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Article

Relation between age and carotid artery intima-medial thickness: a systematic review

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Abstract

Background: Assessment of carotid artery intima-medial thickness (cIMT) represents a popular measure of atherosclerosis and is predictive of future cardio- and cerebrovascular events. Whilst older age is associated with a larger cIMT, little is known whether this increase in cIMT follows a linear relationship with age or that this relation is affected under influence of cardiovascular diseases (CVD) or risk factors.

Hypothesis: We hypothesize that the relation between cIMT and age is non-linear and is affected by CVD or risk factors.

Methods: A systematic review of studies that examined cIMT in the general population and human populations free from cardiovascular disease/risk factors was undertaken. The literature search was conducted in PubMed, Scopus and WebofScience. Seventeen studies with 32 unique study populations, involving 10,124 healthy individuals free from CVD risk factors, were included. Furthermore, seventy-five studies with 147 unique study populations were included, involving 75,898 individuals from the general population (with and without CVD risk factors).

Results: A strong positive association was evident between age and cIMT in the healthy population, demonstrating a gradual, linear increase in cIMT that did not differ between age decades ($r=0.91$, $p<0.001$). Although populations with individuals with CVD demonstrated a higher cIMT compared to populations free of CVD, a linear relation between age and cIMT was also present in this population.

Conclusion: Our data suggests that cIMT is strongly and linearly related to age. This linear relationship was not affected by CVD or risk factors.

Key words: wall thickness; atherosclerosis; cardiovascular risk; cardiovascular disease; aging

Running title: Relation between age and cIMT

Introduction

Atherosclerosis plays a major role in the development of cardiovascular disease (CVD),(1) and is characterised by thickening of the tunica media and intima of the arterial wall.(2) Since thickening of the arterial wall occurs before clinical presentation of plaque formation, measurement of the carotid artery intima-medial thickness (cIMT) is a common and early surrogate marker for atherosclerosis. cIMT has a strong and independent predictive capacity for future cardiovascular (CV) and cerebrovascular events.(3-6) More specifically, an increase of 0.10 mm in cIMT is associated with an increased risk of 18% for future stroke and 15% for myocardial infarction.(5)

Several previous studies, typically adopting a cross-sectional design, provided compelling evidence that middle-aged and older people have a larger cIMT than young adults.(7-13) However, relatively little is known whether the relation between advancing age and cIMT follows a linear or non-linear relation. The relationship between the occurrence of cardiovascular events and age is non-linear, characterised with a sudden increase in event rate after the age of 50 years.(14) In accordance, annual progression in cIMT may be non-linear and moderated by the specific age-group that is studied, possibly demonstrating a smaller increase in cIMT in young *versus* older individuals. The reported annual rate of increase in cIMT per year varies substantially (0.003-0.010 mm/year) between studies.(9, 15-18) Such heterogeneity may, at least in part, relate to the different age groups studied, but also the presence of CV disease/risk factors. Therefore, the first aim is to explore whether cIMT holds a non-linear relationship with older age in a healthy older population.

In addition to the impact of age on the progression of cIMT, little work explored whether presence of CV disease/risk can moderate the steepness of the relation between age and cIMT. Therefore, the

second aim of this review was to examine the influence of the presence of CV disease/risk factors on the relationship between age and cIMT. We expect a strong relation between age and cIMT in healthy individuals, with a stronger age-related increase after 50-years, an observation that would match the sudden increase in CV events in those older than 50 years. Furthermore, we expect that the presence of CV disease/risk will accelerate the steepness of the relation between age and cIMT.

Methods

Data source

A systematic review of peer-reviewed studies that examined cIMT in asymptomatic human populations was undertaken. The literature search was conducted using Pubmed (1-1-2003 until 30-6-2014). Key MeSH subject terms and keywords pertaining to the carotid artery IMT were included. The following search string was employed: *((wall thickness[tiab]) OR ((intima media[tiab]) OR (intimal medial[tiab]) AND (Thickness[tiab])) OR (imt[tiab]) OR ((Tunica Intima/ultrasonography[Mesh]) AND (Tunica Media/ultrasonography[Mesh]))) AND ((Carotid artery[tiab]) OR (cca[tiab]) OR (Carotid Artery, Common[Mesh])) AND (Aged[MeSH Terms]) NOT disease'.* We cross-checked this search with EMBASE and WebofScience. Reference lists of relevant published works selected were also examined to identify additional pertinent studies.

Data extraction

The search process identified 684 studies for potential inclusion. The first stage of the filtration process reviewed titles and abstracts. This process was completed independently by two authors (IvdM, BvD) who later met to reach mutual consensus. Two hundred and fifty six studies met the initial inclusion criteria, defined as: 1) individuals without established cardiovascular risk or disease, 2) full text

availability, 3) sample size (n≥60) and 4) individuals ≥18 years old. Subsequently, two other independent members of the research team (HJ, DHJT) independently reviewed all remaining studies. After the initial selection step, resulting in 246 manuscripts (Figure 1), another 167 studies were excluded because of an incomplete data set or a lack of description of the study population. We also identified one study that presented a data set that was published more than once (the RISC, Relationship between Insulin Sensitivity and Cardiovascular disease, Study). For this data set, we selected the study with the largest population and carefully checked whether the other studies indeed included individuals that were also included in the study with the largest sample size. We also checked for every publication the ultrasound technique that was used and the way the cIMT was subsequently analysed. All studies measured the cIMT in the far wall of the common carotid artery, except for 3 studies. They calculated the mean of the cIMT for the far and near wall in the common carotid artery.(19-21) As the outcomes of these studies were in line with the other studies, we did not exclude these studies. All studies used non-contrast enhanced scans and have adopted an (semi)automated analysis technique. No study used the presence of carotid plaque as an exclusion criteria, just one study used carotid stenosis of more than 40% as an exclusion criteria.(22)

Finally, this resulted in 75 unique manuscripts, from which 147 populations were included (see Table 1 for detailed information of each study). At whole study level, demographics for combined data ranged from 18 to 96 years and included 75,898 individuals. For our second aim, from these 75 studies, we selected the studies that included healthy asymptomatic individuals only. They excluded individuals who reported having previously confirmed diabetes, dyslipidemia, hypertension or CVD. This resulted in a group of 17 manuscripts, including 32 study populations. In total 10,124 individuals were included for the analysis of the healthy asymptomatic individuals.

Statistical analysis

Data on cIMT and age were extracted as group mean ± SD for each study. To explore the impact of age on cIMT, we calculated a regression coefficient using a linear regression model. This analysis was repeated for the subgroup analysis of studies that included healthy individuals only. All statistical analysis was performed with SPSS version 22 (Armonk, NY: IBM Corp). Statistical significance was set at $p \leq 0.05$.

Results

Relation between age and carotid IMT in the healthy population

We included 32 study populations encompassing n=10,124 healthy, asymptomatic individuals without cardiovascular risk and/or disease. The mean age for these individuals was 44±8 years and the mean cIMT was 0.61±0.11. This population of healthy asymptomatic individuals demonstrated an age-related, linear increase in cIMT of 0.008±0.001 mm/year (R^2=0.84, Figure 2). cIMT could be estimated using the following equation: cIMT (mm) = 0.249 + 0.008 * age (years). Non-linear curves did not improve the fit between age and cIMT, indicating that the annual increase in cIMT follows a linear relation.

Influence of CVD disease/risk on the relation between age and carotid IMT

To assess the influence of the presence of CVD disease/risk, we also included 147 populations from the general population, encompassing 75,898 individuals ranging from 18 to 96 years. Across all age groups, cIMT was higher in the population with possible CVD disease/risk compared to healthy, asymptomatic individuals (0.70±0.13mm *versus* 0.61±0.11mm, respectively). Whilst the general population demonstrates a comparable age-related (linear) increase in cIMT compared to the healthy,

asymptomatic population (0.007±0.001 mm/year), the strength of this relation was lower (R^2=0.36; Figure 3). The equation for the whole group was: cIMT (mm) = 0.323 + 0.007 * age (years). Adopting non-linear curves to examine the relation between age and cIMT did not improve the fit between both parameters.

Discussion

We found a strong linear relation between age and cIMT in healthy, asymptomatic individuals, suggesting that cIMT progresses linearly with older age. Secondly, the general population (including individuals with CV risk and/or disease) demonstrated a larger cIMT across all age groups, whilst the annual increase in cIMT was comparable to healthy, asymptomatic individuals. This suggests that CV disease and risk affects cIMT, but does not impact the relation of age on cIMT. Taken together, this systematic review highlights the presence of a consistent, linear increase of cIMT across lifespan, whilst presence of CV disease and/or risk does not affect the direction and linear nature of this relation.

Various papers have demonstrated a steeper increase in risk of cardiovascular events later in life (>50 years).(14) Accordingly, we expected to find a larger annual increase in cIMT after the 4^{th} or 5^{th} life decade, especially given the strong and independent predictive capacity of cIMT for future cardiovascular events. Nonetheless, we observed a strong, linear relationship between age and cIMT, which suggests that the relation between age and cIMT is similar across the age span. A recent study, that reported reference intervals for cIMT, confirms the presence of a strong, linear relationship between age and cIMT.(9) Furthermore, in a previous paper we reported that age-related wall thickening in healthy asymptomatic individuals occurs similarly between the carotid artery as well as peripheral arteries in upper and lower limb.(10) These data support the idea that the annual increase of

cIMT closely follows the chronological ageing process. More specifically, our data from healthy individuals even suggests that 84% of the cIMT can be explained by age itself.

As a second aim we assessed whether the presence of CVD affects the relation between age and cIMT. Interestingly, those with CV disease or risk factors demonstrated a larger cIMT, which was present to a similar extend across all age decades. This suggests that the presence of CV disease and/or risk increases cIMT, but does not affect the annually increase in cIMT that can be attributed to age *per se*. Interestingly, the strength of the correlation between cIMT and age attenuated when populations that included individuals with cardiovascular risk/disease were included.

Our findings raise the question which mechanisms contribute to the gradual, age-related thickening of the carotid wall, and whether this relates to local and/or systemic processes. In a previous study, we examined the impact of age on wall thickening in atherosclerosis-prone (i.e. carotid and lower limb) and atherosclerosis-resistant arteries (i.e. upper limb), and whether sex alters the impact of age on wall thickening using a cross-sectional design. We found that age-related wall thickening, evident in the carotid artery, is similarly present in conduit arteries of the upper limbs in men and women.(10) This suggests that conduit artery wall thickness increases to a similar extent in all vessels with advanced age and that this process is comparable between men and women. This supports the hypothesis that wall thickening represents a systemic process that is present in all vessels, and may be independent from the process of developing plaque formation and/or plaque vulnerability in healthy, asymptomatic individuals.

Clinical importance. The strong correlation of cIMT with age in healthy populations raises questions about the independent predictive capacity of cIMT for future cardiovascular events in healthy

individuals. Not only the predictive capacity for cardiovascular events, but also the use of cIMT to study the effect size in intervention studies is probably limited. A meta-analysis found that the addition of cIMT to the Framingham Risk Score (which includes 'age' as a factor) led only to a small improvement in the 10-year risk prediction of first-time myocardial infarction or stroke.(23) Furthermore, the 13-year follow-up of The Tromsø study demonstrated that plaque area was related to traditional risk factors for atherosclerosis (blood pressure, cholesterol, smoking), while cIMT was more closely related to age.(24) A recent publication from the USE-IMT collaboration, a large ongoing meta-analysis, supports this latter hypothesis.(25) Given the strong relationship between age and cIMT in our study, cIMT may be more a marker of chronological age rather than cardiovascular risk *per se* in healthy volunteers. Therefore, adding cIMT to a risk prediction model that already included age as a factor may have limited additional value when examining healthy individuals. Besides this plaque presence,(26-29) burden (30, 31) and stability,(32-35) rather than wall thickness *per se*, may serve as a stronger predictor for future cardiovascular events in healthy, asymptomatic individuals.

Limitations. A possible limitation of our review is the heterogeneity in techniques to measure the cIMT across the studies. Values of cIMT can be obtained by manual or automated analyses techniques of B-mode ultrasound imaging, whereas automated edge-detection on the basis of radiofrequency signal processing ('echotracking') of B- and M-mode ultrasound imaging is preferred over manual analysis techniques and has been shown to be more accurate.(36-38) Since we included articles from 2003 onward, all studies have adopted the (semi)automated analysis technique and, therefore, the heterogeneity in techniques for cIMT assessment are unlikely to have impacted our primary outcome.

In conclusion, our systemic review reveals that advanced age is strongly and linearly associated with an increase in carotid artery IMT in the general population as well as in healthy individuals. The presence

of cardiovascular risk factors in the general population led to a consistently thicker cIMT compared to healthy individuals. Despite this difference in cIMT between populations with and without CV risk factors, the age-related increase in cIMT is comparable in both populations (0.007 *vs* 0.008 mm/year). This suggests that CV risk factors itself affect cIMT rather than the CV risk factors affect the process of ageing on the cIMT. These observations may have clinical relevance, since the strong association between age and cIMT questions the potential independent predictive capacity of cIMT for future cardiovascular events in healthy individuals.

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FIGURE LEGEND

FIGURE 1. PRISMA Flow Diagram with schematic presentation of the study assessment and exclusion stages.

FIGURE 2. Relation between age and carotid artery intima-media thickness (cIMT) from 32 studied populations that included healthy asymptomatic individuals (n=10,124). Each symbol represents a single studied population, with the size of the symbol being related to the sample size (n=<250; n=250-1,000; n=>1,000).

FIGURE 3. Relation between age and carotid artery intima-media thickness (cIMT) from 147 studied populations that included individuals from the general population (n=75,898). Each symbol represents a single studied population, with the size of the symbol being related to the sample size (n=<250; n=250-1,000; n=>1,000).