Among 508 subjects who participated in the health examination, we noted that hepatitis B virus seropositivity in the 87 subjects was not associated with an increased severity of CA [61].

One study analyzed the data from physical examination at a medical center between 1996 and 1998 [62]. The presence of CA was associated with the increase in the counts of all leukocyte, neutrophil and monocyte; after adjustments for age and body mass index, there were significant positive links between these three leukocyte counts and the severity of CA in 571 non-smoking subjects, in terms of either the sum score of all carotid plaques or the score of the most severe carotid plaque. On the contrary, in female non-smokers ($n=614$), there was no such significant link between leukocyte counts and CA. This study suggested that monocytes and neutrophils are the main types of leukocytes involved in atherosclerosis [62]. Between 1998 and 2001, another study used the data from physical examination to evaluate the determinants of carotid IMT in 1,781 asymptomatic subjects [63]. The mean IMT was 0.68 $\pm$ 0.12 and 0.66 $\pm$ 0.11 mm for men and women, respectively. Among them, 37% had carotid plaques which were positively associated with age and IMT. Age, systolic blood pressure and fasting blood sugar were independent risk factors related to both CA and thicker IMT [63].

Some parts of Taiwan are known to be endemic areas of high arsenic exposure. An interesting study was conducted to examine the biologic gradient between ingested inorganic arsenic and CA in 199 male and 264 female adult residents from the southwestern area of endemic arseniasis in Taiwan [64]. Indices of long-term exposure to ingested arsenic were all significantly associated with prevalence of CA in a dose-response relationship. The biologic gradient remained significant after adjustment for associated covariates. The multivariate-adjusted odds ratio (95% CI) was 3.1 (1.3–7.4) for those who had a cumulative arsenic exposure of $\geq 20$ mg/L-years compared with those without exposure to arsenic from drinking artesian well water. This study demonstrated that CA by ultrasonography is associated with ingested inorganic arsenic in a pattern of biologic gradient [64].
Conclusion

Application of carotid ultrasound in clinical practice is feasible. The proper use of ultrasound, measurement protocols and available IMT software is important to obtain an accurate and reliable image for clinical research. The potential indications for risk stratification that is proposed in a report from the American Society of Echocardiography and the Society of Vascular Medicine and Biology [45] are as follows: “In asymptomatic persons over 45 years, carefully performed carotid ultrasound examination with IMT measurement can add incremental information to traditional risk factor assessment. In experienced laboratories, this test can now be considered for further clarification of CHD risk assessment at the request of a physician [65].” However, the noninvasive cardiovascular testing should be arranged based on physicians’ recommendation and referral and only after a careful consideration of known medical history and evaluation of major standard cardiovascular risk factors by office-based techniques [66]. Some studies also suggest that high-risk patients, such as those with existing CVD (stroke or CHD), hypertension, higher pulse pressure, age over 45 years, DM, metabolic syndrome and hyperlipidemia, may benefit from this simple and noninvasive examination in the perspectives of primary or secondary prevention of CVD.

References

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