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Age-related changes in reservoir and excess components of central aortic pressure in asymptomatic adults

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Abstract— **Study of humans aging has presented difficulties in separating the aging process from concomitant disease and/or in defining normality and abnormality during its development. In accordance with this, aging associates structural and functional changes evidenced in variations in vascular parameters witch suffer alterations during atherosclerosis and have been proposed as early markers of the disease. The absence of adequate tools to differentiate the expected (normal) vascular changes due to aging from those related with a vascular disease is not a minor issue. For an individual, an early diagnosis of a vascular disease should be as important as the diagnosis of a healthy vascular aging. Recent studies have proposed that the capacitive or reservoir function of the aorta and large elastic arteries plays a major role in determining the pulse wave morphology. The arterial pressure waveform can be explained in terms of a reservoir pressure, related to the arterial system compliance, and an "excess" or wave-related pressure, associated with the traveling waves. The aim of this study was to evaluate, by means of a mathematical approach, age-related changes in measured, reservoir and excess central aortic pressure in order to determine if age-related changes are concentrated in particular decades of life. Central aortic pressure waveform was non-invasively obtained in healthy subjects (age range: 20-69 years old). Age-related profiles in measured, reservoir and excess pressure were calculated.**

I. INTRODUCTION

Despite atherosclerosis is not a normal aging change, but a disease condition quite different from true vascular aging, when discussing about vascular aging in humans, the analysis is frequently referred to the mentioned disease and its prevalence with age [1]. Furthermore, during the study of humans aging, difficulties have arisen in performing the separation of normal aging process from concomitant disease and/or in defining normality and abnormality during its development. Concerning this, aging associates structural and functional changes evidenced in variations of vascular parameters witch suffer alterations during atherosclerosis and have been proposed as early markers of vascular disease. The aforementioned could contribute to explain the controversial and/or limited data about age-related cardiovascular changes in different populations. The absence of adequate tools to differentiate the expected (normal) vascular changes due to aging from those related with vascular diseases is not a minor issue. In accordance to this, it should be kept in mind that, for an individual, an early diagnosis of a vascular disease should be as important as the diagnosis of a healthy vascular aging. In this way, it is necessary to develop sensitive approaches in order to detect systemic and local age-associated arterial changes. Recently, an European study has suggested the marker of preference for evaluating arterial age and/or preclinical atherosclerosis could change, depending on the patient's age [2, 3].

Recent studies have proposed that the capacity or reservoir function of the aorta and large elastic arteries plays a major role in determining the pulse wave morphology. Regarding this, the arterial pressure waveform can be explained in terms of a "reservoir" pressure, related to arterial compliance, and an "excess" or wave-related pressure, associated with traveling waves [4].

In this context, the aim of the present study was to evaluate age-related changes in measured, reservoir and excess aortic pressure. This analysis might contribute to characterize the vascular properties' age-related profile. In turn, the knowledge of the expected age-related vascular and pressure changes, might help to identify (differentiate) pathological changes (i.e. due to atherosclerosis and/or hypertension) and physiological variations associated with normal aging.

II. MATERIAL AND METHOD

A. Study population and subjects groups

Forty three asymptomatic subjects (65% female), 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 latter, with an area of approximately 176,000 Km^2 (the second-smallest nation of South America), has a population of approximately 3.5 million, of which 1.8 million live in Montevideo and its metropolitan area. Most

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Uruguayans (88%) are Caucasian of European origin, descendants of immigrants (mainly Spanish, followed by Italian).

The subjects' age range was selected in agreement with recent international consensus. It is recommended both starting with non-invasive arterial evaluation at ~twenty years old and the development of programs for atherosclerosis screening in subjects between ~forty-seventy years old [1]. Subjects with history of cardiovascular disease, diabetes mellitus and/or renal failure were not included in the study. Patients with traditional risk factors were also excluded. The study was approved by the Institutional Ethic Committee. Subjects were studied 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 the examination. Subjects' height and weight were measured, and body mass index (BMI) was calculated (Table 1).

Table 1

	G1	**G2**	**G3**	**G4**	**G5**
	MV ± SD	MV ± SD	MV ± SD	MV ± SD	MV ± SD
Number subjects	9	8	8	9	9
Age [years]	25 ± 1	35 ± 3	46 ± 3	56 ± 2	64 ± 3
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.

Table 1. Anthropometric and biomedical measurements of different age groups.

B. Laboratory measurements

Venous blood samples were drawn and immediately processed by means of 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 and/or currently taking hypolipidemic agents, were excluded at the time of the data analysis (Table I)

C. Central aortic pressure waveform: windkessel and excess pressure components

Pulse wave analysis (PWA) was used to obtain the ascending aortic pressure waveform from the radial pulse (measured by applanation tonometry) using customized software (SphygmoCor 7.01, AtCor Medical, Sydney, Australia) with a previously validated generalized transfer function [5, 6]. The radial pulse wave was obtained with the subject sited with its arm resting on a table. The radial pulse waveform was calibrated using diastolic and mean pressures obtained at the brachial artery (HEM-433INT Oscillometric System; Omron Healthcare Inc., Illinois, USA).

The SphygmoCor device generates an output ASCII format data matrix, consisting on a ten second snapshot of measured radial artery and the derived aortic ascending pressure signal (P). A set of algorithms specially developed under Matlab® platform (MATHWORKS INC, Massachusetts, USA), were used to process the data. Reservoir and Excess pressures (P_{res} and P_{exc} respectively) were calculated by applying the "only pressure known" method [7, 8] in the absence of a measured input flow (Q). A three element Windkessel model was considered, where P_{exc} consists of the difference between P and P_{res} and it is related to the model's characteristic impedance (z_0, a resistor considering this analysis) [Fig 1]. In consequence, P_{exc} is proportional to the flow (similar in shape). The impedance constituted by the system peripheral resistance (R) and the arterial compliance (C) is related to P_{res}. Both parameters (R and C) were obtained during diastole, when the three element and the two element windkessel models behave similarly [9]. The ordinary differential equation (ODE) that governs the relationship between P_{res} and the input flow can be expressed as follows:

$$C\frac{dP_{res}(t)}{dt} = Q(t) - \frac{P_{res}(t) - P_{\infty}}{R} \qquad (1)$$

where P_{∞} is the pressure at which the flow through the microcirculation ceases. The pressure P_{∞} is larger than zero and closer to the diastolic pressure more than the venous pressure [8]. Since P_{exc} is proportional to the input flow, the Q parameter in equation (1) can be substituted by the expression $aC(P\text{-}P_{res})$, where a is a constant value [8]. Therefore, reservoir pressure may be obtained by finding the solution of the resulting time dependent ODE:

$$\frac{d\left(P_{res} - P_{\infty}\right)}{dt} + \left(a + \frac{1}{\tau}\right)\left(P_{res} - P_{\infty}\right) = a\left[P(t) - P_{\infty}\right] \qquad (2)$$

in witch τ is the time constant of the two element windkessel model (product between R and C). Time constant (τ) and P_{∞} were obtained by fitting the last third of the diastolic period [10] to an exponential [7]:

$$P_{dia}(t) - P_{\infty} = (P_0 - P_{\infty})e^{-\frac{t}{\tau}} \qquad (3)$$

where P_{dia} is the measured pressure during last third of diastolic period whereas P_0 is the initial measured value of the time interval. Parameter a was determined (iteratively) finding the value that minimizes the square difference between the estimated decay during P_{dia} and P_{res} expression, obtained by solving equation (2). The beginning of diastolic period was assessed by finding the time at witch dP/dt reaches a minimum. This point correlates better with the time of closure of the aortic valve [10]. Once a was found, the resulting P_{res} was used to perform P_{exc} calculation, as mentioned:

$$P_{exc}(t) = P(t) - P_{res}(t) \quad (4)$$

Maximal P, P_{res} and P_{exc} values as well as the integral (mean value) over the cardiac cycle were calculated.

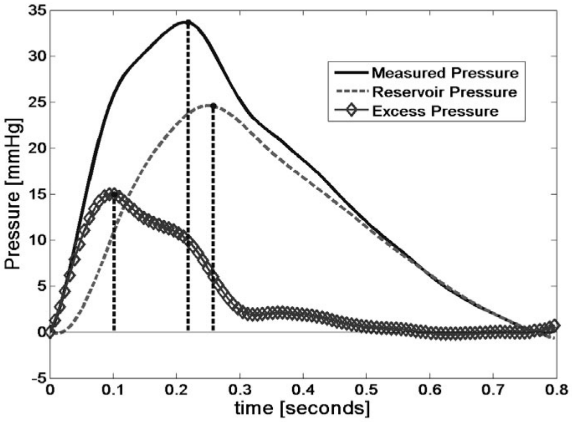

Fig. 1: Example of measured (solid), reservoir (dotted) and excess (diamonds) pressure waveforms (referenced to their initial value) obtained from a single case. Maximal values (and time of occurrence) were calculated for the three pressures.

D. *Statistical analysis*

Baseline characteristics are provided as mean ± standard deviation (SD) for continuous variables. Subjects (Range: 20-69 years old), were divided into the following age groups: G1: 20-29; G2: 30-39, G3: 40-49, G4: 50-59, and G5: 60-69 years old. The relationship between age and the arterial parameters was performed by means of linear regression analysis.

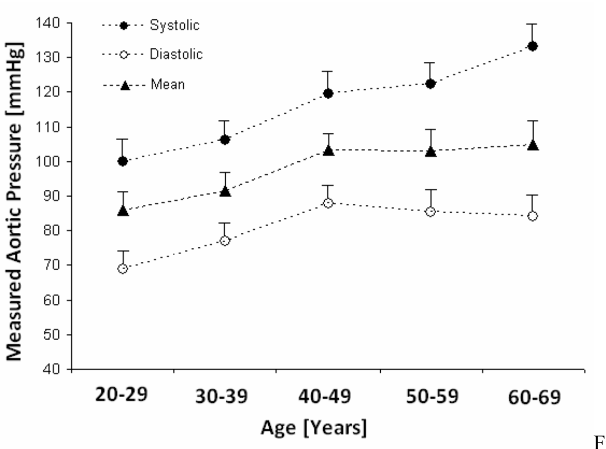

Fig 2. Age-related measured aortic blood pressure profiles. Note the increase in systolic pressure with aging, and the reduction in the diastolic pressure beyond 50 years old.

III. RESULTS

As expected, central systolic blood pressure showed an increase with age [Fig 2].

Measured central aortic systolic and mean pressure (pressure waveform normalized area) increased with an average of 8.3 mmHg/decade (y=8.26x+ 91.50; $p<0.05$) and 4.9 mmHg/decade (4.91x+ 82.98; $p<0.05$), respectively. Diastolic pressure showed lesser age-related changes, but it decreased beyond sixty years. Heart rate showed a tendency to decrease with age.

Both, maximal and mean components of the reservoir (Windkessel) pressure suffered an increase with age [Fig 3], with an average of 6.7 mmHg/decade (y=6.70x+85.15; $p<0.05$) and 4.6 mmHg/decade (y=4.63x+79.26; $p<0.05$), respectively.

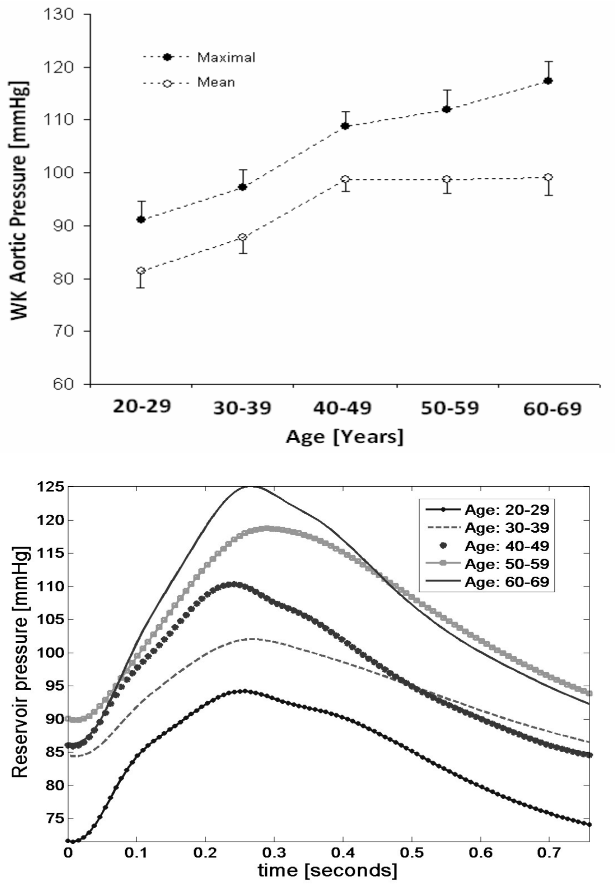

Fig 3. Top: Age-related reservoir pressure profiles. Bottom: Age-related changes in Windkessel pressure waveforms.

The age-related profile of the excess pressure showed a non-linear behavior. Beyond forty years it increased with age [Fig 4], with changes concentrated beyond fifty years. Regarding this, the increase in maximal pressure averaged was 4.9 mmHg/decade (y=4.91x- 4.93; $p<0.05$) between the 6th and 7th decade.

IV. DISCUSSION

The aim of this study was to assess age-related changes in measured, reservoir and excess aortic pressure. The potential concentration of the changes in particular decades of life was analyzed.

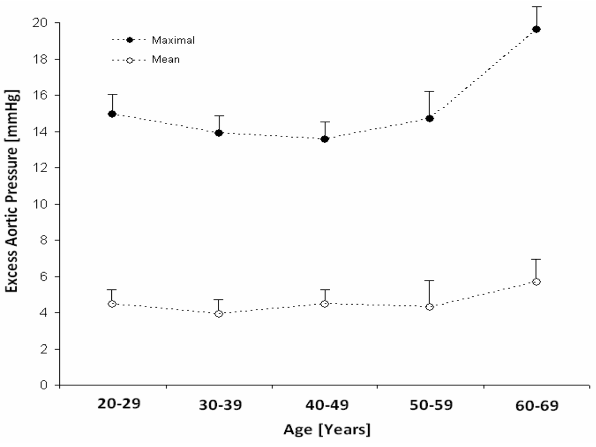

Fig 4. Age-related excess aortic blood pressure profiles. Note the higher maximal excess pressure levels in the elderly subjects.

Central aortic pressure was estimated non-invasively by transfer function (pulse wave analysis, SphygmoCor 7.01), applied to tonometry measured radial pressure and reservoir/excess pressures were assessed by assuming a three element windkessel model. It has been demonstrated that the application of pulse wave analysis or impedance analysis to aortic pressure might develop inconsistent results, based on backward components behavior, which do not travel as expected. More adequate results could be obtained by applying the same analysis to the excess pressure component.

Blood pressure changes with age have been evaluated in several studies and it has been described that systolic blood pressure increases with advancing age. Despite age-related pressure variations, the mentioned increase would not be uniform and would differ depending on the population characteristics [1]. On the other hand, minimum changes have been described for diastolic pressure, except for a reduction beyond sixty years [1]. The analyzed groups showed the expected age-related pressure changes.

Reservoir and excess pressure components analysis revealed that both increase with aging, but the age-related profile would differ between them. The increase in reservoir and excess pressure with aging is in agreement with data published, based on a study of 18 subjects [4]. As was mentioned, reservoir pressure is related to systemic properties. Then, its changes are the result of the combination of systemic variations. On the other hand, excess pressure manifests better the local behavior, since systemic response (reservoir component) is not involved in its analysis. In consequence, different and complimentary information can be obtained from the analysis of excess and reservoir pressure, and a particular arterial waveform (levels and morphology) would be more adequately analysed if its different pressure components were previously identified. It is noteworthy that a given pressure wave (and/or a change in it) is the result of different combinations of excess and reservoir components. In this context, the knowledge of the expected age-related profiles of pressure and its identified components would be remarkably useful in the differentiation of normal aging and abnormal/disease related vascular changes. To summarize, these latter could be analysed in terms of systemic and/or local variations. Further studies should be developed in order to assess the arterial pressure components profiles in different populations and/or different conditions.

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