Vascular Aging and Cardiovascular Disease

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The vascular system goes through a distinct set of biologic changes with chronological aging [1]. In parallel, aging increases the time of exposure to vascular insults and the time of deterioration of repairing mechanisms, increasing the possibility of cumulative vascular damage [2]. The objective of this chapter is not to present an exhaustive review of all the structural, biochemical, genetic, and metabolic changes occurring in the vascular system, as they have been presented in detail elsewhere. Instead we aim to discuss the main changes occurring and to understand their role in the establishment of a cardiovascular (CV)-disease-prone status. Furthermore, we aim to investigate the current evidence for a possible additive value of evaluating whether the status of these biological changes in a subject is concordant with what would be expected by their chronological age or whether they present characteristics of an older or younger CV system, with the inherent CV risk for the development of disease or fatal/non-fatal events.

**CHANGES WITH AGE IN THE ARTERIAL TREE**

The arterial tree can be divided into three main types of vessels: large elastic arteries, muscular arteries, and arterioles. Even if sharing the same structural organization (intima, media, and adventitia) they differ not only in the relative importance of each layer but also in its cellular/matrix components [3]; at the same time, these different types of arterial vessels are subjected to different hemodynamic conditions and adapt in response to injury or atherogenic factors [1,4]; thus, their function within the system is diverse—a fact that also bears reflection in their structure/geometry and aging process [5].

For that reason, each type of vessel has a different structural/functional evolution during aging, and as a consequence, the analysis and measurements of these different processes provide information with different meaning in terms of CV disease risk [5].

The arterial system as a whole works to fulfill two different functions: to serve as conduit of oxygen and nutrients carried in the blood, between the heart and the other organs of the body; to provide a buffering system that complies with pressure changes and pressure waves produced by the heart and produces a laminar/continuous blood flow to the organs, defending them of pulsatile variations [6,7]. Thus, pulsatile flow would be confined to arteries with a caliber greater than 200\,µm, and not usually extend into arterioles or more distal capillaries (i.e., pulsatile flow should be excluded from the so-called “resistance vessels”) [6]. The combination of the two main arterial functions (conduit and buffer) and the existence of this mismatch (pulsatile versus laminar flow) between large elastic and resistance arteries leads to pressure wave travel and reflection [5,6]. All points of geometric discontinuity of the arterial tree generates a reflective wave [3].
The efficiency and synchronization of these hemodynamic aspects (left ventricular ejection translating into an incident pulse wave, and reflection of pulse wave at distal arterial sites translating into a reflected wave) should be in such a degree as too allow that the reflected wave would not increase pressure during systole (arriving after aortic valve closure, during diastole and boosting diastolic perfusion). This ventricular—vascular coupling is insured by, amongst others, a greater distensibility of the proximal (compared with distal) aorta and a dispersion of peripheral reflecting sites [5,6].

**Aging and Structural Changes in the Arterial Wall**

With age, elastic arteries dilate and stiffen, especially in the ascending aorta [6,7]. The arterial intima thickens (via hyperplasia) and the load-bearing media suffers changes explained using a simple mechanistic approach: being dependent on its load-bearing elastin component to face pressure variability, there is a fatigue effect of the accommodation of hemodynamic changes during the cardiac cycle, that will contribute to its progressive wearing down. After three to four decades sustaining stretching and pressure loads, elastic fibers are progressively replaced by more stiff collagen fibers and non-load-bearing material [8]. At the same time the organization of the elastic layers and its structural and functional relation to smooth muscle cells is being disrupted, with advanced glycation end-products as one of the main contributors to this reconfiguration of arterial wall properties toward stiffness [1,5–7,9,10].

Aortic pulse wave velocity (aPWV), a marker of arterial stiffness will increase at least twofold between 20 and 80 years of age, a fact that will not have a comparable translation into brachial pulse pressure due to the amplification phenomenon [2,7,11]. The main results of this medial arteriosclerosis are an increase in stiffness, increase in incident wave pressure (increase in systolic blood pressure), and dilation of the arterial wall [10].

These changes with age via a cyclic stress mechanism do not occur at the more distal muscular arteries and arterioles, that are subjected to lower pressure loads [8]. This will progressively promote a decrease in pulse pressure amplification [9,10]. The resistance role of these muscular arteries and arterioles is modulated by medial vascular smooth muscle cells that are present in an increased proportion than registered in large central arteries [5].

Looking at subjects with accelerated aging syndromes like Hutchinson-Gilford Progeria [12,13], it is clear that the mechanistic effect of medial layer dysfunction mediated by vascular smooth muscle cell progressive loss (without observable influence of other processes that accelerate the aging of the system—inflammation, oxidative stress, endothelial dysfunction) is by itself enough to promote the accelerated evolution of the aging process, and that it is especially accelerated when it is unmet by an effective repairing/regenerative process [14].

**Aging and Pressure Wave Reflection**

As a result of the stiffening process occurring in large artery walls, the progression of the pressure wave and its reflection from distal sites occurs more rapidly; the reflected wave then returns to the heart not during diastole, but during late systole. This encompasses two main consequences: increased central systolic and pulse pressure; and increased afterload—the full extent of this effect depends not only on the magnitude of wave reflection, but also on the duration/timing of the wave reflection. While the reflection magnitude is dependent mainly on properties of smaller arteries/arterioles (e.g., vasoconstriction), the reflection timing depends mainly on proximal large arteries properties (stiffer large arteries hasten the return of the reflected wave) [3,8−10,15].

These changes in wave reflection support the concept of Augmentation Index, as an indirect marker of arterial aging and reduced compliance of the aorta. It has been described more accurately as a composite determined by both magnitude and timing of the reflected wave [9,10]; the augmentation index is usually higher in women than men, and it increases progressively until 60 years of age, when it flattens off (interpreted as a consequence of impaired left ventricular contractility) [7,16–18].

Pulsatility has been described as having a different behavior according to gender. Women present a steeper increase in pulse pressure after 50 years of age, and a higher systolic and pulse pressure amplification has been reported after menopause, increasing significantly CV mortality. The impact of hormones on these findings is an ongoing debate [19–21].

Two of the above mentioned parameters of wave reflection (amplitude and duration of the reflected wave) bear mechanic consequences to the left ventricle, which promotes the need to generate more work to produce the same cardiac output and generates the well-known spiral of degradation of cardiac function: left ventricular hypertrophy (LVH), diastolic dysfunction, increased tension-time index and myocardial oxygen demand, reduced coronary perfusion, and congestive heart failure [7,9,22] (Figure 24.1). A vascular-ventricular dysfunction is generated that can
be expressed in terms of energy wasted during each cardiac cycle to ensure the same cardiac output [8]. A new index of surplus work by the left ventricle has recently been proposed by the CAFE investigators, and presented itself as a significant predictor of CV events in treated hypertensive subjects [23].

The wave reflection process can be targeted and changed by exercise and/or drug intervention, via their effect in the distal muscular arteries—vasodilation—decreasing augmentation pressure and pulse flow and their harmful effects in the heart and brain/kidney [7]. The ability to achieve wave reflection reduction has been matter of research in the REASON [24] and the CAFE [25] studies.

The Arterial Stiffening Gradient and the Impedance Mismatch Between Macro/Micro Circulation

We have already discussed that stiffening/arteriosclerotic changes of the arterial wall occur mainly in the large arteries. At the same time it is clear that more muscular and distal arteries and arterioles have a resistance function in the arterial tree, regulating distal arterial flow and changing their tone in response to acute and chronic hemodynamic changes, via vascular smooth muscle cells and endothelial-related functions [1,9,17].

These muscular/distal arteries are exposed earlier than central vessels to wave reflection, and therefore their pulse wave contour and local blood pressure are different than those recorded centrally—which explains why peripheral blood pressure is higher than central blood pressure (CBP) [8]. This amplification that is seen from central to peripheral blood pressure is progressively diminished as aging occurs and stiffness and CBP/central pulse pressure increases [17].

As central systolic and pulse pressure increase and are transmitted to the periphery, another aging consequence decreases the protection of target organs from these higher pulsatile components: the decreased ability of peripheral muscular arteries and arterioles to modulate their tone, as endothelial dysfunction, vessel remodeling, and capillary rarefaction take over and limit arterial compliance at this level: the impedance mismatch between macro and micro circulation is lost, and the consequences of pulsatile energy transmitted to target organs are produced [26]. The main effects are felt in organs with high perfusion and low constrictor tone [10] such as the brain and the kidney [27], where smaller and non-elastic arterial vessels and capillaries are subjected to elevated pulse pressures and subsequent damage promoting parenchymal damage through microhemorrhages and infarcts [6]; these changes are associated with the progressive loss of function in the kidney and the development of dementia; in fact, in the brain this increased pulsatility and its damage impact in the parenchyma (infarcts, microhemorrhages, dementia) has coined the terminology of “pulse–wave encephalopathy.”

Therefore, the reversion of the arterial stiffness gradient and the loss of the macro–micro circulation mismatch are landmarks of the evolution of the vascular aging process and of increased exposure of the target organs to CV disease/CV events.
On the other hand, microcirculation damage also impacts on arterial stiffness and large artery dysfunction: progressive arteriolar remodeling and increase in peripheral resistance will increase blood pressure large artery damage [28].

**Links Between Arteriosclerosis and Atherosclerosis**

The vascular aging process in large arteries is mainly reported as arteriosclerotic changes induced through time and effect of both mechanical and biochemical action of diverse origins. On the other hand, the end-product of aging and deterioration of vascular function is the establishment of CV disease with many of its manifestations presenting as a result of atherosclerotic disease.

The intersection of these two distinct processes (arterio- and atherosclerosis) has been elegantly described in the CV-aging continuum [29]. Interestingly, a pathophysiologic link can also be established between these two processes, placing the endothelium and endothelium-modulated metabolic and biochemical functions as well as vascular mechanobiology at the center of the discussion [30]. First, we pinpoint the controlled release of endothelin-1 and nitric oxide as well as the modulation of angiotensin II effects by the endothelial cell as mechanisms of controlled vasodilatation and modulators of reflection site distance to the heart (endothelial dependent vasodilation is progressively decreased with aging) [1,3,10,31]; second, we remember the endothelial influence on different phenotypes of vascular smooth muscle cells and fibroblasts (with an effect on arterial remodeling and arteriosclerosis) [5]; third, we document the endothelial-cell response to inflammatory stimulus, angiogenesis, and molecular adhesion as well as the endothelial permeability associated with its dysfunction to recall atherogenic effects of disease and aging [1,32]; finally, we recall the shear stress effect promoting disruption of the endothelial barrier, protein exudation, inflammatory cellular adhesion, and thrombosis [6].

These intermediate and related steps intertwine the progression from arteriosclerosis and its consequences in hemodynamics (increased arterial stiffness, increased and faster wave reflection, decreased amplification) and target organ damage (heart—LVH, diastolic dysfunction, reduced coronary perfusion [33]; kidney—albuminuria and reduce glomerular filtration rate; brain—mild cognitive impairment, dementia [34–36], lacunar infarcts, and microhemorrhages [15], to the progression of atherosclerotic disease and its consequences (plaque formation and thrombosis—coronary heart disease, myocardial infarction, stroke).

**Accelerators of the Aging Process**

After going through key elements of the aging process at different levels of the arterial bed, it is imperative to distinguish between arterial functions that deteriorate at an expected rate as a part of a normal aging process, and arterial wear that surpasses this biologic—chronologic equilibrium that ultimately translates into survival free of CV disease. In other words, it is fundamental to acknowledge the existence of pathologic influences on this established (normal) aging deterioration of arterial function: influences that accelerate the arteriosclerotic changes of the arterial wall as well as its biochemical and metabolic function’s deterioration, which promotes its earlier progression and places the individual at an increased risk of CV disease development. It is important to stress the role as accelerators of vascular aging, of both the traditional CV risk factors (such as hypertension, diabetes, dyslipidemia, tobacco use, family history of CV disease, metabolic syndrome) and the nontraditional ones (chronic kidney disease, inflammation, genetic and fetal programming, telomere biology, oxidative stress, salt consumption).

High blood pressure plays a pivotal role and, along with age, is one of the main determinants of arterial stiffness. In longitudinal studies, increased signs of arterial damage through objective observation of increased arterial stiffness have preceded blood pressure elevation [37]. Still, sustained increased pressure will load the stiffer collagen fibers in the large elastic arteries, promote hypertrophy of the vascular smooth muscle cells in the muscular arteries, induce vascular remodeling and capillary rarefaction [10,38], in a self-sustained vicious and deleterious cycle [28].

Subjects with end-stage kidney disease present with increased/accelerated stiffness also because of an elastocalcinos is effect on the media [39]; in these subjects, PWV, central pulse pressure, augmentation index, and carotid internal diameter have proven to be independent markers of CV disease and mortality, as described in distinct studies [17,40–42].

The elevated CV morbidity and mortality of diabetic patients is well known. Early presentation of stiffness of the large arteries and reduced ability to vasodilate peripheral muscular arteries are important features of these patients, that present with higher PWV, higher carotid stiffness, and augmentation index than matched controls [43].
These changes have been reported as both a consequence of deposition of advanced glycation end-products in the arterial wall and insulin resistance [17]. Recent studies associates central hemodynamic parameters to albuminuria and CV disease [44] as well as to reduced heart rate variability in these subjects [45].

Dyslipidemia has been related to increased arterial stiffness, CBP, and augmentation index, a fact that has been associated to mediation via endothelial dysfunction and reduced nitric-oxide production. Studies showing decrease of those central hemodynamic parameters with prolonged statins treatment have produced conflicting evidence [17,46–48].

The cumulative effect of either different CV risk factors, or of distinct associations of components of the metabolic syndrome, have shown to bear impact on vascular aging [49–51].

Fetal programming has also been identified as playing a role in acceleration of the vascular aging process. Whether by influencing a reduced production of elastin in utero, or in line with the development of a mismatch growth in the post-natal period (through which children born with low weight are at increased risk of CV disease development) [1,5,52–54].

Curiously, it has been hypothesized that arterial stiffness itself can contribute to the vascular aging process, through non-CBP-dependent changes: inflammation, oxidative stress, cell proliferation, and increased blood pressure variability [1,55].

As a summary of the first part of this chapter, it would be fundamental to recall that the vascular aging process translates into structural wall damage and functional and hemodynamic changes. Landmarks of the aging process should be recognized when they reflect an increased risk of CV disease development: increased stiffness; increased central and peripheral blood pressure; increased cardiac afterload; loss of central to periphery arterial stiffness gradient (decreased amplification); loss of the macro/microcirculation mismatch; and atherosclerosis manifestations. More importantly, landmarks of the aging process should be identified especially when they occur earlier than expected, disrupting the biologic/chronologic equilibrium of survival. The current use of brachial blood pressure measurements to evaluate vascular aging and the appearance of increased CV risk signs is misleading and underscores the importance of the central aging changes in structure and dynamics: systolic blood pressure increases on average 20% from 20 to 80 years of age; in the same time frame, brachial pulse pressure increases by 70% and aortic pulse pressure increases by 200% [2,7,11].

It is on how to identify manifestations of CV aging that we will dedicate the second part of this chapter.

**MONITORING VASCULAR AGING AND DETECTING ACCELERATED SIGNS OF VASCULAR DETERIORATION**

It is evident from all of the above mentioned that peripheral blood pressure and peripheral blood pressure–derived measurement can be misleading in ascertaining both arterial aging and response to antihypertensive treatment, due to the amplification and central pressure augmentation phenomena.

Looking for signs hinting to the development of (premature) vascular aging is challenging for the clinician. The debate about the definition of an accelerated aging syndrome is ongoing, including components of a hemodynamic-aging syndrome [56] and signs of arterial wall damage [53,57]. For practical purposes it should encompass two different sets of information: the one described by the patient reporting symptoms that should prompt further CV investigation and the data obtained by the physician during CV evaluation of the subject. In relation to the first set of information, we will not include clinical symptoms of established CV diseases, as they refer to the high-risk extremity of the CV continuum and override the main objective of early identification of subjects with accelerated aging in order to delay progression and prevent disease. Therefore, we would start by including subjects with a history of familial CV disease or reporting themselves CV risk factors, including obstructive sleep apnea; we would add patients suffering from chronic disease, especially if with a persistent inflammatory underlying mechanism [31,58]; finally we would include subjects with description of exertion dyspnea and symptoms of orthostatic hypotension or relatable to increased blood pressure [53]. In relation to the second set of information, we would include variables measured during the subjects’ investigation: high blood pressure, especially if documented as isolated systolic blood pressure or presenting with increased pulse pressure; orthostatic hypotension [59–61]; increased blood pressure variability [55]; and low heart rate variability [33]. The list is incomplete and should be debated for clinical utility, especially from the point of view of early detection and reclassification of individual CV risk with subsequent possible clinical intervention.
Several measures of arterial damage have been proposed and are available to determine progression of vascular aging. The role of PWV as gold-standard of arterial stiffness evaluation has been extensively recognized and accepted, and a recent review of the methodology of its measurement was performed to allow for more accuracy [62]. Carotid intima–media thickness (cIMT) relates to local central artery stiffness and has been included alongside with PWV as target organ damage markers in the European Society of Hypertension guidelines [63]. Other indirect measures of stiffness and/or arterial aging are available and deserve growing attention and interest by the medical/research community: augmentation index (a measure of pressure augmentation and wave reflection, that should be interpreted taking into account that it is also dependent on heart rate and distance to the reflection site) and central aortic systolic blood pressure and pulse pressure (as a reflection of the “true” pressure that the target organs deal and that therefore better justify/predict damage) [53]. The European Reference Values Collaboration has been contributing to the generalization of the use of these concepts in clinical CV medicine, by producing reference values for PWV [64], common cIMT [65], and CBP [66]. These reference values have been established by age, class, gender, and blood pressure category, making it easier to know when a subject in the clinic is presenting signs attributable to an inappropriate or early vascular aging (for subject’s age and gender). In the “normal” aging subject, PWV will increase with age but present a more steeper increase in men after the age of 50 years [16,64,67,68]; augmentation index will increase until the age of 60 years (after which if flattens off) in a non-linear way, with higher increases occurring at younger ages [16]; and systolic and pulse pressure amplification will decrease progressively with age [10,66]. For the researcher, other variables are interesting even if not prepared to widespread use in the clinical setting; reflection wave analysis (duration, amplitude) and cardiac energy expenditure are examples, particularly because of their therapeutic implications [23,69]. Recently, the decrease of ascending aorta distensibility (detected by MRI) in younger (<50 years of age) subjects has been reported as an early manifestation of arterial stiffness in a population of subjects with different CV risk factors but no overt CV disease [70]. On a different perspective, telomere attrition rate has been independently linked with the risk of development of CV disease [71], opening new perspectives of vascular aging evaluation [72,73].

Estimating Vascular Age

From all that has been exposed earlier, it seems that there is a setting to allow the physician to identify subjects with “normal” versus “early” or “accelerated” vascular aging, based on PWV or other surrogate measures of arterial stiffness assessment. Still, significant debate has been occurring on where to establish the limits that differentiate these states, if only PWV should be used or if any other parameters should be added to this characterization. The focus should be placed on the concept of exploring variables that allow the clinician to assess the cumulative previous exposure of a subject to numerous risk factors for arterial damage and consequent risk derived from the actual damage inflicted [1,4].

Recent meta-analysis has established that an increase in 1 m/s in PWV would imply a concurrent increase in risk of CV events of 14%, CV disease of 15%, and all-cause mortality of 15%; in the same analysis, using a different effect measure, an increase of 1 standard deviation above the mean PWV value for age/gender would imply a 40% increase in CV risk [74]. Using a different approach, identification of subjects with early vascular aging has been proposed to be defined either as 2 standard deviations above the “normal” mean PWV for age or as above the 97.5th percentile of a z-score distribution adjusted to age [75].

All of the above proposed definitions are based on an objective measurement of PWV as a tissue biomarker of vascular aging. Other options have been explored to estimate vascular age. Using participants in the Framingham study, sex-specific multi-variable risk factor algorithms were created to assess general CV disease risk; these risk estimates were then transformed into heart/vascular age estimates [76]. The European SCORE and FINRISK investigators developed the concept of CV risk age [77]. The shorthand of both these approaches is that they have not been validated against objective measurements of arterial damage. They are intuitive and practical ways of communicating risk in clinical practice.

New Definitions of Accelerated Vascular Aging

Other hypotheses as how to identify subjects with accelerated or early vascular aging should be discussed. Should PWV be the only variable admitted to define vascular aging? Should other measurements of arterial aging that include the influence of wave reflection be included in a compound evaluation—augmentation index or CBP amplification (for example)? Other measurements, and their incremental value to this compound evaluation, like flow mediated dilatation, could be researched but are further away from disseminated use in clinical practice.
A similar statement could be expressed concerning telomere length analysis (as a marker of cellular accelerated replication that has been associated with vascular aging) [71], and new integrals of vascular-ventricular dysfunction as the XSPI proposed by the CAFÉ researchers and above mentioned [23].

In summary, estimating vascular aging, more than a precise exercise to determine a subject’s biologic arterial age, is a quest to attribute a more accurate CV risk profile, reclassify low and intermediate risk subjects whenever direct and indirect measurements of arterial damage indicate an inappropriate or unsuccessful aging process, and curtail an increased risk of disease. The following section of this chapter will, therefore, be dedicated to reviewing how the different measurements of vascular damage associate with the risk of CV risk development.

**CENTRAL HEMODYNAMIC VARIABLES AND ASSOCIATION TO CV RISK**

*Carotid–femoral PWV*—Carotid–femoral PWV is a tissue biomarker that has proven to yield independent prognostic value for the development of CV disease above and beyond traditional risk factors and traditional risk scores [78–85]. Moreover its prognostic value is stronger than other subclinical organ damage markers in subjects with lower CV risk [86,87]. The increase in CV risk per increase in PWV has already been discussed above [74]. A new meta-analysis has confirmed the risk reclassification capability of PWV, particularly for younger age (<50 years) groups at intermediate risk, and shows that it has good predictive power for stroke [88].

*Central arterial pressures*—Central arterial pulse pressure is a better predictor of cIMT, restenosis after coronary angioplasty, coronary artery disease severity, left ventricular mass, and mortality in end-stage renal disease [8]. In subjects with end-stage renal disease and hypertension it is a better predictor of CV outcome than peripheral blood pressure [9]. A recent meta-analysis has studied the predictive ability of central over peripheral blood pressure variables concerning CV disease and all-cause mortality. It was possible to ascertain that a 10% increase in the augmentation index would increase the relative risk of CV event by 30%, and all-cause mortality by 33%; a 10 mmHg increase in central pulse pressure increased the relative risk of CV events by 11.5%, and the same amount of increase in central systolic blood pressure increased the risk of CV event by 9% [11,87,89]. With a different approach, and working in a two-step analysis with a derivation and a validation cohorts, Cheng and co-workers proposed a threshold for increased CBP, showing that subjects with CBP above 130/90 mmHg, after a mean follow-up of 10 years, had an increased risk of CV death and especially stroke death (risk increased sixfold for fatal stroke) [90]. The SAFAR study has reported a stronger association of LVH with central ambulatory blood pressure measurements (ABPMs), when compared to peripheral ABPM [91]. Recently, the reference values for CBP have been published, establishing the expected values for “healthy” (no CV risk factors) and “reference” (with CV risk factors but no CV disease or diabetes) population, according to age, sex, and blood pressure class [66]. This multicentric collaboration also dealt with discrepancies in measurements performed with different devices addressing a poignant issue best described elsewhere [92].

*Carotid intima–media thickness*—Existing evidence suggests that cIMT is a strong predictor of CV events, with a net reclassification index around 10% in different studies [87,93]. Still, in the PROG-IMT Collaborative project (a general population meta-analysis of individual data for more than 36,000 subjects) [94], the predictive ability of change in cIMT between two measurements taken 4 years apart, was nonexistent.

Knowing the risk association of central hemodynamic variables will allow the clinician to quantify the added CV risk of each subject by comparing them with the expected values already established as normal and reference for age and blood pressure category. Other indexes and variables, already above described, have not yet translated into a more widespread utilization, either because of its novelty or due to its lack of feasibility in a routine CV assessment.

**CONCLUSIONS AND FUTURE PERSPECTIVES**

The concept of early identification of subjects with accelerated or early vascular aging is of growing scientific interest; on one hand, age is understood as an emerging CV risk factor; on the other, several aspects of its pathophysiology can be a target for therapeutic intervention that delays progression [95] into the atherosclerotic arm of the CV-aging continuum. The detailed knowledge of these pathologic pathways and the identification of the landmarks that signal unsuccessful aging and progression to increased risk of CV disease are fundamental tools for the precise evaluation of the individual CV risk as well as targets for research encompassing new drugs or intervention strategies: early recognition of vascular aging accelerators, early signs of arteriosclerosis, pulse wave analysis particularly focused on wave reflection, ventricular–vascular coupling, and impedance mismatch are

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some of these landmarks. New data pertaining genetic determinants of vascular aging and arterial stiffness [96–98], as well as telomere biology [71,99], are also emerging and increasing the options for research and possible future clinical interventions.

The first interventional studies using central hemodynamic variables to either guide blood pressure treatment or as intermediate endpoints have been devised. The BP-Guide study has reported significant differences in blood pressure management when central aortic blood pressure is taken into consideration, allowing for a reduction in the number of drugs used to achieve targeted blood pressure levels, without increasing signs of target organ damage [100]; in a phase III, multicenter, randomized, double-blind, parallel-group study, hypertensive subjects with metabolic syndrome treated with an angiotensin receptor blocker, have registered a dose-dependent decrease in arterial stiffening, after a 1 year follow-up [101]. Other ongoing studies can soon bring more scientific evidence to the debate.

References


References


