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Blood pressure variability: a potential marker of aging

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Abstract

Aging is characterized by alterations in neuro-cardiovascular regulatory mechanisms, leading to impaired physiological variability patterns. Repeated evidence has shown that increased Blood Pressure Variability (BPV) is associated with organ damage and exerts independent predictive value on several health outcomes: cardiovascular events, neurocognitive impairment, metabolic disorders and typical geriatric syndromes such as sarcopenia and frailty. Accordingly, it may constitute the epiphenomenon of the alterations in homeostatic mechanisms, typical of late life.

Aging and altered BPV share the same molecular mechanisms, in particular the clinical state of subclinical inflammation has been widely ascertained in advanced age and it is also related to BP dysregulation through altered endothelial function and increased production of ROS. Arterial stiffness and autonomic dysfunction have been associated to impairment in BPV and also represent key features in elderly patients. Furthermore, accumulating evidence in the field of Geroscience has reported that several molecular changes described in cardiovascular aging and altered BPV also relate with the majority of the 9 identified hallmarks of aging. Indeed, BPV may be linked to genomic instability, epigenetic modification and mitochondrial oxidative damage, which represent milestones of aging process.

The aim of the present paper is to analyse the interplay between BPV and the pathophysiology of the ageing process, in order to stimulate discussion about the potential role of BPV as a new marker of aging.

1. Introduction

Over the last decades, a progressive aging of the world population has been observed and demographic projections show that this trend should continue for the next 30 years (Nations, 2019). Aging is a physiological process characterized by an important heterogeneity, with phenotypes ranging from successful aging to frailty and dependency (Rodríguez-Mañas et al., 2013). In an attempt to detect the factors associated with such diverse expressions, the field of Gerosciences has recently expanded, driven by the need for understanding the biological processes underlying aging, identifying its biomarkers, and implementing interventions aimed at promoting healthy aging. Accumulating evidence has led to the identification of 9 hallmarks of aging, summarizing the main cellular and molecular pathways involved in the aging process (López-Otín et al., 2013). Most of them are related to several pathophysiological changes associated with Blood Pressure Variability (BPV). Furthermore, many pieces of literature described similar molecular mechanisms underlying aging and fluctuations in Blood Pressure (BP), and, notably, BPV has been independently associated with age-related clinical outcomes.

To date, BPV has been described as a phenomenon associated with the conditions typical of late life, rather than as a specific variable characterizing aging. With these premises in mind, the authors aim to provide a critical review of the main evidence on the topic from basic, clinical and population sciences, in order to initiate discussion about the potential role of BPV as a new marker of aging.

2. Blood Pressure Variability

BP is well known to fluctuate over time around average values, possibly as the result of complex interactions among external environmental stress, intrinsic cardiovascular regulatory mechanisms, humoral influences, and rheological factors (Parati et al., 2013). It has been ascertained for several years that aging is associated with alterations in neurocardiovascular regulatory mechanisms that result in impaired physiological variability patterns (Veerman et al., 1994). Accordingly, dysregulated BP may constitute an epiphenomenon of the alterations in homeostatic mechanisms, typical of late life.

2.1 BPV types and assessment

BPV is characterized by short-term (within minutes and hours), mid-term (days and weeks) and long-term (months and years) fluctuations and can be assessed through ambulatory BP monitoring (AMBPM), home measurements or repeated clinical visits (visit-to-visit BPV)(Lattanzi et al., 2018). The different BPV types seem to provide specific clinical information, with ultrashort (beat-to-beat) and short-term (minutes-hours) assessments reflecting more neurohumoral involvement, elastic properties of arteries and target organ damage. On the other hand, day-to-day/visit-to-visit BPV has been mainly associated with clinical outcomes, seasonal change influence and treatment adherence(Höcht, 2013; Tai et al., 2015a). It is worth mentioning that long-term variability has been investigated in more detail compared to short- and mid-term patterns, which need to be further studied given their higher susceptibility to publication bias, as demonstrated by a meta-analysis on the association between BPV and cardiovascular and mortality outcomes(Stevens et al., 2016).

Several indicators of variability have been proposed to assess BP fluctuations(Rouch et al., 2020a). Standard deviation (SD) and coefficient of variation (CV) are the most commonly used because they are easier to calculate and probably more practical than other methods. However, different issues arise in the appropriate quantification of BPV, particularly the extent to which the different indices depend on mean and absolute BP and the influence of the temporal order of BP measurements. For instance, although providing accurate intra-individual estimate of BPV, CV does not take into account the sequence of BP measurements(Abellán-Huerta et al., 2018). Accordingly, alternative indicators were thus developed in order to overcome these limits(Fischer et al., 2012; Rothwell et al., 2010b): variation independent of mean (VIM), residual SD, successive variation and average real variability, which allows to also consider the BP time dependent variability(Del Giorno et al., 2019).

To date, no gold-standard approach and ranges of normality have been established to measure BPV, thus concurring to make its clinical interpretation challenging. Probably, within the field of scientific research, VIM may constitute the ideal measure because its results are not influenced by differences in mean BP. Nevertheless, CV can be a good compromise to be implemented in routine clinical practice, being easier to estimate(Rouch et al., 2021).

2.2 BPV and health outcomes

BPV, far from being a background noise, a measurement artifact, or a random phenomenon, has received growing attention in recent years(Lattanzi et al., 2018), particularly due to its association with various health outcomes, independently of absolute BP values. Very interestingly, BPV has been found to increase with advancing age (≥ 75 years) in the Second Australian National Blood Pressure Study(Chowdhury et al., 2014) and in several other findings(Hata et al., 2002; Rothwell, 2010; Rothwell et al., 2010b). The potential mechanisms involved in BPV in older adults may differ

from those operating in younger adults (Palatini, 2018). Increased arterial stiffness and impaired baroreflex function are one of the mechanisms that may contribute to greater BPV with aging whereas in young people, BPV may merely occur in response to the activities of everyday life (Maseli et al., 2017). The growing interest in BPV is related to the repeated demonstration of its independent predictive value for target-organ damage and several health outcomes associated with aging (Table 1). Several observational studies have shown associations between greater BPV and higher risk of stroke, coronary events, heart failure, cardiovascular and all-cause mortality (Laurent and Boutouyrie, 2018; Mehlum et al., 2018; Rothwell et al., 2010b; Tai et al., 2015b). Notably, higher systolic BPV has been associated with occurrence of major adverse events in a post hoc subgroup analysis from the AFFIRM (Atrial Fibrillation Follow-Up Investigation of Rhythm Management) trial on 3843 patients with atrial fibrillation after a median follow-up of 3.6 years. Interestingly, an inverse correlation emerged with quality of anticoagulation (Proietti et al., 2017). BPV has been suggested to correlate with hypertension, left ventricular hypertrophy and systolic dysfunction (Irigoyen et al., 2016). The association between BPV and cerebral small-vessel disease (CSVD) was reported by a systematic review collecting data on 12,309 brain scans: both higher systolic (OR, 1.27; 95% CI, 1.14–1.42) and diastolic BPV (OR, 1.30; 95% CI, 1.14–1.48) were associated with CSVD, independent of mean BP (Tully et al., 2020). Other findings reported associations with lower hippocampal volume, presence of cerebral microbleeds, cortical infarcts and white matter hyperintensities (Havlik et al., 2002; Laurent and Boutouyrie, 2018; Mehlum et al., 2018; Sabayan et al., 2013; Tai et al., 2015b; van Middelaar et al., 2019). Given this relationship to structural brain changes, it is not surprising that BPV is also linked to cognitive impairment and dementia (Alpérovitch et al., 2014; Ma et al., 2021; Rouch et al., 2020a, 2020b). Importantly, a recent systematic review and meta-analysis on nearly 8 million patients from 20 studies, showed stronger association between higher systolic and diastolic BPV with dementia and cognitive impairment, than mean BP (OR, 0.92; 95% CI, 0.87–0.97) (De Heus et al., 2021). Other studies showed associations between increased BPV and increased albuminuria and progression of kidney disease, typical condition of late life (Kawai et al., 2012). A meta-analysis including 14 studies reported a significant higher risk of chronic kidney disease (CKD) onset in patients with greater baseline systolic BPV, consistent through several indicators: relative risk (RR) of 1.69 (95% CI, 1.38–2.08) for SD, 1.23 (95% CI, 1.12–1.36) for CV, 1.40 (95% CI, 1.15–1.71) for VIM. Likewise, diastolic BPV also predicted CKD (Li et al., 2020). Within-visit systolic BPV determined higher progression to pre-diabetes and diabetes (RR = 1.77, 95% CI: 1.30–2.42) in 950 Hispanic participants with no alterations in glycemic metabolism at baseline, from the San Juan Overweight Adults Longitudinal Study (Joshi et al., 2018). Furthermore, BPV has been found to play an

independent role in predicting fractures, that represent another major problem in geriatric medicine(Li et al., 2019; Yoo et al., 2021). Finally, greater BPV has been associated with several age-related conditions such as sarcopenia(Hashimoto et al., 2018), functional decline(Ogliari et al., 2016), hearing loss(Bao et al., 2019) and frailty, which represents the most accurate expression of the global status impairment in older adults(Rouch et al., 2021).

Taken together, these findings suggest that BPV might be a potential new biomarker of aging, beyond vascular considerations.

3. Mechanisms linking BPV and aging

Several explanations have been proposed regarding the associations between BPV and different health outcomes. Most of the potential underlying mechanisms such as hemodynamic instability, advanced artery remodeling and atherosclerosis, arterial stiffness, baroreflex impairment, endothelial dysfunction and subclinical inflammation, are related to aging(Donato et al., 2018). Furthermore, the physiological process of aging is accompanied by a generalized loss of complexity (LOC) in the biological function of organs and systems (Figure 1). LOC contributes to the reduced capacity of homeostatic adaptation to stress, as evidenced by the alterations in the physiological dynamics of multiple physiological processes, especially cardiovascular and neurological stability or the pulsatile release of hormones(Lipsitz and Goldberger, 1992). BPV might help predicting the onset of several age-related conditions and diseases, independently of chronological age. In other words, BPV could be a potential clinical marker of biological aging.

3.1 Hemodynamic instability and arterial stiffness

BP fluctuations, through hemodynamic instability and shear stress on the vascular wall, are well-known to be associated with microvascular damage and arterial remodeling(Cecchi et al., 2011). Findings from the Maastricht study reported correlations between higher BPV and increased carotid intima-media thickness (IMT), a marker of advanced artery remodeling and atherosclerosis associated with aging(Zhou et al., 2018). Thus, BPV could reflect diffuse atherosclerotic process, particularly in the older adults. Atherosclerosis may also lead to greater BPV through increased arterial stiffness(Tedla et al., 2017), one of the key vascular modifications associated with aging. In older people or patients with long-term hypertension, the reduced elasticity of the vascular bed may magnify BP fluctuations. A complex interplay has also been described between arterial stiffness and endothelial dysfunction(Laurent and Boutouyrie, 2020). The two phenomena, which involve age-related mechanisms such as oxidative stress and inflammation, mutually worsen and may contribute to the greater BPV observed in the elderly(Palatini, 2018). Arterial stiffness has also been associated with baroreflex impairment, another typical feature of the aging process(Mancia et al.,

1986). These latter mechanisms are also related to orthostatic hypotension, another common condition in the geriatric population related to BPV, with a relevant impact on quality of life and increased risk of negative outcomes(Cremer et al., 2020).

3.2 Endothelial dysfunction and Nitric Oxide

BP fluctuations have also been associated with endothelial dysfunction(Diaz et al., 2013), a major contributor of the vascular aging phenotype. Endothelial dysfunction is primarily due to the imbalance between increased degradation and reduced synthesis of nitric oxide (NO), a key mediator of vasorelaxation and anti-atherogenic processes(Widlansky et al., 2003). Indeed, decreased NO bioavailability determines haemodynamic instability through enhanced arterial resistance, sustained shear stress on the vascular wall, and arterial remodeling(Donato et al., 2018). This could in turn lead to hypertension and atherosclerosis, which are common in older adults. Several experimental models have identified the role of NO in regulating BP fluctuations, and BPV has been shown to increase with blockade or knockout of the endothelial NO synthase(Stauss et al., 2000). Thus, BPV could represent another independent biomarker of vascular aging. Very interestingly, BPV has been associated with sarcopenia(Hashimoto et al., 2018), a common condition of late life characterized by loss of skeletal muscle mass and function. Several mechanisms have been proposed to explain the relationship between BPV and sarcopenia. The loss of neuronal NO synthase in muscle mass could lead to endothelial dysfunction which in turn could increase BPV. Conversely, considering the effect of BPV on the adequate supply of blood flow to the peripheral tissue, hemodynamic influence may play an important role in the development of sarcopenia(Kim et al., 2019).

3.3 Subclinical inflammation

More recently, BPV has been considered as a marker of subclinical inflammation, one of the pillars of aging, given its association in both preclinical and clinical studies with inflammatory biomarkers such interleukin-6 (IL-6), C-reactive protein (CRP) and E-selectin(Kim et al., 2019; Tatasciore et al., 2007). Chronic, low-grade inflammation occurring during aging, otherwise called “inflammaging”(Franceschi et al., 2018), represents a key feature of vascular aging(Ungvari et al., 2018). A complex interplay also exists between inflammation and endothelial dysfunction, both highly prevalent in the elderly(Libby et al., 2002). Aging is associated with impairment in endothelial function, disrupting arterial homeostasis and activating oxidant and pro-inflammatory pathways, which in turn lead to increased risk of cardiovascular disease and BPV(Donato et al., 2007). With aging, renin-angiotensin-aldosterone system (RAAS) activity may increase NO inactivation and the production of reactive oxygen species (ROS), thereby promoting vascular inflammation(Dikalov and Nazarewicz, 2013). Interestingly, higher BPV also activates the RAAS

system(Su, 2006). Finally, BPV itself could increase the secretion of pro-inflammatory cytokines and ROS, through inconsistent perfusion and repeated episodes of tissue hypoxia-ischemia(Su, 2006). The association between BPV and the subclinical form of “inflammaging” is remarkably interesting from a geriatric standpoint and may constitute an additional argument to suggest BPV as a potential new candidate biomarker of aging.

3.4 Loss of Complexity

Finally, BPV has been associated with frailty, a common condition in the elderly(Rouch et al., 2021; Woo et al., 2018) , which is defined as a lack of homeostasis, an age-associated multisystem reduction in reserve capacity and a generalized LOC of several physiological systems, leading to an increased vulnerability to stressors(Clegg et al., 2013). Our findings in the Multidomain Alzheimer Preventive Trial (MAPT) showed, in 1,394 community-dwelling patients aged ≥ 70 years, that higher 5-year visit-to-visit systolic BPV and pulse pressure variability were significantly associated with greater frailty risk (1-SD increase of CV, systolic BPV: HR = 1.18, 95% confidence interval [CI]: 1.02-1.36)(Rouch et al., 2021). As above mentioned, aging is associated with alterations in neuro-cardiovascular regulatory mechanisms, including those involved in BP control, resulting in impaired physiological variability patterns(Veerman et al., 1994). BPV may represent a decline in homeostatic mechanisms in BP regulation. Healthy human functioning requires an integrated network of physiological systems to maintain homeostasis in response to internal and external stressors. Several studies reported a deterioration of homeostatic regulatory mechanisms with aging and underlying pathologic conditions, leading to a decrease in complexity, which is the physiological adaptability of a system in response to stressors. Previous findings showed a significant decrease in BP complexity assessed with BPV among patients with frailty, with impaired autonomic control and aging as potential underlying mechanisms(Rangasamy et al., 2020). The LOC hypothesis has been introduced 30 years ago by the work of Lipsitz et al.(Lipsitz and Goldberger, 1992) on heart rate variability. LOC is considered as a generic driving principle of aging in a wide range of functional systems and could be an indicator of the transition from normal aging to frailty(Sleimen-Malkoun et al., 2014). Thus, BPV may represent a LOC and resilience associated with aging and thereby constitute a potential new biomarker of aging.

4. BPV and hallmarks of aging

Nowadays, the progress made in the field of Gerosciences has led to the identification of 9 cellular and molecular hallmarks of aging: a) genomic instability, b) telomere attrition, c) epigenetic alterations, d) loss of proteostasis, e) deregulated nutrient-sensing, f) mitochondrial dysfunction, g) cellular senescence, h) stem cell exhaustion, i) altered intercellular communication(López-Otín et

al., 2013). They can be also grouped into three categories: 1) the primary hallmarks (a-d) determining alteration to cellular functions; 2) the antagonistic hallmarks (e-g), providing response to primary ones to counteract molecular damage, but becoming detrimental over time; 3) the integrative hallmarks (h-i) resulting from the previous two groups and ultimately concurring to the typical features of clinical ageing, as reduced resilience and impaired function(Aunan et al., 2016). Notably the majority of them has been shown to relate with pathophysiological modification found in cardiovascular aging and BPV (Figure 2). Although their relationship has not been directly investigated, here we report the most relevant pieces of literature suggesting a potential association between BPV and certain hallmarks of aging.

4.1 Primary Hallmarks

Over time, genetic damage accumulates in aged cells due to progressive dysfunction in Deoxyribonucleic Acid (DNA) repair mechanisms and genomic instability particularly affects the cardiovascular system. Experimental models of genomic instability have shown early age-related conditions such as endothelial cell senescence, hypertension, and arterial stiffness. These biological processes, which also occur in models of increased BPV, are associated with altered NO signalling pathways(Paneni et al., 2017), known to regulate BP fluctuations.

Accumulation of senescent cells in the vascular wall and heart also contributes to age-related impairment in cardiovascular system. Increasing evidence implicates telomere attrition in cellular senescence. Telomeres shorten progressively due to successive cell divisions up to a critical measure determining the impossibility of new replications and leading to cellular senescence. A meta-analysis of human studies revealed a shorter leukocyte telomere length in the group suffering from hypertension compared to normotensive patients(Tellechea and Pirola, 2017). Telomere length has also been found to correlate with oxidative stress, endothelial dysfunction and inflammation(Zhang et al., 2016), which in turn exert pivotal role in the occurrence of BPV. Moreover, an association has been suggested between subclinical atherosclerosis and telomere attrition, whose faster rate, irrespective of cardiovascular risk factors, is related to increased IMT and arterial stiffness(Honkonen et al., 2020; Masi et al., 2014). BPV is strongly correlated with the aforementioned parameters, allowing us to speculate on a potential association with telomere shortening, an important hallmark of aging, especially through common inflammatory pathways alterations.

Aging has also been linked to DNA methylation, post-translational histone modifications, and changes in nucleosome occupancy(Zhang et al., 2018). Such epigenetic modifications, which represent another typical hallmark of aging, can derail transcriptional programs implicated in the

molecular mechanisms well-known to play a major role in BPV(Zhang et al., 2018). Changes in DNA methylation have been described at the promoters of several genes, including the NO synthase and the vascular endothelial growth factor receptor (VEGFR). Histone methylation by the mammalian methyltransferase Set7 regulates endothelial NF- κ B signaling, involved in inflammation and longevity but also in the modulation of cardiovascular homeostasis(Paneni et al., 2017). Although specific investigations are needed, BPV may also be directly associated with epigenetic modifications.

4.2 Antagonistic hallmarks

Mitochondrial oxidative damage has been established as a key contributor to aging, through enhanced inflammatory activation. The age-dependent decline in mitochondrial function, listed among the “antagonistic” hallmarks of aging, is considered to be a compensatory response to damages but whose chronic activation turns into deleterious effects(López-Otín et al., 2013). Mitochondrial overproduction of ROS, which is associated with BPV, contributes to cellular senescence. Indeed, according to a unifying hypothesis several age-dependent damages can activate ROS-dependent, beneficial, stress-response pathways. Nevertheless, these protective mechanisms do not prevent the gradual accumulation of ROS-independent age-related alterations, whose increase induces hyperstimulation of ROS production as cell reaction to stress. With aging, ROS generation escapes control and its toxicity concurs to cellular damage, typical of the second half of the lifespan(Hekimi et al., 2011). Age-dependent alteration of the mitochondrial adaptor p66Shc signalling, whose pivotal role in ROS generation is well-known, strongly affects CV homeostasis. Interestingly, deletion of p66Shc in mice protects from age-dependent endothelial dysfunction through decreased ROS production and conserved NO bioavailability(Paneni et al., 2017). Given the importance of NO in regulating BP fluctuations, an association between BPV and mitochondrial dysfunction is likely and needs further investigations.

4.3 Integrative hallmarks

Stem cell exhaustion and impaired intercellular communication constitute the final phenomena leading to clinical ageing, but these changes represent intrinsic alterations of late life not directly studied from the perspective of BPV. Nevertheless the pathophysiological mechanisms of inflammaging described as directly connected to the alterations of the variability patterns of BP are also consequences of the reduced regenerative capacity of the tissues and of the molecular alterations observed over time(López-Otín et al., 2013). Indeed, inflammatory pathways mechanisms are critical for blood pressure regulation, and immunosenescence also exert a crucial role since hypertension has been associated with activation of immune cells in the renal and cerebrovascular systems. Accordingly, accumulation of immune cells in target organs due to

angiotensin II activation and other pro-hypertensive stimuli, provides oxidative stress, vascular dysfunction which in turn concur to BP alteration(Kirabo et al., 2014). In particular, the role of several inflammatory chemokines has emerged in the context of hypertension and further evidence is expected in the next years for developing chemokine-targeted treatments and implementing the use of anti-inflammatory therapies in cardiovascular diseases(Mikolajczyk et al., 2021).

Finally, in the field of altered cellular pathways occurring with aging, T cell senescence has been detected to exert a pivotal role in several cardiovascular conditions including arterial hypertension and increased arterial stiffness, which constitutes one of the key contributors to increased BPV(Yu and Shin, 2014).

5. BPV and therapeutic implications

Given the evidence supporting the contribution of BPV to organ damage and clinical outcomes, the reduction of BP fluctuations through specific drug classes in the short-, mid- and long-term has been investigated in several studies, which highlighted differences in the efficacy of targeting this emerging risk factor(Höcht, 2013). It is worth mentioning that poor patient compliance and non-adherence with the dosage of the suggested prescriptions may also lead to higher BPV, especially in the elderly, whose management is further burdened by polypharmacotherapy and numerous comorbidities(Bencivenga et al., 2017).

Almost all the antihypertensive agents contribute to reduce BPV, with Calcium Channels Blockers (CCBs) possibly being the most effective class, either in combination or as monotherapy, probably due to their vasodilatory effects on arteries, leading to attenuated stiffness, improved arterial compliance, and autonomic nervous system function and reduced baroreceptor dysregulation(Nardin et al., 2019). Indeed, a metaanalysis on 47,558 patients from 5 randomized controlled trials reported that amlodipine was more effective in minimizing BPV with a treatment difference of -1.23 (SE, 0.46) mmHg through SD and -0.86 (0.31) by CV vs. all active comparators(Wang et al., 2014). Accordingly, the effect of different antihypertensive drug classes on short-term BPV has been studied in 2,780 hypertensive patients, taking into account major confounders including mean BP, age, gender, heart rate and other factors impacting on the choice of therapeutic agent prescription. The authors found that CCBs and diuretics significantly reduced SD of 24-h systolic and diastolic BP (mean differences: -0.50 ± 0.50 mmHg, -0.17 ± 0.15 mmHg, respectively)(Levi-Marpillat et al., 2014). Conversely, β -blockers have been demonstrated inferior in reducing BPV compared to other classes(Rothwell et al., 2010a).

The reduced systolic BPV determined by CCBs and diuretics as monotherapy is also maintained when these agents are combined with other classes. Furthermore, higher doses of CCBs are more

effective in reducing BPV, which in reverse is increased by higher doses of BBs(Webb and Rothwell, 2011).

Notably, sub analysis from the Combination of OLMesartan (COLM) trial showed higher BPV in the very elderly Japanese hypertensive patients (75–84 years) compared to the younger ones (65–74 years), and reported CCBs superiority in reducing BPV over diuretics, both associated with olmesartan(Rakugi et al., 2015). Moreover, a wide meta-analysis exploring the differential effect of antihypertensive drugs on risk of stroke, showed that CCBs could be the most effective class compared to ACE inhibitors, angiotensin II receptor blockers, β -blockers and diuretics in reducing interindividual BPV(Webb et al., 2010).

Nevertheless, to the best of current knowledge, it is not yet possible to establish the effectiveness of antihypertensive therapeutic interventions in preventing age-related health outcomes.

6. Perspectives

In conclusion, accumulating evidence from basic and clinical sciences suggest that BPV could be a potential candidate marker of aging. Although repeated reports showed independent associations between higher BPV and health-related outcomes, BPV variability still constitutes a research issue with no tangible effect in daily practice(Stergiou et al., 2021). Accordingly, despite the growing interest of the scientific community towards aging and Geroscience, knowledge is still limited, and further research is needed to clarify the pathophysiological mechanisms of increased BPV in the elderly and to investigate whether it could be an independent marker of the aging process. On the other hand, following the reported evidence on the close relationship with age-related clinical outcomes and shared pathophysiological mechanisms, in addition to the emerging relationship with hallmarks of aging, the potential of BPV as a marker of aging represents a concrete perspective rather than just speculation. Further work is certainly required to assess whether controlling BP instability could also be a promising interventional target to promote healthy aging. Aging is an extremely heterogeneous process, and its experimental study is further complicated by the use of animal models with homogeneous characteristics. As typical in geriatric medicine, clinical research in the elderly is limited by the specific features of older patients, in particular those with frailty and multimorbidity Thus, in order to broaden the knowledge in the field of Gerosciences, a translational approach is critical to fully understand the mechanisms linking BPV and aging. It is likely that in the next few years there will be many innovative results from the research on the mechanisms that regulate the patterns of variability in humans and further evidence on the less explored hallmarks of aging. The multidirectional integration of clinical and biological data might constitute the best strategy to fill the gap in the field of BPV and aging, moving from bench to bedside up to

community. Further support can also derive from the assessment of BPV in large populations with the possibility to evaluate the most relevant biomarkers of aging. Given the association between BPV and several health outcomes related to aging, from a preventive standpoint, BP values should be recorded as accurately as possible to analyze short and long-term fluctuations, and to also clarify the therapeutic impact of the different classes of antihypertensive drugs and the non-pharmacological interventions. Converting multidisciplinary knowledge and discoveries of basic research into results that directly benefit humans could help researchers test new hypotheses and ascertain the potential role of BPV as a clinical marker of aging.

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Figure 1. Mechanisms linking BPV and aging

The pathophysiological mechanisms implicated in aging and BPV. (Created with BioRender.com)

Figure 2. The relationship between BPV and the hallmarks of aging

The interplay between BPV and molecular mechanisms that underlie the hallmarks of aging.
(Created with BioRender.com)

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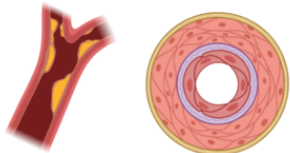
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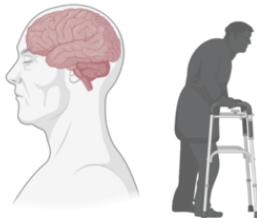
Aging

↑ shear stress
hemodynamic instability
baroreflex impairment

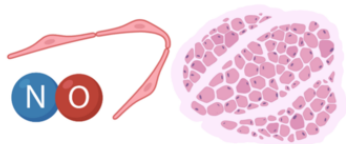


Atherosclerosis and arterial stiffness

↓ reserve capacity
response to stressors
autonomic regulation

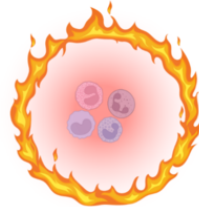


Loss of Complexity



Endothelial dysfunction and sarcopenia

↓ NO bioavailability
vasorelaxation
peripheral blood supply



Inflammaging

↑ pro-inflammatory pathways
RAAS activity
tissue hypoxia-ischemia



Increased BPV

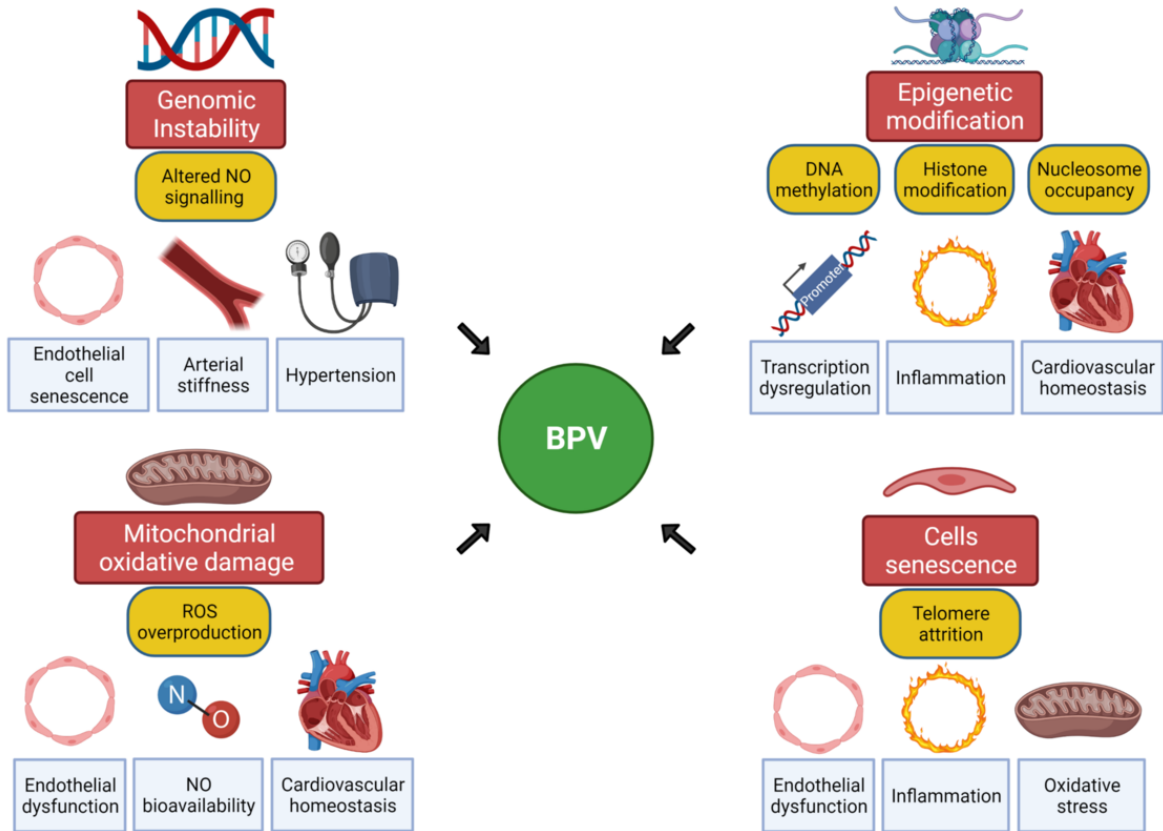


Table 1. Associations between BPV and age-related health outcomes

<i>Health Outcome</i>	<i>References</i>	<i>Study population</i>	<i>BPV assessment</i>	<i>Main findings</i>
Neurological and cardiovascular events	Mehlum et al., 2018	13803 patients with hypertension and at least one additional risk factor for cardiovascular events, from the VALUE trial	Systolic visit-to-visit BP variability (SD) from all visits from 6 to 60 months	Patients in the highest quintile of SD had an increased risk of cardiovascular events (HR 2.1, 95% CI 1.7–2.4)
	Proietti et al., 2017	3843 patients with atrial fibrillation from AFFIRM trial	Systolic visit-to-visit BP variability (SD), median follow-up of 3.6 years	Patients in the 4th quartile of systolic BP variability (SD) had the highest risk for stroke (HR 2.33, 95% CI 1.30–4.16.), major bleeding (HR 2.88, 95% CI 1.79-4.61) and all-cause death (HR 1.38, 95% CI 1.00-1.91)
	Tai et al., 2015b	A meta-analysis of 13 prospective studies with total of 77299 patients	Systolic visit-to-visit BP variability (SD and CV), mean follow-up of 6.3 years	Adjusted HR for all-cause mortality and cardiovascular mortality: 1.03 (95% CI 1.02–1.04) and 1.10 (1.02–1.17) per 1-mmHg increase in systolic BP variability (SD), respectively
Structural brain changes	Tully et al., 2020	A meta-analysis of 12309 brain scans from 27 studies	Systolic and diastolic visit-to-visit BP variability (SD, CV, VIM, ARV, SV)	Higher systolic (OR, 1.27; 95% CI, 1.14–1.42) and diastolic BPV (OR, 1.30; 95% CI, 1.14–1.48) were associated with CSVD, independent of mean BP
	van Middelaar et al., 2019	Post-hoc analysis in 122 community-dwelling people aged 70–78 years with hypertension from the prevention of dementia by intensive vascular care (preDIVA)	Systolic visit-to-visit BP variability (CV) (baseline and after 2, 4, 6, and 7 to 8 years)	One point increase in CV of systolic BPV was significantly associated with 0.043 mL/y (95% CI 0.015-0.072, unadjusted model) White Matter Hyperintensities progression

		magnetic resonance imaging substudy		
Cognitive Impairment and Dementia	Alpérovitch et al., 2014	6506 non-institutionalized subjects aged 65 years, without dementia from the Three-City Study	Systolic visit-to-visit BPV from three measures (baseline and 2- and 4-year visits)	The risk of dementia (HR) for patients in the highest decile of the systolic BP variability (CV) was 1.77 (95% CI 1.17–2.69)
	De Heus et al., 2021	A meta-analysis on 7,899,697 observations from 20 studies	Systolic and diastolic 24-hour, day-to-day, and visit-to-visit BPV, through all parameters	Higher systolic (OR 1.25, 95% CI 1.16–1.35) and diastolic BPV (OR 1.20, 95% CI, 1.12–1.29) were associated with a combined end point of dementia or cognitive impairment
	Ma et al., 2021	13284 participants aged ≥ 50 years without dementia	Visit-to-visit SBP variability was quantified from repeated annual SBP measurements, over a median follow-up of 5.0 years	Higher visit-to-visit SBP variability was associated with cognitive deterioration (conversion from normal cognition to mild cognitive impairment MCI or dementia, or from MCI to dementia) (adjusted odds ratio in the highest quintile 2.64, 95% CI 2.29–3.04)
	Rouch et al., 2020a	3319 non institutionalized subjects from the S.AGES cohort aged ≥ 65 years	Systolic and diastolic visit-to-visit BP variability (SD, CV, VIM, ARV, SV), based on every 6 months BP measurements during 3 years	Higher BPV was associated with greater dementia risk (adjusted 1-SD increase of CV: HR=1.23, 95% CI 1.01–1.50 for systolic BPV; 1.28, 1.05–1.56 for diastolic BPV)
Metabolic disorders	Joshi-pura et al., 2018	950 Hispanics with no diabetes mellitus, from the San Juan Overweight Adults	Within-visit systolic BPV, the maximum difference among three measures	Systolic BPV accelerates development of pre-diabetes/diabetes in overweight or obese adults (RR = 1.77, 95% CI: 1.30–2.42)

		Longitudinal Study		
Kidney disease	Li et al., 2020	A meta-analysis of 14 studies with a total of 11407535 participants	Visit-to-visit systolic and diastolic BPV using SD, CV and VIM	CKD onset is significantly higher in patients with greater baseline systolic BPV consistent through several indicators: RR of 1.69 (95% CI, 1.38–2.08) for SD, 1.23 (95% CI, 1.12–1.36) for CV, 1.40 (95% CI, 1.15–1.71) for VIM. Similar results obtained for diastolic BPV
Sarcopenia	Hashimoto et al., 2018	146 patients aged ≥ 65 years with diabetes from the KAMOGAWA-DM cohort study, without physical inactivity	Systolic visit-to-visit BP variability (CV) from at least four BP readings in 1 year	CV of systolic BP, rather than average systolic BP, is associated with sarcopenia in older patients with diabetes ($\beta = 0.20$, $p = 0.024$)
Hip fracture	Li et al., 2019	21160 patients aged ≥ 50 years with diabetes retrospectively enrolled from the National Diabetes Care Management Program	Systolic and diastolic visit-to-visit BP variability (CV), with average follow-up period of 8.16 years	CV of systolic and diastolic BP constitute a predictor of hip fracture (HR 1.18, CI 95% 1.00-1.40; and 1.21, 95% CI 1.03, 1.43, in the third tertile, respectively)
	Yoo et al., 2021	3256070 aged ≥ 50 years participants from the Korean National Health Insurance System database	Systolic and diastolic visit-to-visit BP variability (VIM), with median follow-up of 7.0 years	Systolic and diastolic BP variability (VIM) are independently associated with fracture incidence (respectively, HR 1.07, 95% CI 1.06-1.08; HR 1.06, 95% CI 1.05-1.07, in the higher quartile)
Frailty	Rouch et al., 2021	1394 non frail community-dwelling participants aged ≥ 70 years from the	Visit-to-visit systolic and diastolic BPV using SD, CV, VIM, ARV, SV. Systolic and diastolic BP	Higher systolic visit-to-visit BPV is associated with risk of incident frailty (1-SD increase of CV: HR = 1.17, 95% CI: 1.01–1.35)

		MAPT study	were assessed regularly over a 5-year follow-up period	
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ARV, Average Real Variability; BPV, Blood Pressure Variability; CI, Confidence Interval; CKD, Chronic Kidney Disease; CV, Coefficient of Variation; HR, Hazard Ratio; OR, Odds Ratio; RSD, Residual Standard Deviation; RR, Risk Ratio; SD, Standard Deviation; SV, Successive Variation; VIM, Variability Independent of the Mean