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Usefulness of carotid intima-media thickness measurement as an indicator of generalized atherosclerosis: Findings from autopsy analysis

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ABSTRACT

Background: Ultrasound-determined carotid intima-media thickness (IMT) is widely used as an indicator of generalized atherosclerotic burden, but there are limited autopsy findings in support of the association, directly.
Methods: We performed an autopsy analysis (n = 111, mean 68.8 years; 65.0% men; 86% non-cardiovascular disease death) to examine the associations of microscopy-determined carotid IMT including plaque thickness with the severity of atherosclerosis in the generalized arteries.
Results: Microscopy-determined carotid IMT was associated with the extent of intima/media layer ratio of the vasculature, a marker of atherosclerosis, in each structure examined, i.e., coronary artery, cerebrovasculature, thoracic aorta, abdominal aorta, and iliac artery (R = 0.31–0.42; all $P < 0.01$). The prevalence of a necrotic core in the coronary artery, cerebrovasculature, thoracic aorta, abdominal aorta, and iliac artery increased in accordance with increasing microscopy-determined carotid IMT (all $P < 0.05$).
Conclusion: Our autopsy analysis confirms the validity of carotid IMT including plaque thickness as an indicator of generalized atherosclerosis.

1. Introduction

Carotid intima-media thickness (IMT) assessed by B-mode ultrasonography is a noninvasive and relatively available imaging modality; in the attempt to refine risk stratification and in response to the need for more aggressive preventative strategies, this approach is now widely used as an adjunct to traditional cardiovascular risk factors in order to assess atherosclerotic burden [1]. Since atherosclerosis is typically considered as a systemic disease, carotid IMT is viewed as a valuable reflection of the generalized atherosclerotic status of an individual. Indeed, several cross-sectional studies have demonstrated associations between ultrasound-determined carotid IMT and the severity of atherosclerosis in the coronary artery, cerebrovasculature, abdominal aorta, and femoral artery [2–5]; moreover, prospective study has found associations between carotid IMT and the incidence of coronary artery disease (CAD) and stroke events [6]. However, few studies have directly examined whether or not carotid IMT is associated with generalized atherosclerotic burden as confirmed by the gold standard of autopsy.

In the present study, we therefore directly examined by autopsy whether carotid IMT is associated with the severity of atherosclerotic changes in other arterial beds, i.e., in the coronary artery, cerebrovasculature, abdominal aorta, and iliac artery.

2. Methods

From 2000 to 2005, 118 autopsies were carried out in order to verify the cause of death at the Department of Pathology, Faculty of Medicine, University of Miyazaki, Japan. These autopsies were included in the present analysis (mean age, 68.9 ± 11.3 years; 64% men). The cause of death was described in Supplementary Table S1. Hypertension was defined as clinic blood pressure ≥140/90 mm Hg or the use of an anti-hypertensive agent. Diabetes mellitus was defined as a fasting glucose level ≥126 mg/dl,

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a random nonfasting glucose level ≥200 mg/dl, hemoglobin A1c ≥ 6.5%, or the use of an anti-hyperglycemic agent. Hyperlipidemia was defined as a total cholesterol level ≥220 mg/dl, low-density lipoprotein ≥140 mg/dl, triglyceride ≥150 mg/dl, or the use of an oral lipid-lowering agent.

The following vascular structures were isolated from formalin-fixed organs as described elsewhere [7]: bilateral carotid arteries, coronary arteries (i.e., right coronary artery, main left coronary artery, left anterior descending artery, and left circumflex artery), cerebrovasculature (i.e., bilateral middle cerebral artery), thoracic aortae (i.e., ascending aorta, aortic arch, and descending aorta), abdominal aorta, and bilateral iliac arteries. The cerebrovasculature could not be directly examined in 60 subjects in whom craniotomy was not permitted at autopsy. We cut the arteries longitudinally for macroscopic observation, and all arteries were immersion-fixed. Isolated arteries were cut transversely at 3 mm, and segments of the vessels showing the most stenosis or the thickest walls were selected for histological examination. Specimens with severe calcifications were decalcified ($n = 7$).

Two pathologists (T.I. and Y.S.) unaware of the patient's characteristics performed the autopsies. Seven autopsy subjects were excluded due to incomplete data sampling; hence, a total of 111 subjects (craniotomy, $n = 57$) were included in the present analysis. Histologic sections were stained with hematoxylin and eosin. To calculate the microscopy-based carotid IMT, we measured the combined thickness of the intimal and medial layers of the common carotid artery (CCA) by light microscopy using equipment that allowed for distance measurement with a precision of 1 μm (Olympus, Tokyo, Japan). In the present study, we calculated the microscopy-based CCA-IMT as the mean of the obtained value for the single thickest point, which includes plaque thickness, on both sides of the structure. Since we could not obtain the autopsy sample of the carotid bifurcation or internal carotid artery (ICA) in a significant number of cases, we only examined the CCA-IMT ranging from the proximal site of the carotid bifurcation to the junction with the subclavian artery. To assess the severity of atherosclerosis in the vasculature except for the CCA, we measured the maximum intima/media layer ratio (I/M ratio) within each vascular wall, since a thinning of the medial layer in relation to intimal thickenings has long been recognized as a validate marker of atherosclerosis [7]. All arteries were measured under non-perfusion-fixed conditions.

Reproducibility was assessed by blinded replicate readings of the CCA-IMT performed by 2 readers ($n = 30$); the mean difference for repeat measurements of CCA-IMT was 27 μm, and the intraclass correlation coefficient was $r = 0.91$ ($P < 0.001$). We also assessed the atherosclerotic burden of the arterial beds via classification into two categories, i.e., preatheromas and advanced lesions. According to the classification system defined by the American Heart Association, preatheromas included foam cell lesions (type II) and intermediate lesions (type III), and advanced lesions included necrotic cores (type IV) and fibroatheromas (type V) [8]. The Ethics Committee of the University of Miyazaki approved the study protocol, and the study was performed in accordance with the ethics standards of the Declaration of Helsinki.

All statistical analyses were performed with SPSS version 18.0 J software (SPSS, Chicago, IL). Since the extent of atherosclerosis in the systemic vasculature showed a skewed distribution, these variables were logarithmically transformed before analysis; associations among these variables were assessed by Pearson's correlation coefficients. Next, we divided our study participants into 3 groups based on the tertile of microscopy-determined CCA-IMT. Then, we compared the prevalence of a necrotic core in each of coronary artery, cerebrovasculature, thoracic aorta, abdominal aorta, and iliac artery among the 3 groups. The P value was obtained by chi-squared test. A 2-sided P value < 0.05 was defined as statistically significant.

3. Results

The clinical characteristics of the 111 autopsy subjects are shown in Table 1. Supplementary Table S2 shows associations of the microscopy-determined CCA-IMT and I/M ratio of generalized arterial beds with clinical characteristics. As shown in the Table, the extent of CCA-IMT was significantly higher in men compared with women, which difference remained unchanged even in non-smokers ($n = 50$) or those without hypertension ($n = 62$) (data not shown). The values of both CCA-IMT and coronary artery I/M ratio were significantly higher in patients with cardiovascular disease (CVD)-related deaths than in those without CVD-related deaths.

There were positive associations between microscopy-determined CCA-IMT and the I/M ratio of the structure in each of the following: coronary arteries, cerebrovasculature, thoracic aorta, abdominal aorta, and iliac artery (Fig. 1A–E). These associations were also examined by the differences of patient characteristics (Supplementary Tables S3–S6).

Next, we divided the microscopy-determined CCA-IMT values into the tertile groups, and we compared the prevalence of a necrotic core at each vascular structure among them. With a higher CCA-IMT, there was a significant increase in the prevalence of a necrotic core in the arterial beds (Fig. 2). The trend in which the prevalence of necrotic cores in the systemic arterial beds increased according to the tertiles of microscopy-determined CCA-IMT was similarly observed in both men and women (data not shown).

4. Discussion

The ultrasound-determined CCA-IMT is closely associated with the combined thickness of the intimal and medial layers of the CCA, as measured by microscopy on pathological examination [9–11]. Previous autopsy studies showed no difference between the ultrasound-determined CCA-IMT and microscopy-determined CCA-IMT [10], with close association ($R = 0.82$, $P < 0.001$) [11].

Table 1
Characteristics of autopsy subjects.

Patient characteristics ($n = 111$)	
Age, years	68.8 ± 11.0
Men, *n* (%)	72 (65)
Smoker, *n* (%)	61 (55)
Hypertension, *n* (%)	49 (44)
Diabetes, *n* (%)	26 (23)
Dyslipidemia, *n* (%)	9 (8)
Cause of death ($n = 111$)	
CVD-related death, *n* (%)	16 (14)
Non-CVD-related death, *n* (%)	95 (86)
Malignancy, *n* (%)	50 (45)
Infection or sepsis, *n* (%)	17 (15)
Collagen disease, *n* (%)	4 (4)
Other, *n* (%)	25 (22)
The extent of systemic atherosclerosis	
CCA-IMT*, μm ($n = 111$)	1360.8 (888.4–2084.4)
Coronary artery I/M ratio* ($n = 111$)	8.0 (3.7–17.4)
Cerebrovasculature I/M ratio* ($n = 57$)	2.1 (0.5–8.0)
Thoracic aorta I/M ratio* ($n = 111$)	3.4 (1.3–9.0)
Abdominal aorta I/M ratio* ($n = 111$)	4.8(1.6–14.6)
Iliac artery I/M ratio* ($n = 111$)	6.6 (2.1–21.4)

Data are expressed as the means ± SD or percentage. Variables with skewed distribution (asterisks) were expressed as geometric means (SD range). Cardiovascular disease (CVD) includes acute myocardial infarction, stroke, and congestive heart failure. Other causes of death included liver cirrhosis, amyotrophic lateral sclerosis, amyloidosis, and intestinal pneumonia.

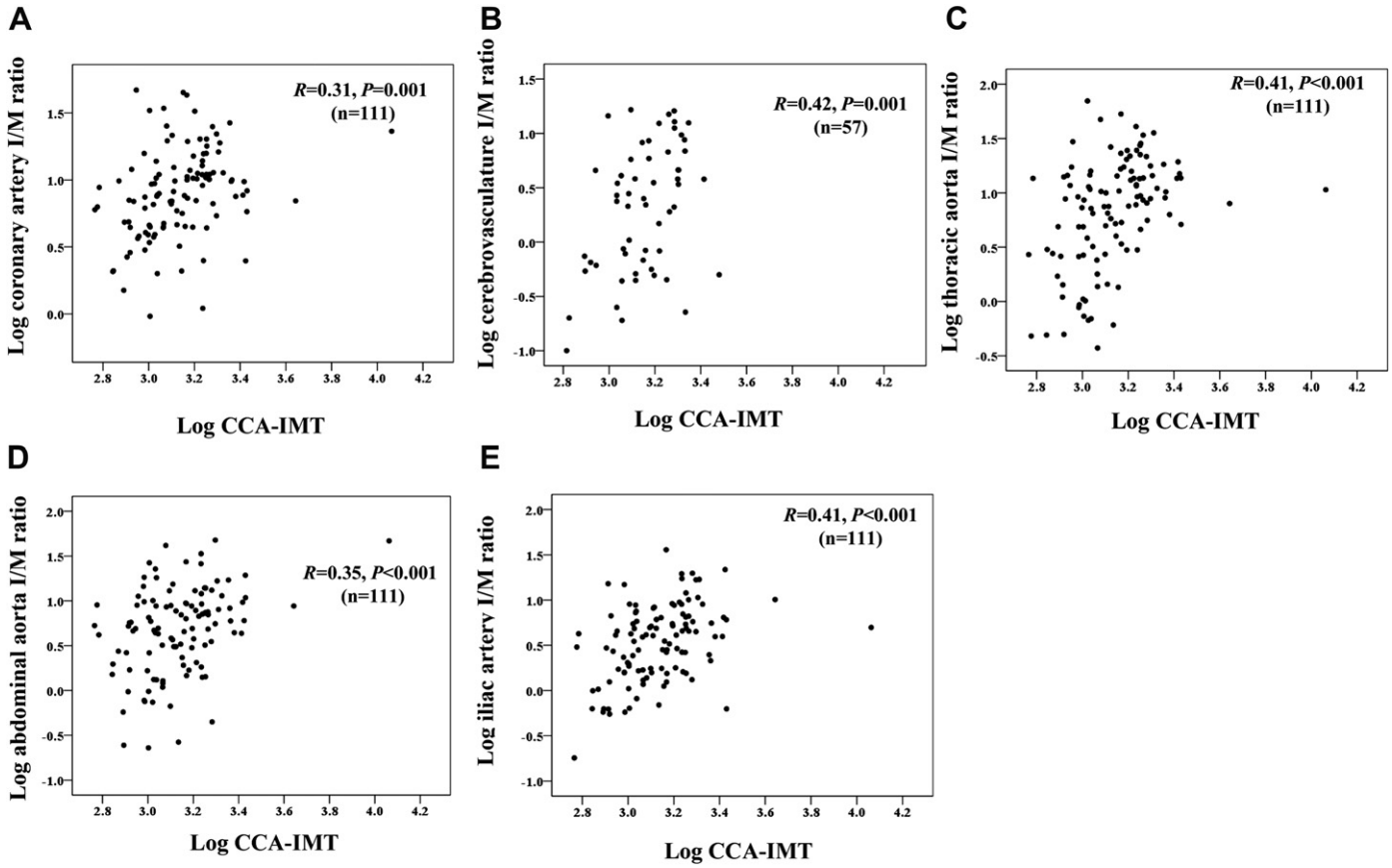

Fig. 1. Associations of microscopy-determined CCA-IMT with the maximum I/M ratio of other arterial beds. Each value was logarithmically transformed. Pearson's correlation method was used, and statistical significance was defined as $P < 0.05$.

Clinically, ultrasound-determined carotid IMT is recognized as reflecting the generalized atherosclerotic burden [2–6], despite the paucity of autopsy data that directly demonstrate such an association. One small autopsy survey ($n = 24$) showed that the CCA-IMT can be representative of plaque accumulation in other peripheral arteries, including the femoral artery, iliac artery, and renal artery [12]. Whereas Mitchell and colleagues demonstrated an association between the severity of coronary artery stenosis and that of carotid

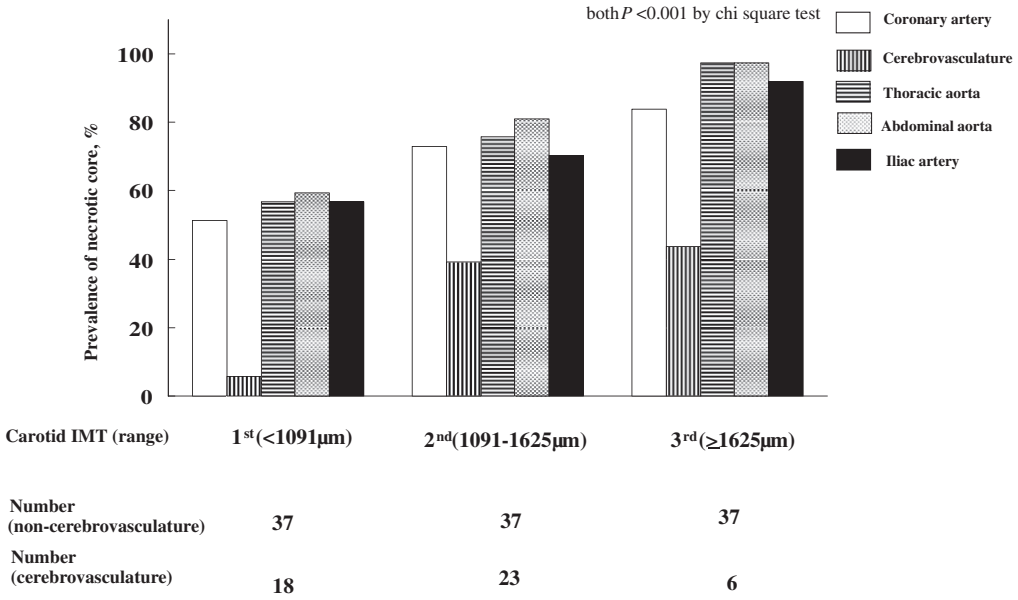

Fig. 2. Prevalence of a necrotic core in the systemic arterial beds according to tertiles of microscopy-determined CCA-IMT. The prevalence of a necrotic core in the systemic arterial beds was calculated for each microscopy-determined CCA-IMT tertile. The *P* value was obtained by chi-squared test among the tertiles.

or iliac artery stenosis, the association was not supported by statistical calculations [13].

Since ultrasound-determined carotid IMT is limited by an inability to distinguish the intimal from the medial layer, we calculated microscopy-based combined thickness of the intimal and medial layers of the CCA without separating them. Vascular intimal thickening does not necessarily imply atherosclerosis, but it does reflect nonatherosclerotic and adaptive responses to aging and mechanical stress. However, vascular intimal thickening and atherosclerosis are linked, as the biochemical, enzymatic, metabolic, inflammatory, and cellular changes within the thickened intima. In the present study, we also demonstrated that the prevalence of a necrotic core in the coronary artery, cerebrovasculature, thoracic aorta, abdominal aorta, and iliac artery increases in accordance with increasing tertiles of microscopy-determined CCA-IMT (Fig. 2). Thus, the CCA-IMT can reflect advanced atherosclerotic changes at other arterial beds that are not solely reflective of physiologically adaptive vascular responses.

Several limitations should also be mentioned. First, we were unable to evaluate the ICA-IMT and the IMT at the bifurcation due to incomplete data sampling upon autopsy. Since atherosclerotic lesions and plaque formation are more often found in bifurcations and the ICA than in the CCA, the pathological evaluation of IMT at the bifurcation and the ICA may yield a more accurate indicator of systemic atherosclerosis [14]. This limitation may have led us to underestimate the applicability of conclusions. Second, the longitudinal distribution/variability of CCA-IMT has recently been reported as being reflective of disease stage; this point could not be evaluated in the present study [15].

In conclusion, our data support a previously introduced concept that the carotid IMT measurements that include plaque thickness are a reflection of generalized atherosclerosis, hence ultrasound-determined carotid IMT including plaque thickness provides valuable information for identifying individuals most likely to develop cardiovascular risk during clinical management.

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Duality of interest

All authors have no relevant conflict of interest to disclose.

Contribution statement

Author contributions are as follows; T.I., Y.Y., Y.S., K.H., K.M., S.F., K.K., K.K., and Y.A. designed the study and collected the data, Y.Y., Y.S., and Y.A. analyzed and interpreted the data, T.I., Y.Y., and Y.S. wrote the paper, K.H., K.M., S.F., K.K., K.K., and Y.A. supervised the study and revised the manuscript. Final approval of the version to be published was achieved in all authors, and Yuichiro Sato takes responsibility for the contents of the article.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.atherosclerosis.2012.10.033.

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