34th Annual International Conference of the IEEE EMBS
San Diego, California USA, 28 August - 1 September, 2012

Aging-related changes and reference values for the carotid intima-media thickness in a Uruguayan Population

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Abstract. **Carotid intima-media thickness (CIMT) is a well-established subclinical marker of atherosclerosis. Non-invasive vascular evaluation has emerged as a useful tool to aid in individual cardiovascular (CV) risk stratification and diagnose. The use of CIMT in CV risk stratification requires knowing the expected reference values for the population studied. Our aim were: a) to evaluate the relationship between aging and CIMT, b) to analyze gender and side (right vs left) related-differences in CIMT and c) to determine the CIMT reference values for an Uruguayan population taking into account aging-related CIMT changes. Methods: 367 asymptomatic subjects without known CV disease or risk factors were included in the study. Subjects were divided into six age groups. High-resolution B-mode ultrasound images of both (right and left) common carotid arteries were obtained based on the techniques and recommendations described in international consensus. Results: No significant age-related differences in CIMT between men and women were observed. The mean left CIMT was thicker compared with right CIMT in groups 4, 5 and 6. However, there were no significant differences in those groups. The nomogram model was constructed from data base, in which the 95% confidence interval was considered. Diagnosis thresholds were determined as well. Conclusion: We define reference values of CIMT for our population using gold standard techniques which contributes to standard techniques which contributes to an improved insight into clinical practice and can be used routinely for evaluation.**

I. Introduction

MAIN focuses and strategies for atherosclerotic cardiovascular disease (ACVD) prevention have been the detection and treatment of cardiovascular risk factors. Results obtained with such approach are limited and ACVD is still a leading cause of morbidity and mortality all around the world. However, ACVD has a long subclinical stage that could provide a unique opportunity for the development of strategies to halt or slow the disease progression and to prevent its complications [1], [2].

Non-invasive vascular evaluation has emerged as a useful tool to aid in individual cardiovascular (CV) risk stratification and diagnosis [1], [3]. Among the different structural and functional vascular parameters proposed to stratify CV risk and to early detect vascular changes associated with ACVD the carotid intima-media thickness (CIMT) has shown to be of value. An increased CIMT is a subclinical marker of atherosclerosis and a predictor of cerebrovascular events including stroke [4]. Additionally, and increased CIMT is associated with the presence of atherosclerotic plaques in other localizations and with an increased risk of coronary heart disease (CHD) [1].

On the other hand, a given value, or changes in CIMT levels do not always represent increased CV risk or vascular disease, but could be explained by factors like normal aging and/or ethnicity.Then, the use of CIMT in CV risk stratification and vascular disease diagnose requires knowing the expected (reference) values for the population studied. Related with this, it is noteworthy that Latin America encompasses a wide variety of geographic, ethnic, and socioeconomic differences. Such diversity would be reflected in the prevalence/profile of CV risk factors, atherosclerotic vascular changes and/or in the normal/reference values of different vascular parameters [5]. For instance, the CARMELA study showed differences in CV risk and vascular characteristics, in particular in the CIMT, among Latin American populations [5].

In this context, this work aims were: a) to evaluate the relationship between aging and CIMT, b) to analyze gender and side (right vs. left) related-differences in CIMT and c) to determine the CIMT reference values for an Uruguayan population taking into account aging-related CIMT changes.

II. Methods

The Human Research Committee of the Republic University (Uruguay) approved all procedures. Subjects gave written informed consent. The study was carried out according to international ethic rules and the Helsinki Declaration principles.

The present study was carried out in the context of CUiiDARTE Project, a population-based national study, designed to assess vascular aging, CV risk and sub-clinical

Manuscript received April 15, 2011. This work was supported in part by the ANII (Agencia Nacionald de Investigación e Innovación) under FCE2007-635 and FCE2007-638.

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atherosclerosis by means of the evaluation of structural and functional vascular parameters

1. *Study population and subjects groups*

By cluster sampling method, subjects (n=367, 196 women) from 5 Uruguayan cities, asymptomatic and without known cardiovascular disease, Diabetes Mellitus, renal failure or CV risk factors (other than age and gender) were included in this study. None of the subjects was taking CV acting medications [6].

Subjects were divided into the following age groups: G1: 10-19 years old (n=38), G2: 20-29 years old (n=124), G3: 30-39 years old (n=34), G4: 40-49 (n=54), G5: 50-59 years old (n=79) and G6: 60-69 years old (n=38).

Experimental protocol

Vascular evaluation started after 9-12 hours overnight fast. Exercise, caffeine, alcohol, and vitamin C were avoided prior (at least six hours) to the examination. Venous blood samples were drawn and processed immediately using commercially available kits and/or laboratory methods. Subjects rested for 5-10 minutes in supine position in a temperature-controlled room, to reach stable haemodynamic conditions.

Ultrasound evaluations in CUiiDARTE are done based on the techniques and recommendations described in international consensus [7].

High-resolution B-mode ultrasound images of both (right and left) common carotid arteries were obtained using a 10MHz linear-array transducer connected to a portable Ultrasound System (MicroMaxx, Sonosite; Bothell, WA, USA). Measurements (still images and video clips/cine loops) were digitally stored for off-line analysis. Before and during ultrasound examination (at 3-minutes intervals), brachial blood pressure measurements were obtained using an oscillometric device (Omron HEM-433INT Oscillometric System; Omron Healthcare Inc., Illinois, USA). The average was considered as the blood pressure level.

Transverse and longitudinal views from the proximal common carotid artery (CCA) to the peripheral segments of the internal and external carotid artery (ICA and ECA respectively) were obtained to determine the presence of carotid plaques in the CCA, bulb, ICA and ECA. Near and far walls were analyzed and images were obtained from anterior, lateral and posterior angles. A carotid plaque was defined as focal wall thickening at least 50% greater than that of the surrounding vessel, a thickening that protrudes into the lumen 0.5 mm or as a region with CIMT greater than 1.5 mm [7].

After plaque screening, longitudinal views of the CCA were acquired and a video (cine-loop) of at least 10 seconds was recorded and stored. The CIMT and beat-to-beat diameter waveforms were obtained and analyzed off-line using a step-by-step border detection algorithm applied to each digitized image (Hemodyn-4M software, Buenos Aires, Argentina) [8] [Figure 1]. A region 1.0 cm proximal to the carotid bulb was identified, and the far wall CIMT determined as the distance between the lumen-intima and the media-adventitia interfaces. The used software performs multiple automated or semi-automated measurements along 1 cm and averages them, increasing the accuracy of the measures. Furthermore, compared with manual techniques, the use of software improves CIMT measurement reproducibility and reduces observer bias.

The instantaneous internal diameter (from the leading edge of the near wall intima-lumen interface to the intima-lumen interface of the far wall) waveform was obtained [Figure 1].

Statistical analysis

The "reference value population" was defined by all included subjects. To determine diagnostic thresholds for men and women combined, we rounded the 95th prediction bands. For each age group, 2.5th, 25th, 50th, 75th and 97.5th percentiles were calculated.

Aging related changes in CIMT were evaluated using ANOVA + Bonferroni test. Linear regression analysis was used to assess the relationship between CIMT and age. Gender difference in CIMT were evaluated using two tailed Student-t test. A $p<0,05$ was considered significant.

Statistical analyses were done using Statistical Package for the Social Sciences 17.0 for Windows software.

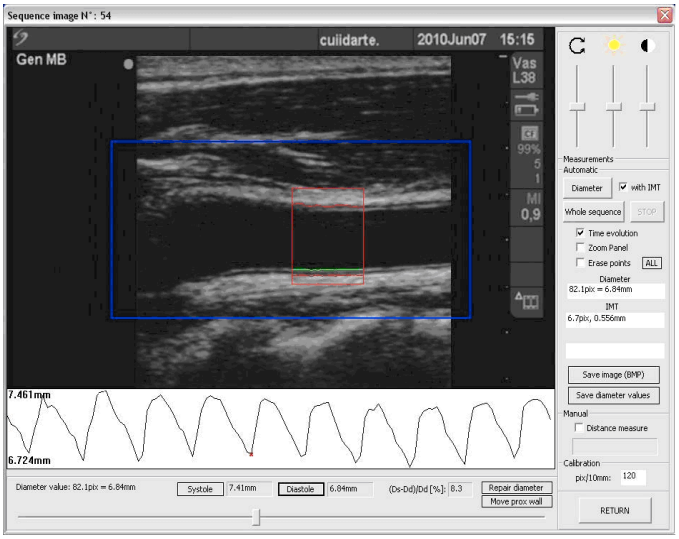

Fig 1. Screen of the Software used to measure CIMT (distance between green and red lines in the far wall) and the instantaneous diameter (distance between red lines) and to obtain the diameter waveforms (bottom) from B-Mode echographic videos.

III. RESULTS

The carotid arteries could be correctly visualized by ultrasonography, and CIMT measurements were carried out in all subjects. None of the subjects in G1 and G2 had atherosclerotic plaques. On the contrary, the incidence of carotid plaque was 2.9%, 15%, 20% and 26% in G3-6 respectively.

Subjects with atherosclerotic plaques were excluded when determining CIMT reference values; 35 subjects were excluded and 332 subjects were considered for further analysis.

Table 1 shows the subjects´ anthropometric, hemodynamic and laboratory data.

Table 1	10-19.	20-29	30-39	40-49	50-59	60-69
N=332	38	124	33	46	63	28
Age (Year)	15 ± 2	21 ± 2	33 ± 2	45 ± 3	54 ± 3	64 ± 4
Anthropometric measurements						
Height (m)	165 ± 9	167 ± 9	166 ± 9	165 ± 9	161 ± 8	160 ± 10
Weight (Kg)	57 ± 11	63 ± 12	71 ± 16	75 ± 16	74 ± 16	71 ± 12
BMI (Kg/m2)	21 ± 3	23 ± 4	24 ± 5	23 ± 3	25 ± 4	24 ± 3
Peripheral hemodynamics parameters						
Systolic Pressure (mmHg)	118 ± 13	125 ± 12	126 ± 12	128 ± 11	123 ± 13	126 ± 12
Diastolic Pressure (mmHg)	64 ± 10	71 ± 8	74 ± 11	78 ± 9	78 ± 11	77 ± 10
Pulse Pressure (mmHg)	48 ± 6	51 ± 8	53 ± 10	54 ± 8	56 ± 9	61 ± 11
Heart Rate (bpm)	78 ± 13	73 ± 11	72 ± 8	72 ± 12	73 ± 12	63 ± 10
Laboratory						
Total cholesterol (mg/dl)		160 ± 23	176 ± 32	196 ± 21	205 ± 31	175 ± 33
HDL cholesterol (mg/dl)		66 ± 20	55 ± 17	51 ± 12	59 ± 19	50 ± 14
LDL cholesterol (mg/dl)		99 ± 25	134 ± 26	139 ± 26	140 ± 31	112 ± 40
Glycaemia (mg/dl)		84 ± 6	76 ± 28	80 ± 18	86 ± 18	84 ± 18

No significant age-related differences in CIMT between men and women were observed. [Figure 3].

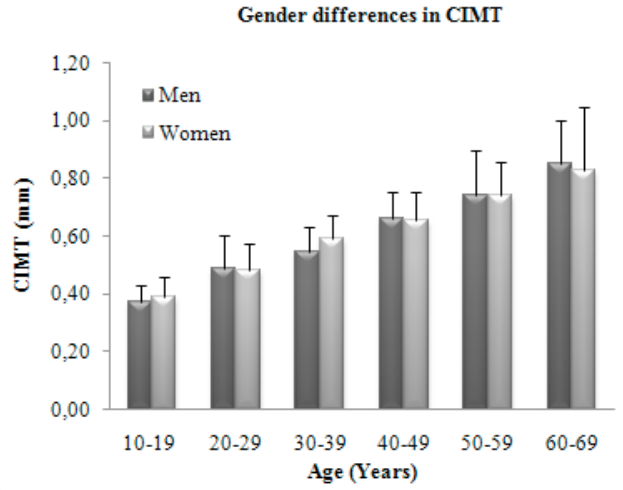

Fig 3. CIMT values between sex. Values expressed as mean ± Standard deviation. p>0.05 in all groups.

Figure 4 shows side-related differences in intima-media thickness of carotid arteries.

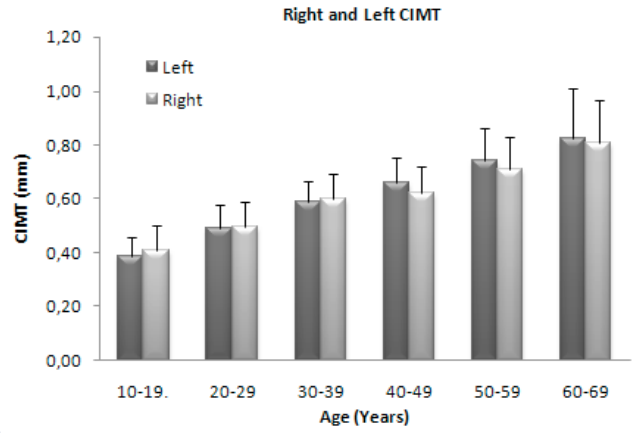

Fig 4. Age related changes of Left and Right CIMT. p>0.05 in all groups.

The mean left CIMT was thicker compared with right CIMT in groups 4, 5 and 6. However, there were no significant differences in those groups.

Taking into account that there were no side and/or gender related differences in CIMT integrated reference values were determined.

Table 2 shows CIMT reference values expressed as mean, standard deviation and 2.5th, 25th, 50th, 75th and 97.5th percentiles. All comparisons were determined using ANOVA + Bonferroni test.

The mean CIMT increased with age from group G1 to G6 ($p<0.001$). The nomogram model was constructed from data base.

The mean value (solid line) and the 95% confidence interval (dashed lines) are shown in Figure 2. In order to determine diagnostic thresholds for men and women combined, we rounded the 95th prediction bands.

Table 2	10-19.	20-29	30-39	40-49	50-59	60-69
N	38	124	33	46	63	28
Mean	0.39	0.49 ^{a}	0.59 ^{ab}	0.66 ^{abc}	0.74 ^{abcdf}	0.82 ^{abcde}
SD	0.07	0.09	0.08	0.09	0.12	0.18
P 2.5	0.30	0.35	0.42	0.44	0.53	0.52
P 25	0.35	0.42	0.54	0.61	0.67	0.72
P 50	0.40	0.49	0.58	0.68	0.73	0.80
P 75	0.40	0.55	0.66	0.71	0.81	0.90
P 97.5	0.50	0.67	0.69	0.81	0.97	1.28

Data are expresed as Mean, standard deviation and 2.5th, 25th, 50th, 75th, and 97.5th percentiles.
p<0.05 was considered statistically significant.

a Compared with 10-19 years old group.
b Compared with 20-29 years old group.
c Compared with 30-39 years old group.
d Compared with 40-49 years old group.
e Compared with 50-59 years old group.
f Compared with 60-69 years old group.

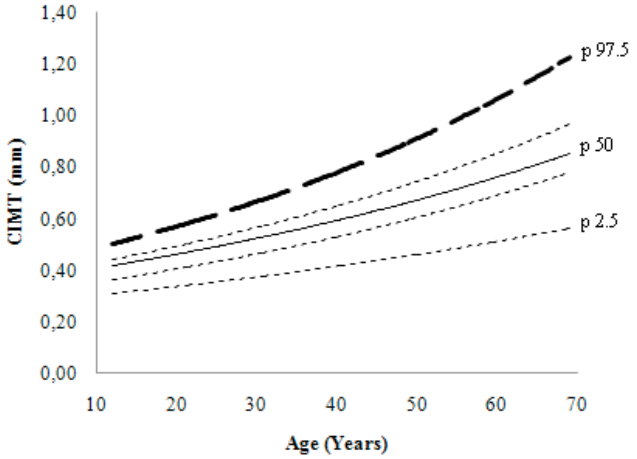

Fig 2. Nomogram for CIMT values and age-related changes. The dashed lines represent the 95% confidence interval 2.5th,50th and 97.5th percentiles and mean (normal distribution).

IV. Discussion

In the present study we contribute in the characterization of CIMT reference values in a Uruguayan Population. The definition of reference values represent a critical step in the implementation of CIMT as a clinical tool for detecting sub-clinical organ damage in routine patient workup.

Additionally, there is a great interest to differentiate the expected (normal) vascular changes due to aging and those related with vascular disease. In this context, many authors contribute in the establishment of reference values of different populations.

This issue was recently assessed in the Cardiovascular Risk Factor Multiple Evaluation in Latin America study (CARMELA) [5], which results underlined the differences in age effects across cities.

CIMT in the Uruguayan population showed similar but not equal levels and age-related changes when compared to other Latin American populations [5]. This is also true when our results are analyzed comparing them with those obtained in other populations. About this, the age-related changes in CIMT evidenced in our population showed a behavior located in the middle between the group in which the variation is large (>0.01mm/year), consisting of USA [9,10], central Europe [11,12] and Nordic countries [13], and that with minor age effects, which comprises Spain [14], and France [13, 15] Taking into account that discussed above, and as was previously suggested, since CIMT levels and changes would differ among regions and ethnic groups, the CIMT distribution in a particular population must be defined prior to its use in cardiovascular diagnosis and/or risk stratification [5].

V. CONCLUSION

Age-related CIMT profiles were obtained in the context of the CUiiDARTE Project for a Uruguayan asymptomatic population. There were no evidences of gender or side (right and left carotid artery) differences.

We define reference values of CIMT for our population using gold standard techniques which contributes to a greater approach into clinical practice and routinely used for evaluation of cardiovascular risk.

ACKNOWLEDGMENT

We thank Elbio Agote for his technical assistance and to the medicine students who agreed to participate in the study.

REFERENCES

[1] Naghavi M, Falk E, Hecht HS, Jamieson MJ, Kaul S, Berman D, Fayad Z, Budoff MJ, Rumberger J, Naqvi TZ, Shaw LJ, Faergeman O, Cohn J, Bahr R, Koenig W, Demirovic J, Arking D, Herrera VL, Badimon J, Goldstein JA, Rudy Y, Airaksinen J, Schwartz RS, Riley WA, Mendes RA, Douglas P, Shah PK; SHAPE Task Force. From vulnerable plaque to vulnerable patient--Part III: Executive summary of the Screening for Heart Attack Prevention and Education (SHAPE) Task Force report. Am J Cardiol. 2006 Jul 17;98(2A):2H-15H.

[2] Greenland P, Alpert JS, Beller GA, Benjamin EJ, Budoff MJ, Fayad ZA, Foster E, Hlatky MA, Hodgson JM, Kushner FG, Lauer MS, Shaw LJ, Smith SC Jr, Taylor AJ, Weintraub WS, Wenger NK, Jacobs AK, Smith SC Jr, Anderson JL, Albert N, Buller CE, Creager MA, Ettinger SM, Guyton RA, Halperin JL, Hochman JS, Kushner FG, Nishimura R, Ohman EM, Page RL, Stevenson WG, Tarkington LG, Yancy CW; American College of Cardiology Foundation; American eart Association. 2010 ACCF/AHA guideline for assessment of cardiovascular risk in asymptomatic adults: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol. 2010 Dec 14;56(25):e50-103.

[3] Bia D, Zocalo Y, Farro I, Torrado J, Florio L, Lluberas R, Armentano R. Health Informatics Design for Assisted Diagnosis of Sub-clinical Atherosclerosis, Structural and Functional Arterial Age Calculus and Patient-specific Cardiovascular Risk Evaluation. IEEE Trans Inf Technol Biomed. 2012 Mar 14

[4] Lorenz MW, von Kegler S, Steinmetz H, Markus HS, Sitzer M. Carotid intima-media thickening indicates a higher vascular risk across a wide age range: prospective data from the Carotid Atherosclerosis Progression Study (CAPS). Stroke. 2006 Jan; 37(1):87-92.

[5] Touboul PJ, Vicaut E, Labreuche J, Acevedo M, Torres V, Ramirez-Martinez J, Vinueza R, Silva H, Champagne B, Hernandez-Hernandez R, Wilson E, Schargrodsky H; CARMELA Study Investigators. Common carotid artery intima-media thickness: the Cardiovascular Risk Factor Multiple Evaluation in Latin America (CARMELA) study results. Cerebrovasc Dis. 2011;31(1):43-50.

[6] Bia D, Zócalo Y, Farro I, Torrado J, Farro F, Florio L, Olascoaga A, Brum J, Alallón W, Negreira C, Lluberas R, Armentano RL. Integrated Evaluation of Age-Related Changes in Structural and Functional Vascular Parameters Used to Assess Arterial Aging, Subclinical Atherosclerosis, and Cardiovascular Risk in Uruguayan Adults: CUiiDARTE Project. Int J Hypertens. 2011;2011:587303.

[7] J. Stein, C. Korcarz, R. Hurst, E. Lonn, C. Kendall, E. Mohler, et al. "Use of carotid ultrasound to identify subclinical vascular disease and evaluate cardiovascular disease risk: a consensus statement from the American Society of Echocardiography Carotid Intima-Media Thickness Task Force," J Am Soc Echocardiogr. Feb 2008, 21(2), pp. 93-111.

[8] Bia D, Zócalo Y, Armentano R, Laza S, Pérez H, Craiem D, Saldías M, Alvarez I. Non-invasive biomechanical evaluation of implanted human cryopreserved arterial homografts: comparison with pre-implanted cryografts and arteries from human donors and recipients. Ann Biomed Eng. 2009 Jul;37(7):1273-86.

[9] O'Leary DH, Polak JF, Kronmal RA, Manolio TA, Burke GL, Wolfson SK Jr. Carotid-artery intima and media thickness as a risk factor for myocardial infarction and stroke in older adults: Cardiovascular Health Study. N Engl J Med. 1999;340:14-22

[10] Chambless LE, Heiss G, Folsom AR, Rosamond W, Szklo M, Sharrett AR, et al. Association of coronary heart disease incidence with carotid arterial wall thickness and major risk factors: the Atherosclerosis Risk in Communities (ARIC) Study, 1987-1993. Am J Epidemiol. 1997;146:483-94.

[11] Allan P, Mowbray P, Lee A, Fowkes G. Relationship between carotid intima-media thickness and symptomatic and asymptomatic peripheral arterial disease. The Edinburgh Artery Study. Stroke. 1997;28:348-53.

[12] Abrahim S, Papacosta O, Whincup P, Wannametheee G, Walker M, Nicolaides A, et al. Carotid plaque, intima media thickness, cardiovascular risk factors, and prevalent cardiovascular disease in men and women. The British Regional Heart Study. Stroke. 1999;30:841-50.

[13] Zureik M, Touboul P-J, Bonithon-Kopp C, Courbon D, Berr C, Leroux C, et al. Cross-sectional and 4-year longitudinal associations between brachial pulse pressure and common carotid intima- media thickness in a general population. The EVA study. Stroke. 1999;30:550-5.

[14] Junyent M, Gilabert R, Núñez I, Corbella E, Vela M, Zambón D, Ros E. [Carotid ultrasound in the assessment of preclinical atherosclerosis. Distribution of intima-media thickness values and plaque frequency in a Spanish community cohort]. Med Clin (Barc). 2005 Dec 3;125(20):770-4.

[15] Ferrieres J, Elias A, Ruidavets JB, Cantet C, Bongard V, Fauvel J, et al. Carotid intima-media thickness and coronary heart disease risk factors in a low-risk population. J Hypertens. 1999;17:743-8