33rd Annual International Conference of the IEEE EMBS
Boston, Massachusetts USA, August 30 - September 3, 2011

Uruguay eHealth Initiative: Preliminary Studies Regarding an Integrated Approach to Evaluate Vascular Age and Preclinical Atherosclerosis (CUiiDARTE Project)

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***Abstract*—In this work we present an initiative to develop a national (Uruguayan) program to evaluate vascular age and to detect pre-clinical atherosclerosis using: gold-standard technologies; complimentary and integrative approaches to asses arterial functional and structural indexes; data bases systems to process, analyze and determine normal and reference values and to identify the most sensitive markers of vascular changes for different ages. We evaluated, in a Uruguayan population complementary structural and functional vascular parameters that associate aging-related changes and are considered markers of sub-clinical atherosclerosis. Traditional CV risk factors were assessed. The subjects (n=281) were submitted to non-invasive vascular studies to evaluate: 1) Common carotid artery (CCA) intima-media thickness and diameter waveforms, 2) CCA stiffness, 3) aortic stiffness (pulse wave velocity) and 4) peripheral and central pressure pulse wave derived parameters. Age groups: 21-30, 31-40, 41-50, 51-60, and 61-70 years-old. Age-related profiles were obtained for the different vascular parameters, and their utility to assess vascular changes in young, middle-aged and old subjects was evaluated. The work has the strength of being the first that uses, in Latin-America an integrative approach to characterize vascular aging-related changes.**

I. Introduction

Several methods have been developed to stratify cardiovascular (CV) risk. Those methods are mostly based on identification of traditional CV risk factors and on data mainly derived from European and/or North American populations. While recognizing their usefulness several limitations are attributed to the methods referred to. About this, it is noteworthy that due to reasons like ethnic diversity in the vascular disease profile data obtained in a given population could not be directly extrapolated to another population (i.e. data from European people could not fit properly to South-American populations). On the other hand, CV risk approaches based in the assessment of traditional risk factors could not be enough to determine the CV risk of a particular individual [1]. In this context, it is noteworthy that it has been stated that the vascular-age evaluation, the individual CV risk stratification and the early detection of vascular disease could provide a major opportunity to prevent CV events [1].

Among others, vascular indexes derived from central and peripheral pulse waves analysis (i.e. augmentation index, AIx), pulse wave velocity (PWV), and common carotid artery (CCA) intima-media thickness (CIMT) and stiffness have been proposed as valuable markers to assess vascular age, individual CV risk and early detection of atherosclerosis [1]. However, in spite of its emergence as a useful tool in CV evaluation, a widespread implementation of vascular assessment has been hampered, among others, due to the lack of: a) normal and reference values for the vascular parameter in different populations, and/or b) defined criteria in relation to the convenience of using a particular vascular index in a particular subject. About this, in recent European study it was suggested that the marker of preference for evaluating arterial age and/or preclinical atherosclerosis could vary, depending on the subject age [2, 3].

The present study was carried out in a Uruguayan asymptomatic population, to quantify the age-associated profiles of several vascular markers and to evaluate the most sensitive markers of arterial aging. To fulfill the work aims an integrative approach (CUiiDARTE-Project, www.cuiidarte.fmed.edu.uy) was developed and applied so as to measure complementary structural and functional vascular parameters using non-invasive gold standard methods [Fig. 1]. Related with this, it is noteworthy that e-Health could be defined as the use of information technology in the delivery of health care [4]. In this context, the development of the e-health tools considered in this work serves to detect normal aging and early alterations related with vascular disease, which could improve patient evaluation/treatment due to an increased knowledge/understanding of the disease by better data linkage, data mining and data analysis. The development of individualized CV-risk analysis for patients using biological and health data sets will improve health outcomes

Manuscript received April 15, 2011. This work was supported in part by the Agencia Nacional de Investigación e Innovación (Uruguay; FCE-2007-638, FCE-2007-635, PRSCT-020-008).

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II. MATERIAL AND METHOS

A. Study population and subjects groups

Asymptomatic subjects without known cardiovascular disease, consecutively referred for cardiovascular risk stratification in the CUiiDARTE Project, were considered. CUiiDARTE Project is a population-based national study developed in Montevideo, the capital of Uruguay, the second-smallest nation of South America. Uruguayan population approximates 3.5 million, of which 1.8 million live in Montevideo and its metropolitan area. Most Uruguayans (88%) are Caucasian of European origin (descendants of immigrants). The majority of those immigrants were Spanish, followed by Italian.

The study was approved by the Institutional Ethic Committee.

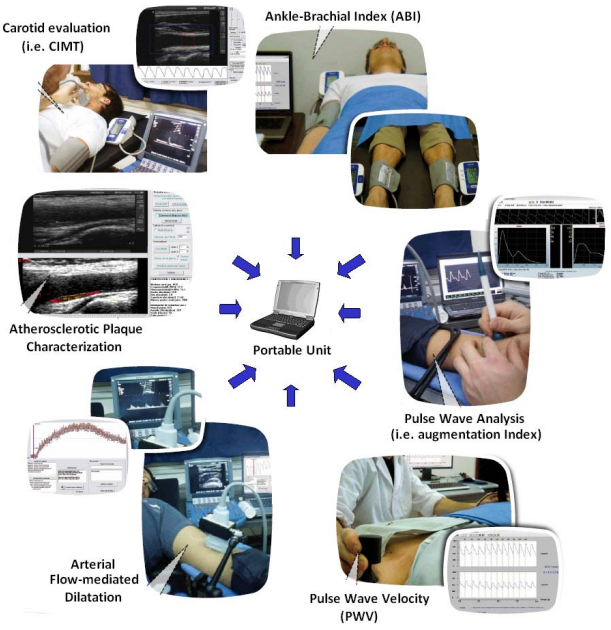


Fig 1. Schema of the integrative complimentary approach designed to evaluate arterial aging and pre-clinical disease, after a medical interview and laboratory measurements. Qualitative and quantitative information obtained/stored in portable (ambulatory) units is transferred (electronically) to the Data Center (School of Medicine - RU).

The subjects age range was selected in agreement with international consensus that recommend both, starting non-invasive arterial evaluation at ~20 years old and the development of programs for atherosclerosis screening in subjects between ~40-70 years old [1]. Subjects with history of cardiovascular disease, diabetes mellitus and/or renal failure were not included. Patients with traditional vascular risk factors (other than age and gender) were excluded. Studies were done in a single visit. Evaluation started after 9-12 hours overnight fast. Exercise, caffeine, alcohol, and vitamin C were avoided prior (at least 6 hours) to examination. Subjects´ height and weight were measured, and the body mass index (BMI) calculated.

B. Laboratory measurements

Venous blood samples were drawn and processed immediately using commercially available kits and/or laboratory methods. Total cholesterol (TC), serum triglycerides (TG), and high and low density lipoprotein cholesterol (HDL-C and LDL-C) were determined. Patients with a lipid profile with one or more of the following conditions: TG≥200 mg/dL, TC≥240 mg/dL, HDL-C<40 mg/dL, LDL-C≥160 mg/dL were excluded at the time of the data analysis. Subjects´ characteristics are shown in Table 1.

Table 1. Anthropometric and biochemical measurements of the different age groups.

	21-30 years	31-40 years	41-50 years	51-60 years	61-70 years
	MV ± SD	MV ± SD	MV ± SD	MV ± SD	MV ± SD
Age [years]	24.8 ± 1.1	35.0 ± 2.7	45.7 ± 3.4	56.4 ± 4.0	64.3 ± 4.9
Body height [cm]	166.3 ± 8.2	163.1 ± 6.5	166.4 ± 10.5	159.4 ± 4.3	166.0 ± 15.1
Body weihht [Kg]	59.9 ± 8.4	56.1 ± 6.8	63.3 ± 10.5	56.6 ± 6.5	65.7 ± 10.0
BMI [Kg/m2]	21.0 ± 4.1	21.1 ± 2.1	22.8 ± 2.2	22.3 ± 2.4	23.8 ± 0.8
CT [mg/dl]	175.2 ± 24.9	190.2 ± 21.6	184.9 ± 18.3	219.4 ± 8.9	190.5 ± 21.8
HDL-C [mg/dl]	64.6 ± 13.8	68.0 ± 27.0	67.5 ± 6.4	73.0 ± 19.5	66.0 ± 10.2
LDL-C [mg/dl]	92.0 ± 19.2	111.7 ± 29.6	100.5 ± 6.4	128.7 ± 12.4	92.0 ± 12.2
TG [mg/dl]	85.4 ± 27.4	58.3 ± 20.5	57.5 ± 2.1	60.3 ± 20.8	64.0 ± 18.1
CT/HDL-C	2.8 ± 0.6	3.0 ± 1.1	2.7 ± 0.1	3.1 ± 0.9	2.9 ± 0.2
Non-HDL-C	110.5 ± 22.8	123.7 ± 32.3	112.0 ± 7.1	140.7 ± 16.8	124 ± 17.3
Glycaemia [mg/dl]	84.1 ± 5.9	69.2 ± 16.5	74.0 ± 19.1	76.0 ± 15.8	72.5 ± 6.4

HDL: High density lipoprotein cholesterol. LDL: Low density lipoprotein cholesterol.

C. Aging and pre-clinical atherosclerotic markers

After blood collection, vascular evaluation consisted in measuring several complementary structural and functional vascular parameters [Figure 1].

1. CIMT and CCA instantaneous diameter waveforms

High-resolution B-mode carotid ultrasonography was done with a linear-array, 10 MHz 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. Studies were done after 10-15 minutes of recumbent rest. Before and during examination (at 3-minutes intervals), brachial blood pressure measurements were obtained (Omron HEM-433INT Oscillometric System; Omron Healthcare Inc., Illinois, USA). The average was considered as blood pressure level.

Longitudinal views of the CCA were acquired so as to measure the CIMT and to obtain the diameter waveforms. A video (cine-loop) of at least 10 seconds was recorded from the anterior, lateral, and posterior angles of interrogation. The CIMT and beat-to-beat diameter waveforms were analyzed off-line using a step-by-step border detection algorithm (Hemodyn-4M software, Bs.As. Argentina) [5]. 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 software performs multiple automated measurements along 1 cm and averages them, therefore increasing the accuracy of the measures. The instantaneous diameter (from the leading edge of the near wall intima-lumen interface to the intima-lumen interface in the far wall) waveform was obtained. Wall-to-lumen ratio was calculated as CIMT/CCA diameter.

2. CCA stiffness

Percentual or fractional pulsatility (FP%) coefficient was calculated as FP%=((SD-DD)/DD)*100, where SD and DD are systolic and diastolic internal diameters, respectively; CCA Compliance (CCA_C) and Distensibility (CCA_D) were quantified as CCA_C=(DS-DD/(cSBP-cDBP) and CCA_D=((DS-DD)/DD)/(cSBP-cDBP), where cSBP and cDBP are central systolic pressure and diastolic pressure, respectively, obtained using Applanation Tonometry (PWA, SphygmoCor, AtCor Medical Pty Ltd., Sydney, Australia).

3. Aortic stiffness (carotid-femoral PWV)

The carotid-femoral pulse-wave velocity (PWVcf) was measured using mechano-transducers placed simultaneously on the skin over the carotid and femoral arteries (Hemodyn 4-M, Argentina) [5]. Straight distance between recording sites was measured on the body surface. PWVcf was automatically calculated as the quotient between the distance and the carotid-femoral pulse transit time difference.

4. Peripheral and central pulse wave analysis (PWA)

PWA was used to obtain the ascending aorta pressure waveform from the radial pulse, using customized equipment (SphygmoCor 7.01, AtCor Medical, Sydney, Australia) [6]. Radial pulse wave was obtained (subject sited with the arm resting on a table) and calibrated using brachial diastolic and mean pressures. From the aortic pulse wave, central pressure was estimated, and indexes of wave reflections were quantified from central and peripheral waves: central augmentation pressure (AP), heart rate corrected (HR75) central AP, central augmentation index (C_AGPH=(AP/PP)*100), heart rate corrected central augmentation index (C_AGPH_HR75), and peripheral augmentation index (P_AIx) [6].

D. Statistical analysis

Based on age, 281 subjects (Range: 20-69 years old), were divided into the following age groups: 20-29 (n=79), 30-39 (n=43), 40-49 (n=50), 50-59 (n=59), and 60-69 (n=50) years old. The relationship between age and arterial parameters was studied using linear regression models.

III. Results

CCA IMT increased with age, with a mean increase of 0.08 mm/decade (P<0.05) [Fig 2]. Systolic and diastolic CCA diameters increased by an average of 0.17 and 0.19 mm/decade, respectively (P<0.05) [Fig 2]. There was an increase in wall-to-lumen ratio with age.

Age-related CCA functional impairment was evident, with marked age-related reductions in percentual distensibility, distensibility and compliance [Fig 3]. Age-related changes in CCA stiffness were markedly nonlinear, and particularly marked in young individuals. The age-related PWV profile was nonlinear, with greater increase beyond 49 years [Fig 4].

PWV increased with aging by an average of 1.15 m/sec per decade. The increase was 0.68 m/sec in young (20-29 to 30-39 years) and 1.72 m/sec in old (50-59 to 60-69 years) subjects. Central and peripheral augmentation pressure and indexes increased with age.

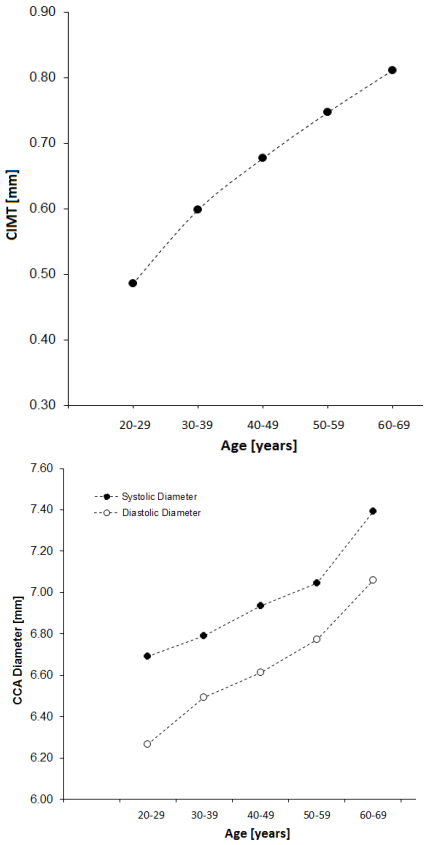


Fig 2. Age-related CIMT and CCA diameter profiles

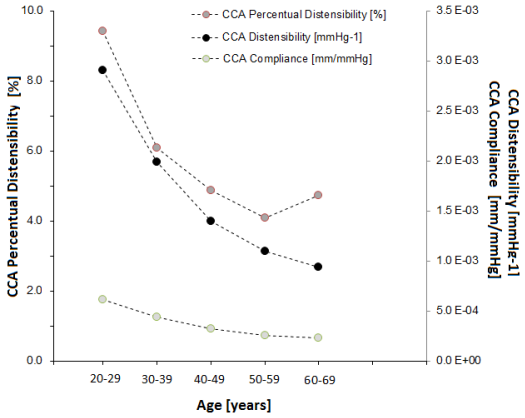


Fig 3. Age-related profiles for the different CCA stiffness indexes.

When the relative changes among decades were analyzed, parameters could be divided into those with high sensitivity at low ages, including structural (CIMT, wall-to-lumen ratio) and functional parameters (wave reflections parameters), and those with high sensitivity at older ages (i.e. PWV) [Fig 5].

IV. Discussion

Age-related structural and functional vascular parameters profiles were obtained in the context of the CUiiDARTE Project, using gold standard methodologies and techniques, to evaluate a Uruguayan asymptomatic population. The vascular parameters sensitivity to aging was analyzed. The work has the strength of being the first in Latin America that applies an integrative approach to characterize age-related

structural and functional parameters using gold standard techniques. The obtained data could be used in vascular evaluation/diagnosis to define/differentiate normal, aging-related vascular changes and abnormal or disease-related vascular variations.

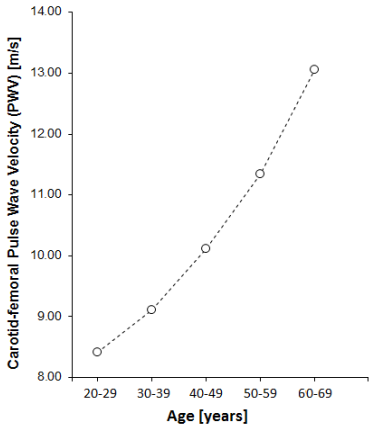
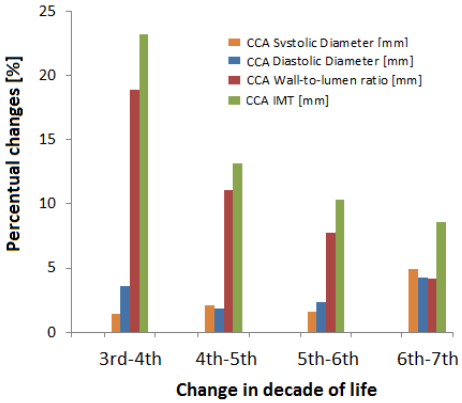
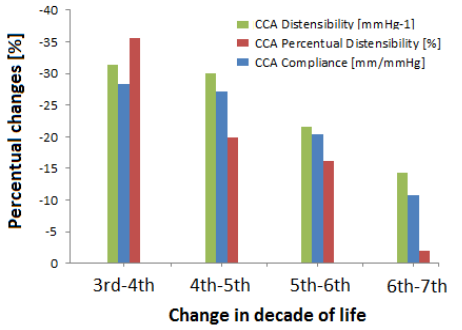
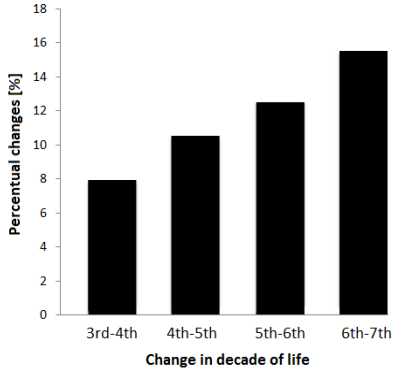


Fig 4. Age-related carotid-femoral pulse wave velocity profile.







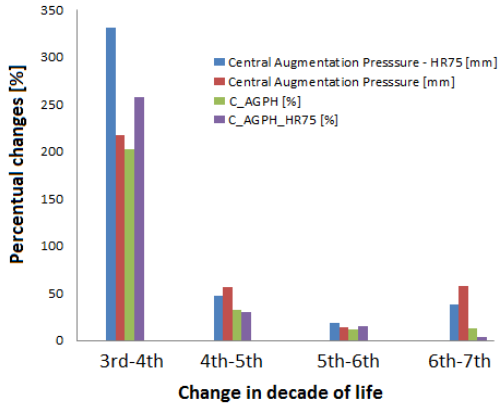


Fig 5. Percentage changes in arterial parameters between decades.

V. Conclusion

The methodology presented in this work is a development of the approach for calculating individual risk of ACVD on the basis of the recent biomechanical risk factors widely accepted. The method may be useful in the context of preparing a public health and e-Health approach where a low cost and repeatable non invasive technology is justified. The method provides a simplified means of obtaining a conservative of the individual risk to members of defined population groups.

The method may be specified within a spreadsheet, making it, especially attractive for use in electronic health records shared by several diagnostic and treatment centers remotely connected to each other.

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