Use of Carotid Intima-Media Thickness to Identify Patients With Ischemic Stroke and Transient Ischemic Attack With Low Yield of Cardiovascular Sources of Embolus on Transesophageal Echocardiography

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Background and Purpose—Carotid intima-media thickness (CIMT) is associated with systemic atherosclerosis and cardioembolic conditions and predicts the risk of recurrent strokes. We sought to establish the relationship between CIMT and cardiovascular sources of embolus (CSE) on transesophageal echocardiography (TEE) and hypothesized that a noninvasive strategy of CIMT assessment and transthoracic echocardiography bubble study would identify patients with ischemic stroke or transient ischemic attack in whom TEE would provide little incremental diagnostic yield.

Methods—In 180 patients with ischemic stroke or transient ischemic attack of undetermined origin referred for TEE, we prospectively performed CIMT measurement/plaque screen (Phase 1, n=96) or CIMT measurement/plaque screen and transthoracic echocardiography bubble study (Phase 2, n=84) before TEE. Phase 1 results were used to construct receiver operating characteristic curves to demonstrate the ability of CIMT to detect CSE on TEE and to identify the optimal CIMT cutoff value for prospective strategy testing (Phase 2).

Results—In Phase 1, CIMT was found to correlate with TEE markers of aortic atherosclerosis, including complex aortic plaques, and combined CSE. The optimal CIMT cutoff for detection of CSE on TEE was 0.78 mm. In Phase 2, a positive noninvasive strategy test (CIMT \( \geq 0.78 \) mm, +carotid plaque, and/or a positive transthoracic echocardiography bubble study) was present in 61%. The prevalence of CSE on TEE was significantly higher among those with a positive compared with a negative noninvasive strategy test (65% versus 9%, \( P<0.001 \)), and this strategy had a sensitivity of 92% and a negative predictive value of 91% for the detection of any CSE on TEE.

Conclusion—In patients with stroke or transient ischemic attack of undetermined origin, a noninvasive strategy of CIMT assessment/plaque screen and transthoracic echocardiography bubble study can identify patients in whom further invasive evaluation with TEE will be of low diagnostic yield. (Stroke. 2008;39:2969-2974.)

Key Words: diagnostic methods | echocardiography | stroke care | TIA

In patients with ischemic stroke or transient ischemic attack (TIA), transesophageal echocardiography (TEE) has become routine for exclusion of potential cardiovascular sources of emboli (CSE). Although TEE is generally a safe procedure, required sedation and esophageal intubation can lead to fluctuations in blood pressure and transient compromise of respiratory status, which are not ideal in the immediate postischemic stroke setting. Thus, the option of a noninvasive diagnostic testing strategy, which might obviate the need for TEE in these patients, would be desirable.

Carotid intima-media thickness (CIMT) can be measured noninvasively, correlates with systemic atherosclerosis, structural heart disease, and conditions associated with cardioembolism, and predicts the risk of recurrent strokes.\(^1\) Among patients with ischemic stroke, a low CIMT has been reported to have a high negative predictive value for the detection of complex aortic plaques, which are among the most prevalent CSE identified on TEE.\(^8\)\(^-\)\(^13\) Other evidence suggests that modern transthoracic echocardiography with bubble study is highly sensitive for the detection of intra-atrial communications, another commonly identified potential CSE after stroke.\(^14\)

We hypothesized that CIMT measurements would aid in the selection of patients with ischemic stroke or TIA of otherwise undetermined origin for TEE. We first sought to establish the relationship between CIMT and cardiovascular sources of embolism in patients with ischemic stroke or TIA. We then sought to prospectively test a noninvasive strategy using a predetermined CIMT cutoff combined with transthoracic echocardiography (TTE) with bubble study for the
identification of patients with ischemic stroke and patients with TIA in whom referral to TEE would be low yield.

Methods
This prospective study was carried out in 2 phases. For both phases, consecutive patients referred for TEE at the University of Chicago to exclude a cardiovascular source of embolus after ischemic stroke or TIA were eligible for inclusion and were prospectively enrolled. In Phase 1, we attempted to establish the relationship between CIMT and carotid Doppler or CSE on TEE and determine the optimal CIMT cutoff value for strategy testing. In Phase 2, a noninvasive diagnostic strategy was tested. In Phase 1, eligible patients underwent carotid imaging for CIMT measurement and plaque screen before their clinically indicated TEE. In Phase 2, eligible patients underwent both carotid imaging for CIMT measurement and plaque screen and a TTE with bubble study using harmonic imaging before their clinically indicated TEE.

For all patients, a brain imaging study (CT and/or MRI or MR angiography) and carotid Doppler or MR angiography was performed before arrival for TEE and all medical records were reviewed. Patients in whom a diagnosis of stroke or TIA was not confirmed, and patients with known pre-existing high-risk embolic conditions, were excluded. High-risk embolic conditions included internal or common carotid stenosis $>50\%$ or prior carotid endarterectomy, documented atrial fibrillation or flutter, left ventricular ejection fraction $<30\%$, left ventricular aneurysm, aortic or mitral stenosis, known valvular vegetation or mass, any congenital heart disease, and any prosthetic valve or previous valve surgery.

Baseline clinical characteristics included age, gender, hypertension, hyperlipidemia, diabetes, current tobacco use, renal insufficiency (creatinine $\geq 2.0\%$), prior stroke, and history of coronary artery disease (defined by history of myocardial infarction or a positive stress test or documented coronary stenosis $>50\%$ on coronary angiogram), and medications.

Cerebrovascular Events
Cerebrovascular events were defined as ischemic strokes or TIA. Strokes were classified according to a modification of the TOAST criteria based on the clinical, radiographic, and diagnostic information available before the TEE. Thus, strokes could be classified as either “suspected cardioembolic” or “small vessel disease” based on pre-TEE data. A TIA was defined as a documented neurological deficit lasting $<24$ hours without definite radiographic evidence of acute ischemia.

Echocardiography
All echocardiograms were acquired using Philips Sonos 7500 cardiac ultrasound machines (Andover, Mass.). TEE images were acquired using omniplane transducers (range, 4 to 7 MHz). TEEs were performed by expert echocardiographers in our laboratory. All patients underwent agitated saline contrast injection during TEE in Phase 1 and during both TTE and TEE in Phase 2. Valsalva and cough maneuvers were used routinely to increase sensitivity of detection of intra-atrial communications. Interpretation of TEEs was performed by the consensus of 2 expert readers blinded to CIMT or TTE bubble study results.

TEE findings known or suggested to be associated with ischemic embolic events were recorded including left atrial thrombus, left ventricular thrombus, intracardiac tumors, spontaneous echo contrast, valvular vegetation or mass, valve straddles/tumor, patent foramen ovale (PFO), and complex aortic atheroma (defined as a plaque in the ascending aorta/aortic arch or descending aorta that protrudes $\pm 4$ mm into the aortic lumen or that is associated with ulceration or mobile features). Any potential CSE of embolus was defined as the composite of any finding described previously.

Thoracic atherosclerosis was assessed on TEE in all patients by measuring the point of maximal aortic intima-media thickness in the ascending aorta/arch and descending aorta from digital images measured offline using electronic calipers. The most severe atheroma for each patient was defined as the maximal aortic intima-media thickness measurement for each patient. Thoracic atherosclerotic burden for each patient was defined as the sum of the maximal ascending/arch and descending aortic intima-media thickness measurements.

Spontaneous echo contrast was defined as dynamic swirling of echodense material in the left atrium or left atrial appendage at standard gain settings.

Carotid Intima-Media Thickness Measurement
CIMT images were acquired with a high-end ultrasound system (SONOS 7500) with an L 11–3 transducer (Philips Medical Systems). Patients were placed in a supine position using a 45° head rotation angle for acquisition. Acquisitions were obtained in a 5-beat loop as well as a still frame at end diastole and images were stored digitally for offline analysis. Long axis images and cross-sectional images of the right and left carotid artery above and below the carotid bulb were obtained with posterior, medial, and anterior transducer angulations. Carotid plaque was defined as a maximal intima-media thickness $>1.5$ mm or a greater than 50% increase from neighboring walls in any view. CIMT was measured on the full wall of the right and left common carotid artery from long axis images obtained with medial transducer angulation. The mean CIMT was measured over 1 cm using automated border detection software (Qlab; Philips) with $\pm 80\%$ tracking required. The CIMT value used for each patient was defined as the greater mean CIMT between the right or left common carotid artery. CIMT measurements were performed by one trained sonographer and read by a single expert reader blinded to TEE results. Sonographer performance was tested in 15 volunteers who underwent repeat scanning. The mean absolute difference of CIMT measurement on repeat scans was 0.039 mm (SD, 0.028). Reader performance was tested by repeat CIMT measurement and plaque assessment in 30 replicate scans performed $>30$ days after initial reading. The mean difference between CIMT measurements on repeat scans was $<0.01$ mm, and the percentage agreement in assessment of the presence or absence of plaque between the 2 readings was 97%.

Statistical Analysis
Comparisons between baseline characteristics and echocardiographic findings between patients in Phase 1 and Phase 2 were performed with $\chi^2$ tests for categorical data and Student $t$ test for continuous data using a 2-tailed probability value $<0.05$ for statistical significance. Correlations between CIMT and TEE findings were performed with Spearman rank correlation coefficients. The sensitivity, specificity, positive predictive value, and negative predictive value of various noninvasive tests for findings on TEE were calculated using TEE finding as the gold standard. Exact 95% CIs were constructed for these values based on the binomial distribution. Logistic regression modeling was performed to determine the relationship between baseline characteristics and carotid imaging results and findings on TEE. The resulting ORs and 95% CIs are presented. The ORs for CIMT can be interpreted as the multiplicative increase in the likelihood of having a positive TEE finding for a 0.05-mm increase in CIMT.

Receiver operating characteristic (ROC) curves were generated based on the corresponding logistic regression model, and the area under the ROC curves were calculated to assess the diagnostic accuracy of CIMT, other noninvasive tests, and/or baseline characteristics in predicting presence of CSE.

Results
Overall, 180 patients were enrolled, 96 in Phase 1 and 84 in Phase 2 of the study. The baseline characteristics of study patients are listed in Table 1. The mean age of the entire study population was 60 ± 11 years, 47% were male, and there was a high prevalence of cardiovascular disease, including hypertension (75%), diabetes (33%), and coronary artery disease (25%). Of the entire study populations, 74% were referred for TEE after stroke and 26% after TIA. TEE findings are...
presented in Table 2. Overall, 43% of patients were found to have a cardiovascular source of embolus on TEE. The most prevalent individual CSE were PFO (19%) and complex aortic atheroma (18%). For the entire study group, the mean CIMT was 0.80 ± 0.20 mm, the median CIMT was 0.76 mm (range, 0.45 to 1.44), and carotid plaque was present in 16%. There were no significant differences in baseline characteristics or TEE findings of patients enrolled in Phase 1 versus Phase 2 of the study.

Phase 1 Results

CIMT measurements were found to strongly correlate with aortic atherosclerosis found on TEE, including both most severe atheroma (r=0.45, P<0.001) and aortic atheroma burden (r=0.48, P<0.001). The individual TEE findings according to CIMT quartile are listed in Table 3. There was a significant correlation between increasing CIMT quartile and the presence of complex aortic atheroma (r=0.45, P<0.001) and a significant but less robust correlation between increasing CIMT quartile and the composite of any CSE (r=0.26, P=0.01). There was no significant correlation between CIMT and PFO on TEE. For the composite end point of any CSE other than PFO, thus excluding the finding likely to be identified with TTE and bubble study, a strong correlation with increasing CIMT quartile was demonstrated (r=0.40, P<0.001). Presence of carotid plaque was also significantly associated with CSE on TEE. Patients with carotid plaque has significantly more complex aortic atheroma (47% versus 12%, P=0.001), any CSE (67% versus 36%, P=0.03), and any CSE other than PFO (60% versus 22%, P=0.003) compared with those without carotid plaque. There was no significant association between carotid plaque and PFO alone.

On univariate logistic regression analysis, CIMT (OR, 1.11; 95% CI, 1.01 to 2.23; P=0.04) and presence of carotid plaque (OR, 3.6; 95% CI, 1.1 to 11.5; P=0.03) were significant univariate predictors of composite CSE on TEE. No baseline characteristics were significant univariate predictors of composite CSE, although there was a trend for increasing age (OR, 1.03; 95% CI, 0.99 to 1.07; P=0.096). For the any CSE other than PFO end point, CIMT (OR, 1.23; 95% CI, 1.10 to 1.39; P=0.001) and presence of carotid plaque (OR, 5.3; 95% CI, 1.65 to 16.7; P=0.005) were strong significant univariate predictors. Among baseline characteristics, only increasing age (OR, 1.05; 95% CI, 1.01 to 1.10; P=0.03) and presence of coronary artery disease (OR, 2.71; 95% CI, 1.03 to 7.10; P=0.04) were significant univariate predictors of any CSE other than PFO. Multivariate modeling was used to determine the independent predictive effect of CIMT testing when added to the baseline characteristics of age and coronary artery disease. When CIMT was included in multivariate models with age and coronary artery disease, only CIMT (OR, 1.19; 95% CI, 1.05 to 1.34; P=0.007) remained a significant predictor of any CSE other than PFO.

Receiver operating characteristic curves were constructed to identify the optimal CIMT cutoff value yielding the maximal combination of sensitivity and correctly classified patients to be used for prospective strategy testing. The area under the ROC curve for CIMT predicting any CSE was 0.644 (95% CI, 0.530 to 0.758). The area under the ROC curve for CIMT predicting any CSE other than PFO was 0.772 (95% CI, 0.671 to 0.874; Figure 1). Because of prior data suggesting modern TTE with bubble study would accurately predict PFO on TEE,14 the optimal CIMT cutoff for prospective noninvasive strategy testing was determined to be ≥0.78 mm from the ROC curve for CIMT predicting any CSE other than PFO.

Phase 2 Results

Patients with a positive bubble study on TTE, a CIMT ≥0.78, and/or carotid plaque were considered to have a positive noninvasive test, because these were all findings that would be expected to predict CSE on the subsequent TEE. Patients without a positive TTE bubble study, a CIMT <0.78, and without carotid plaque were considered to have a negative noninvasive test. Of the 84 patients enrolled in Phase 2, 61%...
had a positive noninvasive test and 39% had a negative noninvasive test. A positive bubble study on TTE was present in 21%, a CIMT ≥0.78 was present in 48%, and carotid plaque was present in 17%.

TTE bubble study using harmonic imaging was found to have a sensitivity of 94% (95% CI, 71% to 100%), a specificity of 97% (95% CI, 90% to 100%), and a negative predictive value of 98% (95% CI, 92% to 100%) for detection of PFO on TEE. Overall, a positive noninvasive strategy test had a sensitivity of 92% (95% CI, 78% to 98%) and a negative predictive value of 91% (95% CI, 76% to 98%) for the detection of any CSE on TEE (Table 4) A CSE was present in only 9% of patients with a negative noninvasive test, but in 65% of patients with a positive noninvasive test (P<0.001).

An ROC curve was constructed from the multivariate logistic regression model considering CIMT, carotid plaque, and TTE bubble study to demonstrate the ability of these variables, performed in combination as a noninvasive strategy, to predict any CSE on TEE. The area under the ROC curve was 0.870 (95% CI, 0.787 to 0.952; Figure 2).

Discussion

In this study, we found that among patients with ischemic stroke or TIA of undetermined origin, increasing CIMT correlates with increasing aortic atherosclerosis and combined CSE identified on TEE. Furthermore, we found that a noninvasive diagnostic management strategy using CIMT imaging and TTE bubble study can be used to select patients with ischemic stroke in whom TEE will be of very low diagnostic yield.

Patients with ischemic stroke are routinely referred for TEE for exclusion of CSE. TEE is the most invasive diagnostic testing modality routinely performed in patients with ischemic stroke. Although TEE is generally a safe procedure, required sedation and esophageal intubation can lead to hemodynamic or respiratory alterations, which may transiently alter cerebral perfusion or oxygenation at a time when consistent perfusion to injured brain tissue is essential. In addition, TEE may not be available in some settings or may not be possible due to oral or esophageal pathology. A noninvasive testing strategy in these patients would provide a diagnostic option to potentially obviate the need for TEE in some patients or allow the delay of TEE until a safer time.

Among patients with ischemic stroke of undetermined origin, thus those in whom high risk cardioembolic conditions identified before TEE are excluded, complex aortic atheroma and intra-atrial communications have been reported to account for a majority of the CSE identified on TEE.10–13 Other common CSEs are frequently associated with cardiac comorbidities such as atrial fibrillation or structural heart disease. CIMT testing is a noninvasive imaging modality that has been shown to correlate to systemic atherosclerosis, structural heart disease, and atrial fibrillation and predicts the risk of recurrent stroke.1–7 The correlation between and CIMT and CSE on TEE among patients with ischemic stroke has not been reported. Furthermore, the ability of a noninvasive testing strategy incorporating TTE bubble study for detection of intra-atrial communications and CIMT for detection of other CSEs has not been investigated.

In this study, we found that increasing CIMT strongly correlates with increasing aortic atherosclerosis and the most severe aortic atheroma present and overall aortic atheroma burden. We also found that carotid imaging, including CIMT measurement and plaque screening, identifies patients who were very unlikely to have complex aortic plaques. Our findings are consistent with recent studies suggesting the use of CIMT testing for the exclusion of significant aortic...
atheroma.\textsuperscript{8,9,17} In a prospective study, Harloff et al reported that use of CIMT testing achieved a negative predictive value of 92% for the detection of complex aortic atheroma.\textsuperscript{9} Complex aortic plaques are particularly important to exclude because they are associated with a increased risk of recurrent stroke and may warrant therapy with statins or warfarin.\textsuperscript{18–21} Additionally, we have previously reported that complex aortic plaques are the only individual CSE found on TEE after ischemic stroke to be associated with an increased mortality.\textsuperscript{11} We included complex aortic plaques in all thoracic locations in our definition of a positive TEE finding because we felt this definition was relevant to clinical practice. Although the evidence that descending aortic atheroma can cause central nervous system events is limited,\textsuperscript{22,23} studies addressing prognostic and therapeutic implications of complex aortic atheroma found on TEE after embolic events have included plaques in all thoracic locations.\textsuperscript{11,19–21}

Not unexpectedly, no correlation between CIMT and PFO was demonstrated. Transthoracic echocardiography with bubble study has long been used to identify intra-atrial shunting. However, recent reports using modern TTE with harmonic imaging have suggested improved diagnostic accuracy, including sensitivities for detection of intra-atrial communications of over 90%.\textsuperscript{14} Our results are consistent with these data and further suggest that TEE is not required solely the identification of intra-atrial communications.

Increasing CIMT was also was found to correlate with combined CSE found on TEE after ischemic stroke or TIA of undetermined origin, although this correlation was weakened by the inclusion of PFO. When only CSE other than PFO was considered, a strong correlation to CIMT was demonstrated. Importantly, CIMT was a more important predictor of finding any CSE other than PFO than all baseline characteristics, including age and coronary artery disease. Although none of the other individual potential CSE was found to significantly correlate with CIMT, it is notable that the majority of the left atrial thrombi and spontaneous echo contrast (83%) were found in the upper 2 quartiles of CIMT, and none was found in the lowest quartile. Increased CIMT has been reported to correlate with a history of atrial fibrillation, which is the predominant risk factor for atrial thrombus or spontaneous echo contrast.\textsuperscript{2} Although documented atrial fibrillation was an exclusion criterion in this study, subclinical atrial fibrillation has been suggested as contributing etiology in patients with unexplained ischemic stroke.\textsuperscript{24,25}

Finally, using a noninvasive testing strategy incorporating carotid imaging with CIMT measurement and TTE bubble study achieved a high sensitivity and negative predictive value for the detection of CSE on TEE. This strategy allowed identification of a significant fraction of patients with ischemic stroke in whom further TEE was of low diagnostic yield. This finding could have important clinical implications for patients with ischemic stroke in whom TEE is not possible or in whom TEE is not ideal due to concerns about hemodynamic or respiratory alterations in the immediate poststroke period.

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Disclosures

None.

References


Table 4. Ability of Noninvasive Strategy Incorporating CIMT Measurement and TTE Bubble Study to Identify Any CSE on TEE

<table>
<thead>
<tr>
<th>Total Phase 2 Study Group (n=64)</th>
<th>Sensitivity (95% CI)</th>
<th>Specificity (95% CI)</th>
<th>NPV (95% CI)</th>
<th>PPV (95% CI)</th>
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<tbody>
<tr>
<td>TTE+ or plaque or CIMT ≤0.78</td>
<td>61%</td>
<td>92% (78%–98%)</td>
<td>63% (47%–76%)</td>
<td>91% (76%–98%)</td>
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NPV indicates negative predictive value; PPV, positive predictive value.

Figure 2. Receiver operating characteristic curve constructed from the multivariate logistic regression model considering CIMT, carotid plaque, and TTE bubble study to demonstrate the ability of these variables, performed in combination as a noninvasive strategy, to predict any CSE on TEE.


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