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Research letter

Carotid extra-medial thickness does not predict adverse cardiovascular outcomes in high-risk adults

1. Introduction

The arterial adventitia has been implicated in the vascular remodelling process of atherosclerosis. Carotid extra-medial thickness (EMT) is a reproducible non-invasive measure of elastic artery adventitial thickness obtained by high-resolution ultrasound [1,2]. Carotid EMT is correlated with both intima-media thickness (IMT) and arterial stiffness from the same arterial segment, yet is associated with cardiovascular risk factors including BMI and diabetes independent of atherosclerotic involvement of the arterial intima and media [1,3–5].

The prognostic significance of carotid EMT, however, has not yet been examined. Thus, we sought to determine whether carotid EMT is associated with risk of incident cardiovascular events, in adults at risk of coronary artery disease (CAD).

2. Materials and methods

2.1. Study design and participants

We retrospectively measured carotid EMT from ultrasound images collected as part of a study that previously demonstrated an association of carotid IMT with cardiovascular events in adults at risk of coronary artery disease (CAD) [6]. Consecutive patients deemed at risk of CAD were prospectively enrolled from cardiology and renal outpatient clinics from December 1998 to July 2002, for risk evaluation and subsequent follow-up, as described previously [6]. Selection criteria included known or suspected vascular disease, renal dysfunction, or the presence of multiple cardiovascular risk factors. Exclusion criteria included a recent (previous six weeks) inpatient stay due to myocardial infarction (MI), acute coronary syndrome, coronary revascularization, heart failure, or sepsis. All patients gave written, informed consent, and the study was approved by the Human Research Ethics Committee of University of Queensland and Princess Alexandra Hospital.

2.2. Clinical and biochemical evaluation

A full clinical history and examination were undertaken by a specialist physician. Baseline demographic data, cardiovascular risk factors, and cardiovascular medications were documented. The presence of CAD was defined as a history of MI, coronary revascularization, or typical chest pain with a positive stress echocardiogram. Diabetes mellitus was defined by the use of insulin injections or oral hypoglycaemic agents.

Two-year CAD event risk in patients with no previous MI was calculated using the revised Framingham risk score [7]. For patients with a previous MI, a two-year CAD predicted event rate was calculated from gender, age, total cholesterol, HDL cholesterol, systolic blood pressure, diabetes, and smoking history [8].

2.3. Vascular structure

Both the left and right common carotid arteries were imaged at the level of the carotid bifurcation in the anterior, lateral, and posterior plane, using longitudinal B-mode ultrasonography. The focal zone was set at or just below the far wall, which was scanned perpendicular to the transducer face. Images were manually assessed for quality and visibility of the extra-medial structures. Off-line analysis of magnified still images was performed by a single observer using edge-detection software (Carotid analyser for Research v 5.10.11; MIA LLC, IA). From these images, carotid EMT and total wall thickness was measured across a length of 0.5–1.0 mm of the near wall of the common carotid artery at varying distances within 0–2 cm from the carotid bulb dependent primarily on where carotid EMT was most clearly visualized [1]. For each subject, up to two images from each of the left and right common carotid arteries were measured. Carotid IMT was calculated as the difference between total wall thickness and carotid EMT, from the same near wall segment of the carotid artery as carotid EMT.

2.4. Outcomes

The primary outcome was the time to the most significant episode, in order, of death [9], MI, or admission with acute coronary syndrome, stroke, or coronary revascularization. In patients with more than one event, only the most significant event was used for analysis. Outcomes were determined by assessment of the death certificate or hospital record survey or by telephone conversation with the patient or treating local medical practitioner. Only participants with outcome data were included in this analysis.

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Table 1
Stratified analysis of carotid extra-medial thickness (EMT) as a predictor for any event.

Stratification[a]	Event (%)	HR [95% CI][b]	*P* value
CAD (n = 348)			
No CAD (*n* = 225)	27 (12)	0.93 [0.74, 1.17]	0.54
CAD (*n* = 123)	30 (24)	1.04 [0.86, 1.26]	0.67
Obesity (n = 307)			
Not obese (*n* = 215)	42 (20)	1.02 [0.86, 1.20]	0.86
Obese (*n* = 92)	14 (15)	0.94 [0.69, 1.29]	0.70
Diabetes mellitus (n = 348)			
Not diabetic (*n* = 247)	37 (15)	0.94 [0.75, 1.18]	0.79
Diabetic (*n* = 101)	20 (20)	1.03 [0.84, 1.25]	0.57
Two-year cardiovascular risk score (n = 295)			
< 4% (*n* = 187)	21 (11)	1.06 [0.82, 1.37]	0.67
≥ 4% (*n* = 108)	29 (27)	1.03 [0.85, 1.25]	0.77
Gender (n = 348)			
Female (*n* = 135)	23 (17)	1.17 [0.86, 1.44]	0.41
Male (*n* = 213)	34 (16)	0.95 [0.78, 1.15]	0.58

[a] Based on data available for both carotid EMT and stratified subgroups.
[b] HR per 0.10 mm increase in carotid EMT.

2.5. Statistical analysis

All data are expressed as mean and SD or frequency (%), unless otherwise stated. Carotid EMT is known to be greater in the right common carotid [1], and our results also showed this as a significant difference (left mean EMT 0.88 mm vs. right mean EMT 0.92 mm; $P = 0.003$). Residuals were used to calculate a side-adjusted mean EMT, which was used for further analysis. Independent predictors of events were calculated using Cox proportional hazards regression. Furthermore, the cohort was stratified by cardiovascular risk based on presence of known coronary artery disease, obesity status, diabetes mellitus, two-year cardiovascular risk score, and gender and modelled in these groups using univariate Cox regression. Significance was assumed at $2P < 0.05$ for all models. All statistical analyses were performed using SPSS for Windows 21.0 (SPSS Inc., Chicago, Illinois).

3. Results

3.1. Clinical characteristics

From the 444 patients in whom we assessed common carotid artery vascular structure, 437 had complete follow-up outcome analyses, and of these 348 (80%) had measurable carotid EMT (0.91 mm; SD 0.17 mm). Participant characteristics did not differ between those included in this analysis, and those without measurable carotid EMT (data not shown).

3.2. Outcomes

The median duration of follow-up was 24 months (interquartile range 12–36 months). Of the 57 events observed, there were 37 deaths (21 cardiovascular), 9 MIs, 1 stroke and 8 episodes of revascularization.

Carotid IMT from the near wall was found to be strongly associated with incident events (HR = 1.24 [95% CI: 1.08, 1.43] per 0.10 mm increase in carotid IMT; $P = 0.003$), consistent with a previous report detailing far wall carotid IMT in this cohort [6].

Cox regression showed no significant association of carotid EMT with cardiovascular outcomes (HR = 0.99 [95% CI: 0.85, 1.15] per 0.10 mm increase in carotid EMT; $P = 0.89$). This was similar after adjustment for BMI (HR = 0.99 [95% CI: 0.85, 1.15] per 0.10 mm increase in carotid EMT; $P = 0.90$). When stratified by presence of suspected CAD, obesity status, diabetes mellitus, 2-yr cardiovascular risk score, and gender, we found that carotid EMT was also not significantly associated with cardiovascular end-points in either high or low risk groups (Table 1). Sensitivity analyses showed similar effect estimates for both left and right carotid EMT (left EMT: HR = 1.10 [95% CI: 0.95, 1.25]; right EMT: HR = 0.98 [95% CI: 0.84, 1.14]).

4. Discussion

This study aimed to investigate the potential value of carotid EMT in predicting cardiovascular events and found that carotid EMT, unlike carotid IMT measured from the same arterial segment, was not significantly associated with cardiovascular events or survival in adults at high risk of CAD.

The prognostic value of carotid IMT as a predictor of cardiovascular events has previously been reported in this cohort and others [6,10]. Due to the comprehensive ultrasound scanning protocol used in this study, we were able to measure carotid EMT from these ultrasound images in 80% of participants. Nevertheless, the scanning protocol was not tailored specifically for prospective assessment of carotid EMT, resulting in the inability to assess EMT in the remaining images primarily due to poor visualization of the carotid media-adventitia interface. The methodology reported by Skilton et al. involves assessment of carotid EMT at a distance of 1 to 1.5 cm proximal to the carotid