

Review Article

Twenty Years of Non-Invasive Vascular Evaluation: from Bench to Bedside from Theoretical to Precision Medicine

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Purpose

To analyze, from a historical point of view, the scientific and technologic progression of the non-invasive vascular evaluation, in particular the huge step ahead in the last 20 years, in parallel with the evolution from a “treatment-after- event” based Medicine to Preventive Medicine. No-invasive vascular Evaluation jumped in the last twenty years from the bench to the bedside, giving rise to a Precision Medicine, detecting and preventing the atherosclerotic disease in the earliest stages, in order to control the huge burden of cardiovascular disease that the human kind has been suffering the last hundred years. A worldwide and widespread use of non-invasive vascular evaluation in the current clinical practice for cardiovascular prevention remains as a challenge, and this review is a call to action to do so

Keywords: Arterial remodeling; Arterial stiffness; Cardiovascular prevention; Endothelial function; Non-invasive vascular evaluation; Subclinical atherosclerosis

An Abridged History

The analysis of arterial properties, especially through the pulse wave, has been used during more than 4000 years, since Chinese during the Yellow Emperor dynasty, wrote down that “if one person’s arteries are stiff, he will develop legs edema, abdomen distention, shortness of breath and jaundice”.

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Later on, a long period of speculation about the arteries since if they were conduits of air (in greek Ar= air therion= conduit) or “neu-ma” and later on, what kind of humors they transported (blood, bile and so on) but always, the stiffening of the arteries was an ominous sign.

Finally, during the XVIth century William Harvey (“The Motu Cordis”) and in the following century Stephen Hales (Haemostatics) presented a dynamic approach to Vesalio’s anatomical observations of the cardiovascular system, during the Renascent period, additionally nicely depicted by Leonardo Da Vinci.

Mainly Harvey, established the hypothesis of the cardiovascular system as we actually know, related to the lungs, and surprisingly estimated the presence of “capillaries”, several years before they were discovered by Malpighi and clearly supported by the physics and experimental analysis of Poiseuille. By the same period, the elasticity law (Hooke) and the elastic modulus (Young) were described and later on, applied to the cardiovascular system.

During the XIXth century the pulse profile was investigated by Marey and Mahomed in deep, as a reflection of the vascular function and a related cause of CV disease with clever devices overcoming the technical limitations at that time. Bright, MacKenzie and Osler recognized its importance in the clinical field. By the end of the century, the presence of atherosclerosis in the arterial wall, described 20 years before was related to sudden cardiac death in young males by Heberden. Atherosclerosis (Cholesterol deposits in the arterial wall) and thus, arteriosclerosis (arterial stiffening) were initially described and studied as the cause of these events.

In the XXth century two different lines separated the investigators: one focused in the arterial function, mainly by pulse analysis and the pressure - volume curves and other, since Riva Rocci first blood pressure measurement by 1900, focused in the blood pressure values independently of the arteries status.

Thus, the first group discovered the arterial stiffness and its threatful meaning for cardiovascular disease and the other, reached to the conclusion, by mid-1900, that “the harder arteries need highest pressures”. Finally, the actuarial analysis revealed that the higher the blood pressure levels, the higher the cardiovascular mortality. Two presidents of the USA (Wilson and Roosevelt) paid with their lives this misunderstanding.

By mid-1900 Florey (Nobel prize) stated that the endothelial layer was rather an endocrine organ than a cellophane boundary, and Moens, Korteweg, and few years later, Braumwell and Hill (Nobel prize) described the pulse wave velocity as a reliable marker of the arterial wall stiffness. Ultrasounds prompted in the Cardiovascular Medicine after World War II and later on, in the 80’s CT and NMR soon were adapted for cardiovascular evaluation.

After the World War II the interest in vascular mechanics was reassumed, by Starling, Frank and Wiggers. Later on, Donald Mc Donald, Yuan Cheng Fung, Michel O’Rourke, Wilmer Nichols, Stanley

Franklin, Michel Safar and John Cockcroft were the founders of a new dawn of experts in Vascular Mechanics and its application in the clinical practice, paving the way to future generations that in the first two decades of the XXI century jumped from the bench to the bedside, from the theoretical models to the clinical applications of vascular evaluation, thus enabling a better understanding of the cardiovascular disease from physiopathological approach leading to the prevention and rational treatment of the vascular disease [1,2].

In parallel, advances in the field of pharmacology provided a huge armamentarium of anti-hypertensives, anti-diabetic drugs and hypolipemians to treat and prevent the main risk factors. However, the progression of risk factors was propelled by the changes in life style post war, with unhealthy cardiovascular diet, the growth of overweight, sedentarism and smoking.

The massive epidemiological impact of cardiovascular disease in terms of disability and death rose steeply after the end of World War II and then the so-called cardiovascular risk factors were individualized. Based on a better knowledge of the physiopathology of the disease, a race started to control the burden of it.

Beta blockers, diuretics, insulin and antidiabetics in the 50's, calcium antagonists in the 70's, ACE Inhibitors in the 80's and ARBs and statins in the 90's are only a few outstanding steps to name out in the search of measures to tackle the cardiovascular disease related to its risk factors and in particular, the atherosclerotic process.

At the same time, several palliative solutions, grouped as "Revascularization Procedures" like thrombolytics, coronary artery bypass surgery and angioplasty (bare or with stents) provided a solution for those cases of advanced obstructive atherosclerotic disease beyond of the pharmacologic control and any kind of prevention.

Entering the new millennium (2000) based on more than two decades of preclinical investigation, the attention was focused finally in the prevention of the atherosclerotic vascular disease, more than only treating the risk factors but using a comprehensive approach to detect it at early age and early stages of development [3].

To assess the endothelial dysfunction, the arterial stiffness and remodeling and even minimal plaques in the "Preclinical Stage" then started a steady rise in priority, in the clinical practice, rather screening younger subjects than waiting to receive symptomatic patients with clinically overt disease and complicated atherosclerotic plaques, needing a revascularization procedure.

This was the introduction of the Non-Invasive Vascular Evaluation, at the beginning of the new millennium, based in premises like:

- 1) Detect the atherosclerotic disease as early as possible
- 2) Start the screening of vascular disease in younger people
- 3) Treat arteries rather than treating risk factors [4,5].

In 2000 the Vth Conference of Primary Prevention in the USA and the birth of ARTERY (Artery Research Into Arterial Structure and Function) Society in Wales (UK) integrated decades of investigation and settled the basis of an irreversible process to include the arteries as a target organ in the evaluation of risk and the treatment of the atherosclerotic cardiovascular disease in the clinical practice. The jump from the bedside to the clinical practice was ready [6].

The Dawn of the Non-Invasive Vascular Evaluation Era

Since the publication of the Framingham study in the 50's the prevention of cardiovascular complications was based in the "clinical" cardiovascular risk projected to ten years and later on, to be more impressive, to thirty years, due to the need to prevent early, it was necessary to show more shocking projections (from 5 to 15% or 10 to 30% of CV events risk).

As stated in the Vth Conference of Primary Prevention, after 50 years of use, the Framingham Score and many others of its kind (SCORE, Rotterdam etc.) showed a wide mismatch of patients with low or intermediate risk but a higher degree of vascular compromise, that could be linked to an increased residual risk. The main drawback of these scores was that the relation between the risk factors (namely hypertension, dyslipemia, diabetes, smoking or obesity) and CV complications was neither lineal nor comparable. The mix of them is highly frequent and the interaction of genetics and epigenetics result in a non-lineal relation.

It meant that the vascular evaluation must be added to the scores at the time of estimating the risk in cardiovascular patients, because arteries are the ultimate target organ of the disease and the main determinant of the evolution. Vascular evaluation must not replace the risk calculation scores; it must improve them by increasing the patho-physiologic coherence and prognostic accuracy [2-7].

At that time, ARTERY Society started gathering the most experienced experts worldwide, and its mission is the awareness of the study of arteries structure and function. Increasing the knowledge in this field working together basic and clinical investigators, engineers, physics and other allied sciences, seeking for a better knowledge of the physiopathology of the vascular disease and to develop clinical applications in the prevention and treatment of it. (<https://www.arterysociety.org>)

FROM 2000 to 2020

The progression of the Non-Invasive Vascular Evaluation (NIVE) grew steadily following several paths but converging in the same direction: Detect the vascular disease at the earliest stage and stage as possible.

As an example, a quick look to the publications along this decade of any of the vascular parameters like carotid Intima Media Thickness (cIMT), plaques number or composition (Plaques Analysis = PA), Pulse Wave Velocity (PWV), Arterial Stiffness (AS) or Endothelial Function (EF) boosted from a few tenths to thousands. As an example, only the papers with the keyword "Arterial Stiffness" in PubMed raised from a hundred in the 80's to more than a thousand at the beginning of the XXI century [2].

At this time studies like CHS, ARIC were ended and MESA study was launched and the evidence for searching preclinical atherosclerosis gave raise, in 2006, to initiatives like the SHAPE task Force (Screening for Heart Attack Prevention and Education) initiative in the USA based on a new profile of prevention: "From Vulnerable Plaque to Vulnerable Patient" [8].

The rationale was to add the vascular evaluation to the scores for screening and prevent CV disease, and was so clearly explained, scientifically and from the sanitary point of view, that was adopted by some states (Texas and Florida) as state policy in CV prevention.

After ten years of the first determinations of endothelial function by David Celermajer (1992) using the forearm ischemia-hyperemia test, there were published the first “Guidelines for the Ultrasound Assessment of Endothelial-Dependent Flow-Mediated Vasodilation of the Brachial Artery” in the USA (2002), followed by ESH guidelines in 2004 and ESC Guidelines in 2011 ruling the way to perform the endothelial function tests and their clinical application [9].

At the same time, O’Rourke, Vlachopoulos and Staessen presented for the first time a guideline with the definitions and reference values for PWV. The way was paved for the inclusion in guidelines and for its use in the clinical practice [10].

In 2007 the Guidelines of the European Society for Diagnosis and Treatment of Hypertension, included for the first time in the evaluation of target organ disease, the artery, including IMT, Plaques, PWV and EF. Noticeably this outstanding document included also, for the first time, the metabolic syndrome for CV risk stratification. This is a cornerstone document recognizing for the first time the artery as a target organ and a risk marker [11].

In this year, the Manheim Consensus gathered the European Experts to standardize the measurement of IMT and defined the atherosclerotic plaque. This document yielded the gold standard for these determinations until 2020 when the new Consensus of the American Society of Echography reviewed this procedure, the boundaries and diagnostic criteria [12,13].

In parallel, the American Society of Echography released a Consensus in 2008 entitled: “Use of Carotid Ultrasound to Identify Subclinical Vascular Disease and Evaluate Cardiovascular Disease Risk” underlining the concept of these techniques to reestratify risk in intermediate risk patients or those with heavy hereditary burden [14,15].

After the presentation of the BOGALUSA study, ARYA, Young Finn’s Study, the China Children study and others, finally in 2009 American Heart Association released a Consensus of “Noninvasive Assessment of Subclinical Atherosclerosis in Children and Adolescents” soon followed, the same year, by the Guidelines of ESH for management of hypertension in children and adolescents which included noninvasive evaluation too. This is also a highly significative evolution in terms of prevention, far from secondary prevention in complicated patients and even, the primary prevention. This shift is to “primordial prevention” (to avoid that the children of CV patients express CV risk factors) a major challenge face to the future [16].

In 2009 Laurent-Boutouryie- Nilsson, nice and precisely, described the Early Vascular Ageing putting into black and white that the biological age and the vascular age could differ substantially, and it is linked to increased CV risk. This is the main reason why arteries must be evaluated at the time of the CV risk stratification of a patient. This concept was reinforced and enlarged in the Lancet Commission on Hypertension paper in 2016 entitled: “A call to action and a life course strategy to address the global burden of raised blood pressure on current and future generations” [7,17,18].

In 2010, Valentin Fuster first presented the PESA Project (Progression of Early Subclinical Atherosclerosis), and in agreement with these findings, he found that two out of three patients at intermediate risk presented advanced atherosclerotic disease. Two parallel studies, the AWHs and the BIOIMAGE, showed many interesting findings: 1) the plaque burden was stronger in terms of predictive value than the plaque vulnerability 2) plaques evaluation allowed to reestratify

patients risk, no matter using US or calcium score and take decisions on treatment (i.e. use of statins) [19,20].

We are waiting the results of this project about the evolution of plaques as predictors of disease and the impact of interventions on the prognosis. It is important to stress the enormous knowledge in terms of physiopathology of the atherosclerotic process that this investigation will provide and the potential to translate it to the clinical practice.

Shifting our focus to arterial stiffness, the extensive investigation during almost 30 years finally gave rise to a Consensus on Central Pressure in 2007 that demonstrated the power of the arterial stiffness as a risk predictor and if therapeutic interventions were focused on it the results could be widely different. This was one of the first impressive interventions of Artery Society members. In 2010 in the European Heart Journal the first Reference Values of PWV was published as “Determinants of PWV in healthy people and in presence of CV risk factors” which was a methodological consensus endorsed by ARTERY and a document for reference values of PWV. Since then, in the European Heart Journal other two documents procedure guidelines and reference values like this, but now, for IMT and Central Aortic Pressure (CAP) were published in 2014 [21-24].

In 2008 a branch of ARTERY Society started in Asia and Oceania, the Pulse of Asia, later on, in 2010 started North American Artery in USA and Canada and in 2016 LATAM Artery in Latin America. Soon the guidelines and reference values spread worldwide and the ARTERY Meetings in Europe enlarged and echoed in the sister societies with very important regional meetings.

In 2015 the ESC Working Group on Peripheral Circulation and ARTERY released a position paper entitled “the role of vascular biomarkers for primary and secondary prevention” that stated clearly according to the level of evidence the indication of vascular biomarkers like IMT, Plaques, PWV and EF. It was closely followed by a AHA statement with “Recommendations for Improving and Standardizing Vascular Research on Arterial Stiffness” which clearly settled the carotid femoral PWV as IA indication for measuring aortic stiffness. Two huge metanalyses of Vlachopoulos (15000 patients follow up 7 years) and Ben Shlomo (17000 patients follow up 1 to 5 years) supported the cPWV as a strong predictor of cardiovascular events and death [25,26].

Since then, the concept of early prevention grew, the need to detect early vascular ageing in younger subjects turn from an interesting concept to a need between doctors and patients [3].

In spite of all these evidences, European and American Guidelines (2018 and 2021) kept neglecting the value of noninvasive evaluation in the clinical practice arguing technical and cost limitations as well as lack of evidence, but a close review of the bibliography shows that most of the evidence showed in this text was ignored in the elaboration of these Guidelines. In contrast, many local guidelines in other continents like Asia and Latin America have included the noninvasive vascular evaluation and are progressively incorporated into the clinical practice even when the lack of resources is a hard reality [27].

However, strong evidence keeps accumulating like a huge met-analysis of IMT with more than 100000 patients (2020), the application of the PWV analysis to the SPRINT study, the results or the SPARTE study of treatment based on PWV. Recent papers like the American US society Consensus (2019), the European Consensus on

Endothelial Function Evaluation (2019) and the state-of-the-art review in *JACC* of Chirinos about Large Arteries in Health and Disease or the Consortium on 24 hour evaluation of Central Pressure give strong support and hope for a great change in the CV Prevention [28-34].

On June 6th 2021 ARTERY celebrated worldwide the “Day of Vascular Ageing”, the first step of a wide awareness program of CV prevention based on vascular care. (<https://vascagenet.eu/vascular-ageing-awareness-day-2021>)

Thus, we arrive to present days, with meetings of ARTERY and sister societies in hybrid format performed in North America, Asia and Oceania and Latin America during 2021 and a new guideline in process and growing interest worldwide of patients and doctors in achieving a better and effective cardiovascular prevention.

Discussion

The history shows the development and rationale for Non-invasive Vascular Evaluation to detect subclinical atherosclerosis and prevent Cardiovascular Disease complications.

However, many concerns rise about this statement, like 1) how we can measure the effectiveness of Preventive Measures; 2) Can we trust in vascular biomarkers? and 3) the technical difficulties to implement their measurement in the clinical practice, in particular to decide therapeutic interventions.

It is clear that the measurement of the effectiveness of preventive measures need a complete reformulation of the typical PROBE studies or daily life studies, where typically Drug A efficacy is compared against Drug B. In preventive studies, we need to know the disease and its epidemiology (incidence and prevalence, trends etc.), the biomarker that we will use in terms of efficacy (C index, the reclassification index), the physiopathology of the disease and the interaction of risk factors and interventions. We need to know all this information in order to design an appropriate study, lasting enough time to demonstrate a significative reduction of the MACE and that this reduction is due to the prevention strategy based in our biomarkers.

Second, biomarkers are always criticized in order if they have enough power to detect the vulnerable, at risk patient to initiate preventive measures and if they will result in benefits that overcome the harms of unnecessary treatment. Plaques, pulse wave velocity demonstrated a strong predictive value and that treatment can modify them. What still remains to be answered if they are modified, it results in a significative reduction of cardiovascular risk, or even better, of cardiovascular events.

Finally, the technical limitations, with the advances in medical technology, in every field like ultrasound, CT and NMR, the computational advances with Artificial Intelligence in imaging processing and diagnostic algorithms and the development of simpler, easy to use devices for doctors and patients, will make easy to measure arterial function soon and vascular health in the clinical practice at lower costs. The challenge is to include the non-invasive vascular evaluation in the diagnostic algorithm in Cardiovascular Prevention. In the last 20 years, people globally know that they have to prevent diseases, education and communication have changed in this sense, now doctors and the Medical System must face the challenge of changing their mindset from Late Intervention to Early Prevention.

Humanity survived mostly based on the wisdom of the elder people. Should we transform our Medicine in the future according to the ancient proverb: “It is better to prevent than to cure (a disease)”?

Taoists, use to say: “what happens is a result of how it happens”..... Cardiovascular disease may happen as result of what happens in the arteries. Let’s take a look.....

Summary

This review summarizes the history of arterial evaluation in the last 4000 years, describing four periods: 1) Ancient history of vascular speculation and later on evaluation until XVIIth Century 2)The development of theories about the cardiovascular system and the first trials to analyze arteries and heart structure and function in the XVII and XIX Centuries 3) the birth of the Cardiovascular Mechanics and in particular the non-invasive vascular evaluation, during the XXth Century, with the dichotomy between evaluating the pulse or measuring the blood pressure and the wonderful and astonishing advances in Cardiovascular Medicine and finally 4)The first 20 years of the XXIth Century with the jump of the non-invasive vascular evaluation from the bench to the clinical practice in parallel with the evolution of the mindset from Medicine based on treating overt Clinical Disease to Medicine based on Prevention. An up to date of the scientific and technical advances, as well as the societies involved in this evolution, is summarized and critically analyzed.

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