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REVIEW ARTICLE

Quantitative Vascular Evaluation: From Laboratory Experiments to Point-of-Care Patient (Clinical Approach)

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Abstract: To enhance the efficiency of patient-specific risk stratification and diagnosis, an assessment of arterial structural and functional changes associated to a vascular disease in both early and advanced stages have been proposed, with the objective of limiting the progression or revert vascular alterations. In this connection, an interdisciplinary international partnership made up by research institutions from France, Argentina, Uruguay and Spain was established, with the objective of contributing to the evaluation and follow-up of factors involved in the physiopathology of cardiometabolic diseases and human aging. Several studies, such as the effect of hypertension in large arteries, alterations in arterial wall viscosity, stiffness and inertia, endothelial function and vascular reactivity, cardiovascular risk improvement, vascular age assessment and cryografts vascular response evaluation were carried out as a result of this international collaboration during the last twenty-five years.

Keywords: Vascular function, hypertension, flow-mediated dilation, central pressure, stiffness, vascular age.

1. INTRODUCTION

Cardiovascular (***CV***) disease remains as the main cause of morbidity and mortality in the world. In this context, alerts have called for the need to have diagnostic as well as therapeutic approaches to overcome the limitations of traditional actions to prevent or treat atherosclerosis, based on the determination of risk factors and the reduction of the impact of the disease [1]. These limitations could be explained, among other factors, regarding the approach applied in the assessment of the probability that an individual may suffer from a ***CV*** event (in terms of low, moderate or high risk), which is basically founded in the presence of risk factors and specific population studies (*e.g*: Framingham Risk Score, FRS; Euro-SCORE).

To aid in patient-specific risk stratification and diagnosis, the evaluation of arterial structural and functional changes associated to a vascular disease in both early and advanced stages was adopted by our group, in order to limit the progression or revert vascular alterations [2, 3]. The participants in this interdisciplinary international partnership were the Georges-Pompidou European Hospital (Paris Descartes Faculty of Medicine, Paris, France), the Broussais Hospital (Paris, France), Universidad Favaloro (Argentina) and the University Center for Research, Innovation and Arterial Diagnosis (CUiiDARTE, Universidad de la República, Uruguay).

The purpose of this paper is to address one of the approaches for modeling the mechanical properties of the arterial wall to contribute to the evaluation and follow-up of factors involved in the physiopathology of cardiometabolic diseases and human aging. This path was initiated 25 years ago through this collaboration and can be evidenced in terms of the numerous publications that constitute the following sections.

2. GENERAL OVERVIEW

One of our first studies was conducted to evaluate the intrinsic effects of hypertension in large arteries in humans, by means of diameter and compliance measurements [4]. In [5], a model developed for the evaluation of wall mechanical properties [6] was applied to pressure-diameter relationships of carotid and femoral arteries, non-invasively obtained from normotensive and hypertensive subjects. Then, a non-invasive assessment of systemic arterial elastic behavior in hypertensive patients was carried out [7].

The alterations of wall viscosity in hypertensive patients and their relationship with intima-media thickness (***IMT***) were then studied [8]. An experimental system was clinically

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validated in [9] in order to obtain measurements of arterial diameter waveforms and intimal media thickness from B-Mode ultrasound images. Vascular effects of antihypertensive drugs in hypercholesterolemic hypertensive subjects were also addressed in [10] in carotid pressure-diameters loops. The wall inertia of the carotid artery was assessed in normotensive and hypertensive subjects using an autoregressive, discrete and linear model (***ARMA***), which permitted the simultaneous estimation of the elastic, viscous and inertial contribution of wall dynamics [11].

Later, noninvasive studies were focused on the endothelial function in human arteries. To that end, a new technique was developed aimed at studying arterial reactivity, offering the possibility to detect an alteration in arterial function related to early atherosclerosis [12]. Also, a comparison of the effects of atenolol versus ramipril in hypertensive patients was established [13] to determine the mechanical and intrinsic effects of an angiotensin converting enzyme inhibitor, vs a beta-blocker, on brachial arterial compliance. Smart dumping modulation of carotid wall energetics in hypertensive patients was additionally evaluated [14].

In terms of a cardiometabolic approach, the arterial wall structure and dynamics in type 2 diabetes mellitus were reviewed [15]. Improvements in cardiovascular risk characterization related to coronary calcium were addressed in [16, 17].

Finally, a solid experience has been additionally gained in the biomechanical and functional study of cryopreserved human and animal vascular homografts, with pre-implant and post-implant analyses regarding vascular wall mechanics, including the implementation of an intercontinental vascular tissue exchange system [18-21].

3. NON-INVASIVE EVALUATION OF ARTERIAL STRUCTURE AND FUNCTION

Different non-invasive methods have been proposed to evaluate arterial structure and function. The approach adopted by our group comprises the use of ultrasound, tonometry, mechanography, doppler velocimetry and blood pressure records to study markers of vascular damage such as carotid intima-media thickness, presence of atheroma plaques, carotid-femoral pulse wave velocity, vascular reactivity and wall mechanical properties.

3.1. Carotid Intima-media Thickness and Presence of Atheroma Plaques

Over the last few years, consensus statements have been recommending the use of ultrasound to evaluate carotid ***IMT*** and to detect carotid atherosclerotic plaques, as a clinical tool for ***CV*** risk prediction and diagnosis [22]. Thickening may take two forms, sometimes not clearly differentiated: atheroma plaque, which corresponds to a focal thickening, or an intima media diffuse thickening. The presence of plaques is truly important in the determination of ***CV*** risk, since it has been shown that the probability of suffering from myocardial infarction increases considerably.

The arterial territories must be analyzed using an ultrasound system with a linear transducer with a frequency higher than or equal to 7 MHz. A standard depth of 4 cm is usually enough for the study while a greater depth could be required in subjects with deep arteries and/or a wide neck. Mode-B images allow ***IMT*** to be evaluated in a region, considering the differences normally exhibited by the parameter. Carotid plaques are evaluated in terms of geometry, hemodynamic compromise and severity, according to standard criteria [23, 24].

The alterations in wall viscosity in hypertensive patients and their relationship with ***IMT*** have been studied in [8]. To perform this analysis, an ultrasound image acquisition and processing system was developed, previously validated through simultaneous measurements obtained from sonomicrometry [9]. The correlation between ***IMT*** and the viscous index, statistically independent from pressure, indicated that vascular hypertrophy is caused by an alteration mainly in the media layer of the artery and not so much in the intima layer. As a result, an image processing tool was proposed to evaluate the probability of plaque events (vulnerability) analyzing the features of the ultrasound images [25]. Mode-B acquisitions were processed with a specific software, studying pixelar composition in a scale of gray levels. This procedure provides information relative to lepidic and fibrous distribution and content, based on previous studies that correlated the ultrasound characteristics (echogenecity) with plaque components determined in anatomo-histological analyses [26]. In addition, common carotid artery ***IMT*** and diameter (among other markers) were obtained and analyzed considering data from other populations [2], being the first in Latin America to use an integrative approach to characterize vascular aging-related changes.

3.2. Regional Arterial Stiffness: Pulse Wave Velocity

The evaluation of aortic stiffness is of great interest since the aorta concentrates most of the arterial damping function and it is an important determinant of ventricular load [27]. The measurement of carotid-femoral pulse wave velocity (***PWV***) is considered the simplest, most direct, non-invasive, robust and reproducible method to evaluate aortic stiffness, thus becoming a gold standard. It has been shown that the addition of ***PWV*** measurement to the determination of classical risk factors increases the ability of ***CV*** risk prediction [27]. When an antihypertensive treatment is given, it is important to analyze the ***PWV*** modifications for the new arterial pressure value found. If ***PWV*** values are over the expected level in relation to age and arterial pressure, it is evident that the results, in terms of vascular alteration, were not optimal [27]. This vascular parameter can be measured through the "foot-to-foot" method applied to pulse wave measurement (determination of points of carotid and femoral curves which are minimally influenced by wave reflections). Waveforms are generally obtained through mechano-transducers (tonometers) (*e.g.* Complior, HemoDyn-4M) or by oscillometric sphygmomanometers (Sphygmocor, Atcor Medical). Basically, carotid and femoral waveforms are acquired and then both the time delay (Δt) measured between the corresponding foot of each pulse wave and the distance (Δx) between the registration sites are quantified. Wave velocity is finally assessed as the ratio between Δx and Δt. It must be taken into consideration that arterial stiffness depends on blood pressure levels: the higher the pressure, the stiffer the

artery, resulting in a higher propagation velocity. Therefore, if ***PWV*** is to be used as a target organ damage marker, its levels explained by hemodynamic conditions should be known. This is not a minor issue considering the impact of hypertension on the vessel structure. In this sense, ***PWV*** has been extensively evaluated in our group in health and disease, being proposed as a marker of preclinical arterial disease in the Uruguayan population [28]. Normal, reference, and threshold levels of ***PWV*** considering normal age-related changes in ***PWV*** and the prevailing blood pressure level were properly characterized.

In some other studies by us, ***PWV*** measurements showed that vascular accesses for hemodialysis in the upper arm cause greater reduction in the carotid-brachial stiffness than those in the forearm, in a gender differences study [29]. A 5-year prospective study on a group of chronically hemodialyzed patients was also performed [30] in order to determine possible time-related differences. The results showed significant decreases in both carotid-brachial and carotid-femoral pathways. Hence, the observed changes in arterial stiffness could be related to the vascular access creation, hemodialysis therapy and to the improvement of arterial pressure management. In a parallel study, ***PWV*** was assessed in chronically hemodialyzed patients by measuring the central arterial pathway (carotid-femoral) and the peripheral pathway (carotid-brachial) [31]. The aim of the study was to determine the association between body fluid status and central and peripheral arterial stiffness levels. It was concluded that volume status and overload are associated with central, but not peripheral, arterial stiffness levels regardless of the blood pressure level, in that kind of patients. Similarly, etiologically-related early vascular aging was evaluated in end-stage renal disease, by [32, 33].

3.3. Local Arterial Stiffness: Systo-diastolic Parameters, Elasticity and Arterial Viscosity

At initial stages, the damaging effects of vascular diseases such as atherosclerosis would be frequently localized in specific vascular segments, such as carotid and/or femoral arteries. In these cases, the measurement of the global or regional arterial stiffness would not be able to detect the alterations. This condition could be achieved by means of techniques permitting a local biomechanical evaluation of the vascular segments [5]. Furthermore, only the local approach allows accurate determination of the biomechanical properties of the arterial segments [27]. The functional capacity of a segment depends on its viscoelastic properties. These properties allow the artery to store, transfer and dissipate energy in every pulsation. Essentially, the determination of the pressure-diameter relationship of an arterial cycle encloses a hysteresis area or loop, which is related to viscous behavior [6]. As a result, the analysis of the associated parameters and hysteresis area provides information about arterial viscosity. This is modified in physiological and/or pathological states in which there are changes in muscle tone and/or wall thickness, and its quantification has proved to be useful to assess the adaptation of the arterial wall to changes in hemodynamic conditions [14, 34, 35]. It is worth mentioning that if the arterial wall did not present viscosity, a hysteresis area would not be observed; and the two-way trajectory during systole and diastole, a purely elastic relationship, would show a non-linear trajectory (*e.g.* determined by the different elastic moduli of elastin, collagen and vascular smooth muscle). During an arterial cycle, the diastolic regression would correspond to the pressure-diameter curve (or stress-strain) if the artery only had elasticity. This is the reason why the indicators of arterial elasticity, obtained from the pressure-diameter relationship are often quantified in the diastolic phase.

In our noninvasive studies carried out in individuals, the arterial pressure signal is obtained by means of applanation tonometry, at the same site than that of the arterial diameter. Applanation Tonometry is a method that employs a high fidelity mechanographic transducer to record pressure wave. When the surface of the artery is flattened by the sensor, the circumferential stress applied on the vascular wall is balanced and the pressure can be recorded as it would have been registered by an intra-arterial catheter [36]. Once the maximum arterial pulsation point is localized by the palpation of a superficial artery (*i.e.* carotid, brachial, radial and femoral arteries, among others), the sensor is placed on the skin pressing against the underlying solid structures. The signal obtained should deliver a reproducible, stable and large amplitude waveform. Subsequently, the systolic and diastolic values of the pressure wave need to be calibrated using sphygmomanometric values, which are taken previously. It is assumed that in prone position, the diastolic and mean pressures remain constant along the arterial system [27].

The arterial diameter signal is obtained noninvasively from an ultrasound record (Mode-B ultrasound) and image processing software. The scanner is connected to an equipment that stores and processes the video, minimally for 10-15 heartbeats. Afterwards, the analysis of the video using a specific software (Hemodyn-4M, Buenos Aires, Argentina) makes it possible to determine, from the automatic detection of borders, the vascular lumen variations (and the intima-media thickness) in each image of the video [37]. The instantaneous diameter waveform is obtained automatically since the software plots the diameter acquired for each image of the video in relation to the number of the sample (image)

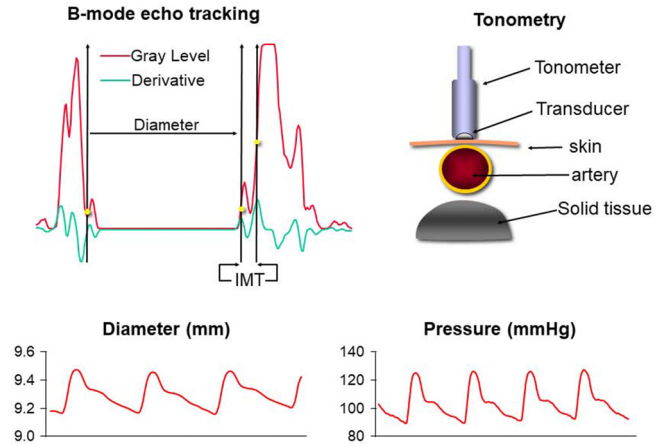

Fig. (1). Left: Arterial diameter waveform and intima media thickness (**IMT**) assessment by means of B-Mode ultrasound images processing. Right: Arterial pressure assessment by means of tonometry technique.

the video in relation to the number of the sample (image) analyzed. The electrocardiographic signal is useful to synchronize (in temporary terms) the pressure and diameter time series, if the acquisition of both parameters was not performed simultaneously [37, 38]. In this sense, an alternative method to assess systolic local arterial blood pressure from non-invasive assessment of carotid and femoral arterial pressure using B-mode ultrasound diameter is proposed in [39] (Fig. **1**).

The wall inertia of the carotid artery was evaluated in [11], in normotensive and hypertensive subjects using an ***ARMA*** model, which permitted the simultaneous estimation of the elastic, viscous and inertial contribution of wall dynamics (Fig. **2**). The inertial index was found to be high in hypertensive subjects and associated to the intima-media thickening of the artery. This reinforces the idea that arterial hypertrophy is related to a vascular growth phenomenon in this pathology.

In clinical terms, the most widely used indices to evaluate local biomechanical properties tend to simplify the arterial biomechanical behavior, only considering the pressure and diameter systo-diastolic variations (*i.e.* maximum and minimum values) in their calculation method. Basically, the more stiffened the artery, the lesser the change in the diameter for a systo-diastolic variation of pressure. These systo-diastolic indices have been used in many works to determine local arterial stiffness, but it has been difficult to interpret and compare the published results since the same index has been named differently while different indexes have been given the same name in different works. On the other hand, the non-linear relationship between stiffness and arterial pressure is taken into account by other indices (*e.g.* beta index), thus providing information considering the subject's pressure level [36].

The pressure, diameter and parietal thickness of muscular (femoral) arteries were measured by our group in patients using tonometry and ultrasound images [40]. A Kelvin-Voigt model of the segment wall was used to derive elastic (***Epd***) and viscous (***Vpd***) pressure-diameter indices, the buffering function (***Vpd/Epd***), and the conduit function (***1/Zc***, where ***Zc*** is the characteristic impedance, obtained from ***PWV*** and diameter measurements). The incremental Young modulus and the pressure-strain elastic modulus were also calculated. The obtained results were then compared to *in vitro* evaluations of cryopreserved homografts, showing similar viscoelastic and functional properties.

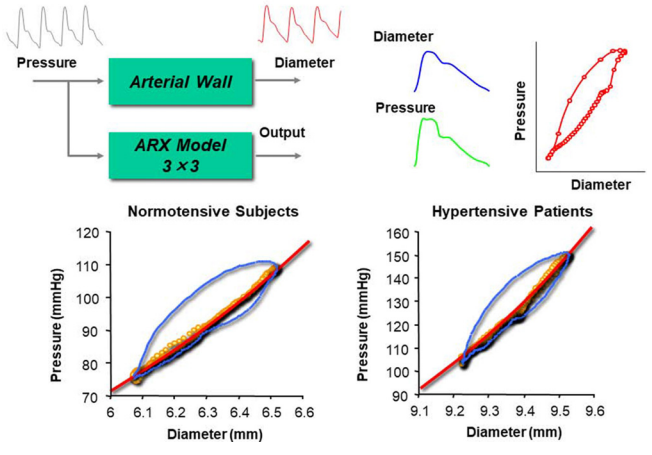

Fig. (2). Evaluation of normotensive and hypertensive subjects using an autoregressive, discrete and linear model (ARMA) for the simultaneous estimation of the elastic, viscous and inertial contribution of wall dynamics.

3.4. Central Aortic Pressure Evaluation

Changes in the peripheral pressure do not always correspond to pressure changes at the aortic level. In addition, in the **CAFE** (Conduit Artery Function Evaluation) study, it was demonstrated that antihypertensive drugs may have different effects on central pressure, despite having similar effects on peripheral pressure. Central aortic pulse pressure (***PP***) and the central Augmentation Index (***AIx***) are predictors of mortality in hypertensive patients [41]. In healthy young subjects whose "augmented pressure" is negative, so will the ***Alx***. In adults, the augmented pressure and ***Alx*** are positive, indicating that the reflected waves contribute to increase systolic pressure [42]. The index can be also influenced by the heart rate, so its value for a heart rate of 75 beats/minute (***AIx@75***) is generally assessed. Radial pressure waveform is usually measured by tonometry and calibrated, and a generalized transfer function is applied to radial records (with adjustments considering gender and age of the subject) in order to assess central pressure [42]. Gender differences and age related changes in central pressure of healthy individuals were analyzed by our group [43, 44] in terms of their "excess" and "reservoir" components. Subsequently in [45], it was demonstrated that aortic blood pressure and wave reflections (***AIx@75***) as well as elastic arteries stiffness (***PWV***) are increased in hypertensive pregnant women. Recently in [46], a non-invasive central blood pressure estimation method based on the pulse transit time principle (***PTT***, estimated from electrocardiogram and ballistocardiogram recordings) was proposed, towards the development of a compact miniaturized device that allows the integration of wireless blood pressure monitoring into a wearable system.

3.5. Endothelial Function

The endothelium is a major modulator of the arterial function, and in particular of arterial biomechanical behavior and geometry, through the release of regulatory factors (vasodilators and vasoconstrictors) that appear to dominate the control of the vascular tone [36]. Consequently, the assessment of the vascular response to factors stimulating the endothelial release of vasoactive substances constitutes a valuable tool in the study of the endothelial function. Generally, the endothelial function is evaluated by means of the reactive hyperemia test, where a change in the diastolic arterial diameter is measured in response to an abrupt of arterial blood flow. This variation is induced by a transitory 'ischemia', performed in a territory related to the artery under study. A decrease in this 'flow mediated dilation' (***FMD***) is interpreted as a reduction of availability of endothelial vasodilating factors (*i.e.* unavailability of nitric oxide) and of endothelial vascular protection. Reductions in the normal levels of ***FMD*** have shown an association with ***CV*** risk fac-

tors (*e.g.* arterial hypertension), and have been detected in early stages of arterial disease development, particularly in atherosclerosis [47, 48].

Our group has evaluated the endothelial function of individuals by analyzing the ***FMD*** of the brachial artery in the forearm. The procedure can be described as follows: An ultrasound probe of 7.5 MHz is used, fixed to a stereotaxic device. In basal conditions, a B-mode sequence of images is registered (video) and profile and blood flow velocities are obtained. A sphygmomanometric cuff is then placed in the forearm, insufflated for 5 minutes, with a pressure of approximately 50 mmHg over the systolic pressure. This determines transitory ischemia in the tissues distal to the occlusion, with the consequent dilation of their resistance vessels. After cuff release, a transitory augmentation of blood flow at brachial level takes place (which reaches its maximum values close to 15 seconds post-release), thus determining the increase of the wall shear stress and the liberation of arterial vasodilation factors. The artery is visualized in a longitudinal cut and it is recorded from 15 seconds before the release until 4 minutes after. The acquisition and analysis of the basal and post-release arterial diameter signals obtained from the ultrasound videos make it possible to quantify the ***FMD*** and the dynamics of the vasodilator response. This technique was applied to study hyperemia-related changes in arterial stiffness of normal young adults [49]. The "stiffness index", which is obtained by the analysis of the pulse contour of the peripheral wave, was positively correlated to carotid-radial ***PWV*** variations. On the other hand, an altered endothelial function can be also associated with hypertension during pregnancy. Women with gestational hypertension and preeclampsia showed endothelial dysfunction during a study carried out in [45]. Furthermore, vascular reactivity was characterized in healthy individuals by means of simultaneous arterial pressure and diameter time profiles [50]. Different exponential functions were fitted to systolic pressure and diameter responses, suggesting a differentiated vascular behavior between genders.

3.6. Multi-gate Pulsated Velocimeters

A different technique was also developed to study the arterial reactivity in human arteries. The technology was based on the automatic manipulation of a doppler probe (DOP1000, Signal Processing Inc., Switzerland), operated by a robot, which provided a permanent velocity profile, the simultaneous estimation of shear rate values and an estimation of the arterial diameter (Fig. **3**). With the help of this technology, the variation in diameter of the humeral artery was tested in healthy subjects, in response to a decrease and an increase in blood output. This was caused by an occlusion in forearm circulation, using a pneumatic cuff. Shear-mediated response of humeral artery diameter was analyzed before, during and after releasing the occlusion in the forearm circulation [12]. The study revealed that vasoconstriction and vasodilation in women were more pronounced than in men. It was suggested that there are different gender-related sensitivities in the regulation of the muscle tone of medium-sized arteries. The arterial dynamics was unified, which is supported by all the previous studies conducted by our team, as well as of arterial wall vasomotricity and its relationship with the endothelium. A similar approach was developed in [51] where the flow behavior (morphology of the velocity profiles) was evaluated for different hemodynamic states in both genders.

3.7. Study of Cryopreserved Homografts

In view of the urgent global need for vascular substitutes (**VS**) capable of overcoming the biomechanical limitations found in those currently used (veins and synthetic materials) and for internal networks for the exchange of cardiovascular tissue, human arteries have been proposed as possible vascular substitutes. However, the adequate hemodynamic and biomechanical behavior of arteries obtained from donors remains unknown, since their functionality may be impaired by the techniques used in tissue banks, the tissue long-distance shipping procedures and the interaction of the artery with the recipient's tissue. As a result, our team evaluated the characteristics of cryopreserved arterial homografts used for therapeutical purposes (pre- and post-implant) in patients [18].

Native femoral arteries anastomosed to cryografts, implanted cryografts, and arteries from subjects, recipient-like and multiorgan donors-like, were studied in [19, 52, 53]. Results showed that implanted cryografts were remodeled, with increased wall thickness, wall-to-lumen ratio and wall cross-sectional area and were stiffer than multiorgan donor-like arteries, but more compliant than recipients' arteries. Consequently, they could be considered as alternatives in arterial reconstructions since they ensure the gradual transition of patients' arteries biomechanical and functional behavior. In the same line, a characterization was performed in [20] of native vessels/implanted cryografts' mechanical and geometrical coupling, evaluating the cryografts' capability to ensure mismatch levels lesser than those expected for expanded polytetrafluoroethylene (***ePTFE***) and cryografts' functional properties considering their histological and ultrastructural characteristics. The results showed that post-implant cryograft remodeling improved native vessels/ cryografts coupling. Additionally, cryografts would have mechanical and geometrical advantages over ***ePTFE*** and anastomotic remodeling differed from that expected only in terms of hemodynamic factors.

In addition, an intercontinental vascular tissue exchange system was designed, in collaboration with the Materials laboratory of Universidad Politécnica de Madrid, in order to analyze if the properties of the arterial tissues could remain unaltered [21].

4. IMPROVING THE CARDIOVASCULAR RISK SCORE

4.1. Vascular Age

With the aim of developing and applying strategies to improve cardiovascular risk stratification and subclinical vascular disease detection, a computational approach was adopted. An complete tool was designed, developed and implemented in **CUiiDARTE**, with the main objectives: to promote screening for subclinical atherosclerosis, to develop a centralized database to store information obtained noninva-

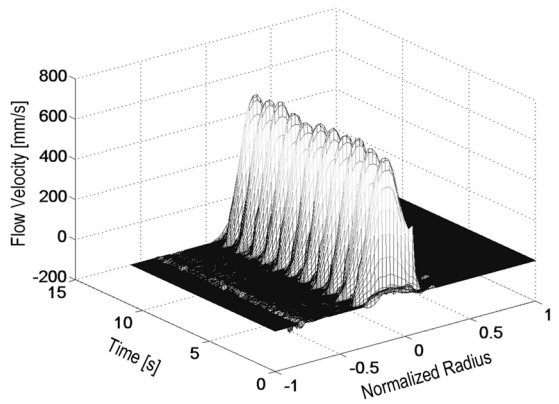

Fig. (3). Three-dimensional image of flow velocity profiles acquired with a multi-gate doppler velocimeter. Near parabolic shapes are observed (radial artery measurements).

sively from anywhere in Uruguay, to develop a biomathematical model integrating values for arterial structure and function into traditional cardiovascular risk assessment, to generate a detailed and comprehensive report for the specialist (comparing patient data with reference data from the healthy population) and to generate a similar report to be delivered to the patients (using a structural and functional arterial age calculator), assessing the general state of their arteries [3]. The approach adopted in **CUiiDARTE** was based on determining the presence of atherosclerotic plaques in common, internal, and external carotid arteries, as well as ***IMT*** and instantaneous diameter assessments, ***PWV*** calculation, peripheral and central pulse wave analysis, endothelial function (by means of ***FMD*** evaluation) and ankle-brachial index. A10-year cardiovascular disease risk (%) was estimated with the Framingham risk model [16], considering age, LDL-C, HDL-C, brachial pressure levels (continuous variables), gender (sex), diabetes, and current smoking (categorical variables). Then, a linear regression model was applied to obtain an age ('calculated or theoretical') as a function of noninvasive vascular markers (***PWV***, ***IMT*** and ***AIx@75***). This value was then used to calculate the integrated 10-year Framingham coronary heart disease (***CHD***) risk estimate. The consideration of the noninvasive vascular markers resulted in differences between calculated (theoretical) and chronological age in subjects with atherosclerotic cardiovascular disease, the former being higher. Finally, the estimated (or readjusted) Framingham risk score for 10-year cardiovascular disease (considering the theoretical age) was higher than the Framingham risk score calculated before the vascular evaluation. In this sense, the integration of vascular parameters to calculate arterial or biological age used to calculate global risk scores could aid in the individualization and accuracy of risk estimation [3, 54].

A monitoring system could be used to measure several of the previously addressed parameters indicating the physical status of the elderly patient. One major health issue arising with age is the increasing prevalence and severity of some infectious diseases, which partly reflects the age-related decline in immune function. The current promising hardware/software platforms for wireless cardiac monitoring could include important measurements such as blood pressure and arterial ***PWV***, and have that information directly uploaded to the system [55].

4.2. Coronary Calcium

The integration of coronary calcium to the 10-year Framingham ***CHD*** risk in asymptomatic untreated hypercholesterolemic men resulted in downgrading rather than upgrading risk and did not change treatment eligibility, except in intermediate risk subjects, less frequently eligible for treatment [16]. Similarly, the 10-year ***CHD*** risk was assessed, jointly with the probability that the ***CAC*** score of an individual fell into four different categories (0, 1-100, 101-400 and > 400) in [56]. A reclassification of ***CHD*** risk was then carried out, thus improving the calculation of overall Framingham risk. As a result, the use of coronary artery calcium (***CAC***) for stratifying coronary heart disease risk may change the proportion of subjects eligible for risk reduction treatment, thus decreasing the cost-effectiveness of primary prevention [16]. The same line was explored in [17], where clustering of cardiovascular risk factors highlighted the coronary artery calcium as a strong clinical discriminator.

CONCLUSION

There is enough evidence suggesting that conduit arteries are clearly involved in both the diagnosis and complications of arterial hypertension [57]. Hemodynamic development of this vascular pathology jointly with ***CV*** epidemiology impose the application of several noninvasive measurements in order to evaluate (and also reduce) the risk of ***CV*** disease (or events) and to improve primary prevention.

Mechanisms of hypertension should be conceived within its steady and pulsatile aspects. ***PP*** plays an important role in the pathogenesis of the disease, particularly after midlife, and higher ***PP*** is related to clinical events [58, 59]. It has to be noted that a stiff conduit (*i.e.* aorta) increases the delivery of pulsatile energy into the circulation, thus transferring the hemodynamic impact to the vulnerable microvasculature of tissues leading to eventual structural damage. As a result, Carotid-Femoral ***PWV*** (a reference-standard method for arterial stiffness assessment and an independent predictor of ***CV*** mortality), ***AIx*** (information on wave reflection) and central ***PP*** assessments can be currently used as markers of vascular damage. However, forward pressure wave amplitude (and not wave reflection) was recently suggested to be the key component of hemodynamic load that is associated with ***CV*** events in a model that adjusts for standard risk factors [60].

Abdominal aortic calcification (***AAC***) and central arterial stiffness are independent predictors of mortality and nonfatal ***CV*** events in dialysis patients. The risk associated with an increased ***PWV*** is less pronounced at higher levels of calcification. Assessment of ***AAC*** and ***PWV*** is feasible in a clinical setting and both may be used for an accurate ***CV*** risk estimation [61-63]. Hence, the treatment strategies should be focused on suppressing or inhibiting the formation of vascular calcifications, maintaining arterial function. Reduction of arterial stiffness (by means of drug administration) and buffering the increased blood pressure variability are likely to further improve the current approach to the treatment of arterial hypertension, reducing ***CV*** risk.

On the other hand, previous studies have shown that arterial stiffness indices are variably associated with each other, ranging from no significant relations to highly significant associations. More specifically, measures of arterial stiffness mainly involve "regional" or "local" assessments, depending on the model (propagative or pulsatile type) assumed for their calculation [61]. In addition, arterial stiffness indices have displayed some degree of blood pressure dependency, regarding different blood pressure perturbation maneuvers, even for those that are thought to be or claimed to be blood pressure independent. This is consistent with the notion that various measures of arterial stiffness may not be interchangeable in clinical and research [62].

It is well known that endothelial dysfunction constitutes an important pathophysiological factor in atherosclerosis and precedes the morphological alterations in the arterial wall, thus playing a critical role in the context of atherogenesis. Since ***FMD*** is the most widely used technique, the need of a highly skilled technician for the acquisition and post-processing of the obtained ultrasound images and a lack of unified criteria related to the specific site of the measurements constitute the main obstacle in clinical practice [64]. In contrast, peripheral arterial tonometry was developed as a more reproducible and simple method. Relatively novel techniques analyze changes in volume pulse waveforms, acquired at the finger's microvasculature zone. However, these type of signals may be affected by agents that are not related to endothelial factors and, due to the fact that measures are in the microvasculature, this approach could be useless in patients with peripheral vascular diseases [50, 65]. As a result, the simultaneous evaluation of both techniques could help to improve vascular reactivity evaluation [50]. Moreover, it has been demonstrated that different measures of vascular reactivity (*i.e*. ***FMD***, hyperemic shear stress, reactive hyperemic flow measured with ultrasound, changes in ***PWV*** between the brachial and radial artery, reactive hyperemia index assessed by fingertip arterial tonometry (EndoPat), fingertip temperature rebound (Endothelix), and skin-reactive hyperemia measured with a laser Doppler monitor) are not strongly associated with each other and this association does not even reach statistical significance [66].

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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