GeroScience (2023) 45:797–809
https://doi.org/10.1007/s11357-022-00697-y

ORIGINAL ARTICLE

Biomarkers of mitochondrial dysfunction and inflammaging in older adults and blood pressure variability

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Received: 27 June 2022 / Accepted: 20 November 2022 / Published online: 1 December 2022

Abstract Most physiopathological mechanisms underlying blood pressure variability (BPV) are implicated in aging. Vascular aging is associated with chronic low-grade inflammation occurring in late life, known as "inflammaging" and the hallmark "mitochondrial dysfunction" due to age-related stress. We aimed to determine whether plasma levels of the pleiotropic stress-related mitokine growth/differentiation factor 15 (GDF-15) and two inflammatory biomarkers, interleukin 6 (IL-6) and tumor necrosis factor receptor 1 (TNFR-1), are associated with visit-to-visit BPV in a population of community-dwelling older adults. The study population consisted of 1096 community-dwelling participants [median age 75 (72–78) years; 699 females, 63.7%] aged ≥ 70 years from the MAPT study. Plasma blood sample was collected 12 months after enrolment and BP was assessed up to seven times over a 4-year period. Systolic (SBPV) and diastolic BPV (DBPV) were determined through several indicators taking into account BP change over time, the order of measurements and formulas independent of mean BP levels. Higher values of GDF-15 were significantly associated with increased SBPV (all indicators) after adjustment for relevant covariates [adjusted 1-SD increase in GDF-15: β (SE) = 0.07 (0.04), $p < 0.044$, for coefficient of variation%]. GDF-15 levels were not associated with DBPV. No significant associations were found between IL-6 and BPV, whereas TNFR1 was only partially related to DBPV. Unlike inflammation biomarkers, higher GDF-15 levels were associated with greater SBPV. Our findings support the age-related process of mitochondrial dysfunction underlying BP instability, suggesting that BPV might be a potential marker of aging.

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Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s11357-022-00697-y.

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Keywords Blood pressure variability · Biomarkers · Aging · Growth/differentiation factor 15 · Interleukin 6 · Tumor necrosis factor receptor 1

Introduction

Several alterations in neurocardiovascular mechanisms occurring with aging lead to impairment in physiological variability patterns, such as those implicated in the regulation of blood pressure (BP). BP values are well known to fluctuate over time as a result of interactions among external stressors, cardiovascular homeostasis and neurohormonal modulation, whose balance becomes less efficient with aging [26, 55]. Beyond BP mean values, accumulating evidence has reported independent associations between blood pressure variability (BPV) and several health outcomes typical of late life [45]. Higher BPV has been found to increase with chronological age, and to be associated with greater risk of cardiovascular events, structural brain changes, altered cognition, and increased dementia risk [22, 46, 51, 60, 61, 66]. BPV has also demonstrated an independent predictive value for several non-cardiovascular health outcomes associated with aging and typical geriatric conditions [30, 36, 38, 53, 62, 75].

Higher BPV may represent a clinical manifestation of the dysregulation in homeostatic mechanisms occurring during aging [6]. Most pathophysiological mechanisms underlying higher BPV are implicated in the process of aging, and several molecular changes associated with BPV and cardiovascular aging are also related to the hallmarks of aging [40, 54, 67]. Activation of inflammatory pathways is one of the seven pillars of aging [39] and chronic low-grade inflammation occurring in late life, known as "inflammaging" [24], has recently gained increasing interest in geriatric research. It has been suggested to play a pivotal role in the process of vascular aging and increased cardiovascular risk in older adults [69]. Efforts to characterize this process in humans have focused on several inflammatory proteins, among which IL-6 and the tumor necrosis factor (TNF) complex are the most widely studied [25]. As a matter of fact, these major pro-inflammatory cytokines significantly contribute to inflammaging also in healthy older adults [23]. Aging is also characterized by impaired endothelial activity, disturbed arterial homeostasis, and mitochondrial dysfunction, which in turn could contribute to higher BPV and risk of cardiovascular disease [19]. The consequent progressive age-dependent functional decline makes the cardiovascular system more vulnerable to the stimuli typical of late life [8], with higher expression of mitochondrial stress-induced cytokines (mitokines) such as growth/differentiation factor 15 (GDF-15) [42]. This molecule has also been proposed to exert a key role in the aging process, indeed it is considered as a pleiotropic factor with beneficial effects that can turn detrimental in chronic over-expression, associated with aging and a variety of age-related diseases. Accordingly, higher circulating levels of GDF15 have been detected in patients with geriatric syndromes such as cachexia, sarcopenia, cardiovascular disorders, and metabolic conditions [12].

The present study hypothesis is that mitochondrial dysfunction and/or subclinical inflammation underlie BPV, which in turn may constitute a possible epiphenomenon of the aging process. We therefore aimed to assess the association between several biomarkers associated with aging and long-term BPV in a population of community-dwelling older adults, from the multidomain Alzheimer's preventive trial (MAPT). We specifically focused on the pleiotropic mitochondrial stress-related GDF-15 and two inflammatory biomarkers, IL-6 and tumor necrosis factor receptor 1 (TNFR-1) [29, 74].

Methods

The present study is a secondary analysis from the MAPT study (clinicaltrials.gov; NCT00672685), which did not find any significant effect of omega-3 polyunsaturated fatty acid supplementation and multidomain intervention on cognitive function of participants aged ≥ 70 years old, followed over a 3-year period [4].

The study protocol was approved by the advisory Committee for the Protection of Persons participating in Biomedical Research. The MAPT study was conducted in accordance with the Declaration of Helsinki and was authorized by the French Health Authority. Written consent was obtained from all participants.

Study population

Participants were recruited among community-dwelling volunteers aged ≥ 70 years if they met at least one of the following criteria: spontaneous memory complaints, limitation in at least one instrumental activity of daily living, and slow gait speed (< 0.8 m/s). Individuals were excluded if they had a mini-mental state examination score < 24, a dementia diagnosis, or a deficit in basic activities of daily living [73]. In this study the population consisted of 1,096 participants from the MAPT study undergone plasma biomarkers measurement one year after the beginning of study.

Blood biomarkers

Assessment of plasma GDF-15, TNFR-1, and IL-6 was performed through the fully automated immunoassay platform, Ella (ProteinSimple/Bio-techne, San Jose, CA, USA). A single disposable microfluidic SimplePlexTM cartridge was employed to quantify all three proteins. After being thawed on ice and diluted 1:4 in sample diluent (SD 13), plasma samples were loaded into cartridges with relevant high and low control concentrates. Every sample was further divided into three unique microfluidic parallel channels into the cartridge, in the specific position for each of the three proteins. Each channel comprises three analyte-specific glass nanoreactors (GNRs), which permit to run in triplicates for each of the three protein samples. Cartridges include a built-in lot-specific standard curve for each defined analyte. Concentrations were expressed as pg/mL. Inflammatory index was calculated through the formula: $0.333 \times \log(\text{IL-6}) + 0.666 \times \log(\text{TNFR1})$ [72]. Outliers were identified and excluded from the analyses as values 4 SD over the mean (9, 2, and 4 exclusions for the GDF-15, IL-6,and TNFR1 variables, respectively).

Blood pressure variability

Systolic (SBP) and diastolic BP (DBP) were measured 9 times during the follow-up (baseline, 6, 12, 18, 24, 30, 36, 48, and 60 months) at the brachial artery, using a validated electronic device (OMRON 750 CP; Omron Healthcare, Co., Ltd, Kyoto, Japan) after ≥ 5 min of quiet rest, with participants in a lying position. All measurements were obtained by adequately trained healthcare professionals. In the present study, the baseline assessment of BP was considered at 12 months after enrollment, corresponding to the time of blood biomarkers assessment. Accordingly, the baseline and 6 months BP measurements were not considered, and visit-to-visit BPV was thus evaluated over a 4-year period using 7 BP measurements (from 12 to 60 months). Six indicators of BPV were considered as continuous variables [61]. Standard deviation (SD) and coefficient of variation (CV%) represent the most common parameters because they are easy to calculate. However, other indicators were developed in order to take into account the influence of average and absolute BP measures as well as their order over time: variation independent of mean (VIM, modified SD uncorrelated to mean BP), residual SD (RSD, the square root of the residual mean square after fitting a linear regression to BP against time), average real variability (ARV, the mean of absolute differences between successive measurements), and successive variation (SV, the square root of the average squared difference between successive BP measurements)[18, 61]. In the present research, BPV was assessed through SD, CV, VIM, RSD, ARV, and SV, for both SBP and DBP.

Statistical analysis

Continuous variables were expressed as median ± interquartile range (IQR) and compared using Mann–Whitney U test, while categorical variables were reported as absolute observation and percentage and compared through the χ^2 test. In the absence of clinically relevant cut-offs for the study biomarkers, baseline characteristics of the population were presented according to low and high level groups by dividing the population according to the median values. Multivariable linear regressions were used to assess the association between either GDF-15, IL-6, or TNFR-1 (independent continuous variables) and visit-to-visit BPV (dependent continuous variable). Models were progressively adjusted for (1) age, gender, body mass index (BMI), MAPT randomization group (multidomain intervention + ω-3 supplementation; multidomain intervention + placebo; ω-3 supplementation; placebo); (2) baseline BP, antihypertensive drugs, and cardiovascular conditions (heart failure, ischemic heart disease, atrial fibrillation, and/or stroke); (3) diabetes mellitus and non-cardiovascular conditions [active cancer, chronic obstructive

pulmonary disease/asthma, and/or chronic kidney disease (CKD)]. We conducted a sensitivity analysis for GDF-15 and SBPV models by further adjusting for baseline physical activity [either metabolic equivalent task (MET) minutes per week (MET—min/week), derived from the Minnesota Leisure Time Activities questionnaire [68] as previously published [58]; or handgrip strength [16], or Short Performance Physical Battery [28]]. We also performed sensitivity analyses with the Inflammatory Index. Analyzes were conducted using a $p<0.05$ as statistical significance threshold, with Stata17 software (StataCorp, Lakeway Drive, Texas 77,845 USA).

Results

The study population consisted of 1,096 participants [median age 75 (72–78) years], mostly female ($n=699$, 63.7%). The most frequent comorbidities were CKD (194, 17.7%) and diabetes mellitus (106, 9.6%). Baseline SBP and DBP were respectively 135.7 (127.4–145.0) mmHg and 76.0 (70.7–81.4) mmHg, while just over half of the participants were treated by antihypertensive drugs (553, 50.4%). Baseline characteristics of the population, including indicators of systolic (SBPV) and diastolic BPV (DBPV), are reported in Table 1. After removing outliers, median values of biomarkers were 997 (803–1304) pg/mL for GDF-15, 2.57 (1.81–3.8) pg/mL for IL-6, and 1142 (957–1383) pg/mL for TNFR1.

Stress-related mitokine: GDF-15

Baseline characteristics of the population according to GDF-15 levels are presented in Table 1. Participants with higher GDF-15 levels were significantly older, predominantly male, had greater BMI, more diabetes mellitus, ischemic heart disease, atrial fibrillation, and chronic kidney disease than those with lower levels. Participants with higher GDF-15 levels were significantly more likely to be treated by antihypertensive drugs, to have high BP levels and high systolic BPV across all indicators. There was no significant difference in DBPV between groups, except for RSD.

Higher values of GDF-15 were significantly associated with increased SBPV (across all indicators of variability) after adjustment for demographics, BMI, MAPT randomization group, baseline systolic BP, use of antihypertensive drugs, diabetes mellitus, presence of cardiovascular, and non-cardiovascular conditions [adjusted 1-SD increase in GDF-15: β (SE) = 0.07 (0.04), $p<0.044$, for SBPV, CV%] (Table 2). Consistent findings were obtained with all adjustment models, even in sensitivity analyses including physical activity as an additional potential confounder (Supplemental Table 1). GDF-15 levels were not significantly associated with DBPV.

Inflammaging: IL-6 and TNFR1

Baseline characteristics of the population according to IL-6 and TNFR1 levels are presented in Table 3. Participants with higher IL-6 levels were significantly older, male, had greater BMI, more diabetes, ischemic heart disease, and were more likely to be treated by antihypertensive drugs. Among SBPV indicators, the high IL-6 group showed increased values of SD, ARV, and SV, while no significant differences were found among DBPV parameters. In our fully adjusted models, IL-6 was not associated with systolic or diastolic BPV (Table 4). Consistent findings were found with other adjustment models.

Participants with high TNFR1 levels were significantly older, predominantly male, had greater BMI, more diabetes, and CKD and were more likely to be treated by antihypertensive drugs (Table 3).

They had significantly greater systolic RSD. Diastolic BPV did not differ according to TNFR1 levels.

In our fully adjusted models, TNFR1 was no longer associated with systolic BPV but partially associated with DBPV (Table 5). Sensitivity analyses by combining IL-6 and TNFR1 into an Inflammatory Index reported similar findings, with no significant association with BPV [adjusted 1-SD increase in Inflammatory Index: β (SE) = 0.14 (0.09), $p=0.123$ for SBPV, CV%; β (SE) = −0.08 (0.09), p = 0.357 for DBPV, CV%] (Supplemental Table 2).

Discussion

In this population of community-dwelling older adults aged ≥ 70 years, higher levels of GDF-15 were significantly associated with increased SBPV, independently of demographics, baseline BP levels, comorbidities, and use of antihypertensive drugs.

Table 1 Baseline characteristics of the population according to GDF-15 levels (median)

Variables *n (%) or median (IQR)*	*Whole population* *(N = 1096 participants)*	*GDF-15 Low levels* *(n = 544)*	*GDF-15 High levels* *(n = 543)*	*p*-value
Age (years)	75 (72–78)	73 (71–76)	76 (72–80)	< 0.001
Gender, male	397 (36.2)	137 (25.1)	257 (47.3)	< 0.001
BMI (kg/m^2)	25.6 (23.2-28.3)	25.3 (22.9–27.7)	26.0 (23.3–28.9)	< 0.001
MAPT group:				
PUFA + MI	272 (25.0)	129 (23.7)	143 (26.3)	
PUFA	264 (24.3)	125 (23.0)	139 (25.6)	0.34
MI	273 (25.1)	147 (27.0)	126 (23.2)	
Control	278 (25.6)	143 (26.3)	135 (24.9)	
Asthma/COPD	77 (7.0)	38 (6.9)	38 (6.9)	0.99
Stroke	23 (2.1)	10 (1.8)	13 (2.3)	0.52
Active cancer	38 (3.4)	17 (3.2)	20 (3.6)	0.61
IHD	67 (6.1)	17 (3.2)	49 (9.0)	< 0.001
Diabetes	106 (9.6)	26 (4.7)	74 (13.6)	< 0.001
Heart ailure	17 (1.5)	6 (1.1)	9 (1.6)	0.43
Atrial fibrillation	39 (3.5)	8 (1.4)	31 (5.7)	< 0.001
Antihypertensives	553 (50.4)	228 (41.9)	316 (58.1)	< 0.001
CKD	194 (17.7)	62 (11.4)	127 (23.3)	< 0.001
Systolic blood pressure (mmHg)				
Baseline mean	135.7 (127.4–145.0)	134.8 (126.8–142.8)	137.1 (128.8–147.5)	< 0.01
SBPV:				
SD	11.6 (8.5–15.0)	11.0 (8.3–14.3)	12.4 (8.7–15.8)	< 0.001
CV%	8.6 (6.3–10.9)	8.1 (6.1–10.5)	8.9 (6.6–11.4)	< 0.01
VIM	25.3 (18.7–32.7)	11.8 (4.6)	12.2 (9.0–15.3)	< 0.01
RSD	18.3 (13.9–24.7)	17.0 (13.5–22.7)	19.9 (14.4–27.3)	< 0.001
ARV	12.6 (9–17.5)	12.1 (8.6–16.2)	13.3 (9.6–18.1)	< 0.001
SV	15.3 (10.9–20.1)	14.5 (10.4–19.7)	16.4 (11.7–21.3)	< 0.001
Diastolic blood pressure (mmHg)				
Baseline mean	76.0 (70.7–81.4)	76.5 (71.4–81.4)	70.0 (65.8–75.8)	0.10
DBPV:				
SD	7.4 (5.6–9.7)	7.3 (5.6–9.6)	7.4 (5.6–10.0)	0.54
CV%	9.7 (7.3–12.7)	9.7 (7.3–12.4)	9.7 (7.4–13.0)	0.47
VIM	7.4 (5.6–9.7)	7.4 (5.6–9.5)	7.4 (5.6–9.8)	0.49
RSD	11.8 (8.8–15.1)	11.5 (8.6–14.7)	12.2 (9.0–16.0)	< 0.01
ARV	8.1 (5.8–10.8)	8.1 (5.8–10.6)	8.1 (5.7–11.2)	0.69
SV	9.8 (7.3–13.0)	9.9 (7.3–12.8)	9.7 (7.3–13.2)	0.69

ARV, average real variability; *BMI*, body mass index; *CKD*, chronic kidney disease; *COPD*, chronic obstructive pulmonary disease; *CV*, coefficient of variation; *IHD*, ischemic heart disease; *MI*, multidomain intervention; *PUFA*, omega-3 polyunsaturated fatty acid supplementation; *RSD*, residual standard deviation; *SD*, standard deviation; *SV*, successive variation; *VIM*, variation independent of mean

High and low levels of GDF-15 were identified according to the median values (997 pg/mL), after removing outliers

Neither IL-6 nor TNFR1, even combined into an Inflammatory Index, were associated with SBPV. To the best of our knowledge, this is the first study investigating the association between different plasma biomarkers related to several mechanisms of aging and BPV, assessed through six different parameters for both systolic and diastolic BP.

Table 2 Association between GDF-15 levels and BPV (multivariable regression)

Visit-to-visit BPV over a 4-year period	*SBPV*				*DBPV*			
	Unadjusted		*Adjusted*		*Unadjusted*		*Adjusted*	
	β (SE)	*p*-value	*β* (SE)	*p*-value	*β* (SE)	*p*-value	*β* (SE)	*p*-value
SD	0.11 (0.03)	< 0.001	0.07 (0.03)	0.03	0.04 (0.03)	0.12	− 0.00 (0.03)	0.88
CV%	0.09 (0.03)	< 0.01	0.07 (0.03)	0.04	0.05 (0.03)	0.06	− 0.00 (0.03)	0.98
VIM	0.08 (0.03)	< 0.01	0.07 (0.03)	0.04	0.05 (0.03)	0.08	− 0.00 (0.03)	0.93
RSD	0.14 (0.03)	< 0.001	0.10 (0.03)	< 0.01	0.08 (0.03)	< 0.01	0.01 (0.03)	0.59
ARV	0.10 (0.03)	< 0.001	0.07 (0.03)	0.02	0.03 (0.03)	0.22	− 0.01 (0.03)	0.66
SV	0.09 (0.03)	< 0.001	0.07 (0.03)	0.04	0.04 (0.03)	0.18	− 0.00 (0.03)	0.95

Multivariable-adjusted models on age (years), gender, BMI, MAPT randomization group, antihypertensive agents, baseline SBP, cardiovascular disease, non-cardiovascular disease, diabetes mellitus

Cardiovascular disease: heart failure and/or IHD and/or atrial fibrillation and/or stroke

Non-cardiovascular disease: CKD and/or active cancer and/or COPD/asthma

ARV, average real variability; *BMI*, body mass index; *CKD*, chronic kidney disease; *COPD*, chronic obstructive pulmonary disease; *CV*, coefficient of variation; *IHD*, ischemic heart disease; *RSD*, residual standard deviation; *SE*, standard error; *SV*, successive variation; *VIM*, variation independent of mean

The repeated evidence that BPV increases with chronological age has opened discussion about the possibility to consider BPV as a potential clinical biomarker of aging [3, 6, 9, 31, 32, 34, 36, 38, 46, 50, 51, 59–61, 63, 64, 66, 71]. BPV may also have a role in predicting typical geriatric conditions and syndromes [5, 30, 47, 53, 75], including frailty [62].

GDF-15 represents a biomarker of the antagonistic hallmark of aging "mitochondrial dysfunction"; antagonistic hallmarks exert opposite activity depending on their intensity: at low levels, they mediate beneficial effects, but at high levels they become deleterious [29, 37]. Mitochondrial bioenergetics undergoes age-dependent decline, which in long term leads to overproduction of ROS and cellular senescence [33]. Nevertheless, the fascinating theory of mitohormesis defines the activation of cytoprotective signaling pathways in the adaptive response to mild repeated or chronic disturbances, which produces greater resistance to stress [48, 65]. Although not fully defined, GDF-15 contributes to this mechanism, leading to systemic beneficial metabolic effects [35], as also described for the protective role on glucose homeostasis [11, 52]. Accordingly, an increase in GDF-15 levels may represent an adaptive reaction to stress [14]. BP control requires a coordinated complex activity of several physiological systems exposed to internal and external stimuli associated with aging [17, 21], and the higher baseline values of GDF-15 detected in the present study may be intended as the body response against increased stress contributing to increased SBPV. As a matter of fact, the plasma levels of GDF-15 have also been associated with physical activity, being significantly higher in active patients, irrespective of age [13]. The additional adjustment for several measures of physical activity, both based on validated performance tests or derived from a validated questionnaire did not change our results, further corroborating our findings.

In view of BPV as an epiphenomenon of the homeostatic alterations that may anticipate the onset of systemic reactions such as inflammation, the involvement of GDF-15 in the dormancy program, recently proposed by Conte and colleagues, is particularly interesting [12]. According to this unifying viewpoint, in the context of body maintenance mechanisms, dormancy represents the arm which promotes response to adverse environment, stress stimuli, and provides tissue protection from the activation of the other arm of the system, represented by defensive inflammatory signals. In this dynamic process of resource allocation, GDF-15 would constitute a key modulator for tissue protection against inflammatory activation and cell apoptosis [49].

GDF-15 plays a key role in the aging process, although its antagonistic pleiotropic biology is still poorly understood. This mitokine has been found to counteract the activity of TNFα, leucocytes, and

Table 3 Baseline characteristics of the population according to IL-6 and TNFR1 levels (median)

Variables *n (%) or median (IQR)*	*IL-6 Low levels (N = 548)*	*IL-6 High levels (N = 546)*	*p*-value	*TNFR1 Low levels (N = 547)*	*TNFR1 high levels (N = 545)*	*p*-value
Age (years)	74 (71–77)	76 (72–79)	< 0.001	73 (71–77)	76 (72–79)	< 0.001
Gender. male	180 (32.8)	215 (39.3)	0.02	168 (30.7)	227 (41.6)	< 0.001
BMI (kg/m^2)	24.8 (22.7–27.5)	26.5 (23.7–29.3)	< 0.001	24.8 (22.6–27.5)	26.5 (23.8–29.2)	< 0.001
MAPT group:						
PUFA + MI	142 (25.9)	132 (24.2)		138 (25.2)	135 (24.8)	
PUFA	144 (26.3)	122 (22.3)	0.19	143 (26.1)	124 (22.7)	0.464
MI	125 (22.8)	151 (27.7)		136 (24.9)	138 (25.3)	
Control	137 (25.0)	141 (25.8)		130 (23.8)	148 (27.2)	
Asthma/COPD	37 (6.7)	40 (7.3)	0.71	38 (6.9)	38 (6.9)	0.98
Stroke	11 (2.0)	12 (2.1)	0.82	14 (2.5)	9 (1.6)	0.29
Active cancer	21 (3.8)	17 (3.1)	0.51	18 (3.2)	20 (3.6)	0.73
IHD	25 (4.5)	42 (7.6)	0.03	26 (4.7)	41 (7.5)	0.05
Diabetes	39 (7.1)	67 (12.2)	< 0.01	39 (7.1)	66 (12.1)	< 0.01
Heart failure	6 (1.0)	11 (2.0)	0.21	5 (0.9)	11 (2.0)	0.12
Atrial fibrillation	14 (2.5)	25 (4.5)	0.07	19 (3.4)	38 (6.9)	0.99
Antyhypertensives	243 (44.3)	310 (56.7)	< 0.001	226 (41.3)	323 (59.2)	< 0.001
CKD	87 (15.9)	108 (19.7)	0.09	58 (10.6)	133 (24.4)	< 0.001
Systolic blood pressure (mmHg)						
Baseline mean	134.7 (126.5–143.2)	136.4 (128.3–146.5)	< 0.01	134.8 (127.0–143.6)	136.5 (127.5–146)	0.06
SBPV:						
SD	11.3 (8.3–14.1)	11.8 (8.7–15.4)	0.02	11.4 (8.3–14.7)	11.8 (8.6–15.2)	0.07
CV%	8.3 (6.1–10.8)	8.7 (6.5–11.0)	0.10	8.4 (6.1–10.7)	8.7 (6.5–11.1)	0.15
VIM	11.4 (8.4–14.8)	11.9 (9.0–15.1)	0.17	11.6 (8.4–14.6)	11.7 (9.0–15.2)	0.18
RSD	17.7 (13.8–23.7)	18.7 (14.0–25.6)	0.06	17.6 (13.6–23.6)	18.8 (14.0–25.8)	0.02
ARV	12.3 (8.6–16.6)	13.0 (9.3–18.0)	0.01	12.6 (8.6–16.6)	12.6 (9.3–18.0)	0.10
SV	14.9 (10.5–20.1)	15.7 (11.3–20.9)	0.03	15.3 (10.6–20.2)	15.4 (11.1–20.7)	0.18
Diastolic blood pressure (mmHg)						
Baseline mean	75.7 (70.5–81.5)	76.3 (70.8–81.4)	0.46	76.4 (71.7–81.6)	76.0 (70.0–81.42)	0.12
DBPV:						
SD	7.3 (5.5–9.5)	7.5 (5.6–9.9)	0.33	7.4 (5.5–9.9)	7.4 (5.6–9.7)	0.63
CV%	9.8 (7.2–12.4)	9.7 (7.4–13.0)	0.50	9.8 (7.3–12.7)	9.7 (7.4–12.7)	0.90
VIM	7.4 (5.6–9.4)	7.5 (5.6–9.9)	0.42	7.5 (5.6–9.8)	7.4 (5.6–9.7)	0.78
RSD	11.6 (8.7–15.1)	12.2 (9.0–15.3)	0.24	11.8 (8.9–15.1)	11.9 (8.7–15.2)	0.88
ARV	8.1 (5.6–10.6)	8.1 (6.0–11.2)	0.27	8.1 (6.0–10.8)	8.1 (5.6–11.0)	0.71
SV	9.8 (7.2–12.8)	10.0 (7.4–13.3)	0.43	9.8 (7.3–13.0)	9.9 (7.0–13.0)	0.60

ARV, average real variability; *BMI*, body mass index; *CKD*, chronic kidney disease; *COPD*, chronic obstructive pulmonary disease; *CV*, coefficient of variation; *IHD*, ischemic heart disease; *MI*, multidomain intervention; *PUFA*, omega-3 polyunsaturated fatty acid supplementation; *RSD*, residual standard deviation; *SD*, standard deviation; *SV*, successive variation; *VIM*, variation independent of mean

High and low levels of IL-6 and TNFR1 were identified according to the median values (2.57 pg/mL and 1141 pg/mL respectively), after removing outliers

interleukines in clinical and preclinical models [10, 44]. Other findings suggested that GDF-15 could protect tissues from local and systemic inflammation occurring with aging, both in humans and aged GDF-15 KO mice [52]. On the other side, repeated evidence has demonstrated GDF-15 increase in chronic

Table 4 Association between IL-6 levels and BPV (multivariable regression)

Visit-to-visit BPV over a 4-year period	*SBPV*				*DBPV*			
	Unadjusted		*Adjusted*		*Unadjusted*		*Adjusted*	
	β (SE)	*p*-value	*β* (SE)	*p*-value	*β* (SE)	*p*-value	*β* (SE)	*p*-value
SD	0.04 (0.03)	0.17	0.02 (0.03)	0.48	0.03 (0.03)	0.23	0.01 (0.03)	0.60
CV%	0.02 (0.03)	0.38	0.01 (0.03)	0.54	0.03 (0.03)	0.26	0.01 (0.03)	0.53
VIM	0.02 (0.03)	0.48	0.01 (0.03)	0.57	0.03 (0.03)	0.24	0.01 (0.03)	0.55
RSD	0.01 (0.03)	0.63	-0.03 (0.03)	0.21	0.01 (0.03)	0.64	0.01 (0.03)	0.55
ARV	0.05 (0.03)	0.07	0.03 (0.03)	0.31	0.03 (0.03)	0.19	0.02 (0.03)	0.46
SV	0.04 (0.03)	0.12	0.02 (0.03)	0.39	0.03 (0.03)	0.25	-0.01 (0.03)	0.52

Multivariable-adjusted models on age (years), gender, BMI, MAPT randomization group, antihypertensive agents, baseline SBP, cardiovascular disease, non-cardiovascular disease, diabetes mellitus

Cardiovascular disease: heart failure and/or IHD and/or atrial fibrillation and/or stroke

Non-cardiovascular disease: CKD and/or active cancer and/or COPD/asthma

ARV, average real variability; *BMI*, body mass index; *CKD*, chronic kidney disease; *COPD*, chronic obstructive pulmonary disease; *CV*, coefficient of variation; *IHD*, ischemic heart disease; *RSD*, residual standard deviation; *SE*, standard error; *SV*, successive variation; *VIM*, variation independent of mean

Table 5 Association between TNFR1 levels and BPV (multivariable regression)

Visit-to-visit BPV over a 4-year period	*SBPV*				*DBPV*			
	Unadjusted		*Adjusted*		*Unadjusted*		*Adjusted*	
	β (SE)	*p*-value	*β* (SE)	*p*-value	*β* (SE)	*p*-value	β (SE)	*p*-value
SD	0.09 (0.03)	< 0.01	0.04 (0.03)	0.15	− 0.01 (0.03)	0.56	− 0.07 (0.03)	0.01
CV%	0.06 (0.03)	0.03	0.04 (0.03)	0.16	− 0.01 (0.03)	0.62	− 0.06 (0.03)	0.03
VIM	0.05 (0.03)	0.06	0.04 (0.03)	0.14	− 0.01 (0.03)	0.59	− 0.07 (0.03)	0.02
RSD	0.10 (0.03)	< 0.001	0.05 (0.03)	0.1	0.01 (0.03)	0.54	− 0.04 (0.03)	0.20
ARV	0.10 (0.03)	< 0.001	0.05 (0.03)	0.08	0.00 (0.03)	0.95	− 0.05 (0.03)	0.10
SV	0.08 (0.03)	< 0.01	0.04 (0.03)	0.16	− 0.01 (0.03)	0.72	− 0.06 (0.03)	0.05

Multivariable-adjusted models on age (years), gender, BMI, MAPT randomization group, antihypertensive agents, baseline SBP, cardiovascular disease, non-cardiovascular disease, diabetes mellitus

Cardiovascular disease: heart failure and/or IHD and/or atrial fibrillation and/or stroke

Non-cardiovascular disease: CKD and/or active cancer and/or COPD/asthma

ARV, average real variability; *BMI*, body mass index; *CKD*, chronic kidney disease; *COPD*, chronic obstructive pulmonary disease; *CV*, coefficient of variation; *IHD*, ischemic heart disease; *RSD*, residual standard deviation; *SE*, standard error; *SV*, successive variation; *VIM*, variation independent of mean

or acute age-related conditions, particularly cardiovascular diseases (heart failure, coronary artery diseases, atrial fibrillation), type II diabetes mellitus, chronic kidney disease, neurodegeneration, active cancer, and chronological age itself [2]. Moreover, GDF-15 has been listed among the components of the senescence-associated secretory phenotype (SASP) effectors, together with IL-6 and TNFR1 [15, 27].

Overall, GDF15 overexpression may constitute an adaptive reaction to stress and the body response to counteract tissue damage and pro-inflammatory stimuli associated with aging. Higher baseline values of GDF-15 detected in the present study may be intended as an early attempt to preserve altered homeostasis, indicated by increased SBPV, and might prevent inflammaging.

Interestingly, BPV has also been suggested as an epiphenomenon of subclinical inflammation, one of the pillars of aging and biological measure of the aging process [67]. Among the different classifications of age-related biomarkers, IL-6 and TNFα (with its receptors) have been listed among the inflammation-related molecules, involved in both the acute phase response and the chronic inflammatory processes [29, 37]. In the present analysis, we decided to focus on TNFR1 and IL-6 as biomarkers of low-grade inflammatory status, as these molecules showed more consistent results than C-reactive protein (CRP) from previous evidence in predicting cardiovascular events [20]. Moreover, both biomarkers induce the expression of CRP in liver, thus suggesting the latter to constitute a less sensitive inflammatory marker than IL-6 or TNFα [41]. Greater levels of IL-6, TNFR1, and Inflammatory Index have been associated with immune-mediated reactions, geriatric pathological conditions, and functional decline [24, 70]. It is also worth mentioning that TNFα receptors (among them TNFR1) are often recommended in the place of TNFα, which is unstable at − 80 °C storage, to reduce analytic variability [37]. In a cross-sectional study enrolling 140 healthy normotensive adults aged ≤ 60 years, a linear trend was found between 24 h ambulatory SBPV and CRP, while no association emerged for TNFα levels [1]. An independent correlation between IL-6 and daytime systolic 24-h ambulatory BPV was reported in 55 adults suffering from essential hypertension; however, no relationship was found with both TNFα and CRP [41]. Finally, an analysis on 3794 participants aged ≥ 70 years from the PROspective Study of Pravastatin in the Elderly at Risk (PROSPER) with previous cardiovascular disease or currently exposed to cardiovascular risk factors revealed an association between higher inflammation, assessed through increased levels of IL-6, and higher visit-to-visit BPV [57]. In our study, after adjustment for relevant covariates, no significant association was found between inflammatory biomarkers IL-6 and TNFR1 with SBPV indicators, neither considered separately nor combined into an Inflammatory Index. In this regard, it is worth remembering that the previous mentioned evidence is based on populations that are not comparable in terms of age or selection criteria (suffering from specific pathological conditions, especially cardiovascular diseases) with the participants enrolled in our study, comprising relatively fit older adults with few concomitant inflammatory conditions. These differences may possibly explain the absence of association between inflammaging biomarkers and BPV in the present study.

Finally, unlike SBPV, we did not find any robust association between the different biomarkers and DBPV, except for only three indicators with TNFR1, in addition not significant in unadjusted models. This result requires further investigation. Consistently with our findings, most studies reported systolic variability patterns to be more related with health outcomes, especially in the older adults [56]. The reason for this is not completely understood and would lie in the pathophysiological role of arterial stiffness, which is notoriously related to aging and SBP values, rather than diastolic ones [7]. A further explanation, in relation to the population of our study, may be that isolated systolic hypertension (ISH) is highly prevalent in older adults, making SBP more significantly fluctuating than DPV. Interestingly, visit-to-visit SBPV was associated with cardiovascular death after adjustment for covariates also in a population of 4736 persons with ISH [43].

Limitations and strengths

The present research is a secondary analysis of the randomized controlled MAPT; however, the associations between plasma biomarkers and BPV were adjusted for the randomization group. The study population comprised mostly healthy older participants suffering from few baseline comorbidities thus attenuating the generalizability of the results. Time-varying comorbidities and medications were not available. Plasma biomarkers were only measured at one timepoint; further analyses using longitudinal assessment of aging biomarkers are needed to provide information about their trajectories and clarify the temporal association with BPV.

The notable strengths of the current research are worth noting. To the best of our knowledge, this is the first study exploring the association between BPV and three biomarkers of aging with different potential clinical implications. It was conducted on a large sample with long follow-up allowing up to seven BP measures. We were able to consider several relevant potential

confounders, including baseline mean BP levels and antihypertensive drugs use. Finally, compared to other studies, we used several indicators of BPV taking into account BP change over time, the order of measurements and formulas independent of mean BP levels. The results were consistent through all indicators, supporting the robustness of our findings.

Conclusion

Higher GDF-15 levels were independently associated with greater visit-to-visit SBPV in a population of community-dwelling older adults, while no significant relationship emerged for IL-6 and TNFR1. Our findings support the age-related process of mitochondrial dysfunction underlying BP instability, even possibly earlier than other typical features of late life such as inflammaging. These results suggest increased BP instability as an early marker of less successful aging phenotype.

Acknowledgements Dr. Leonardo Bencivenga has been supported by the research grant provided by the Cardiopath PhD program, the research grant provided by the FDIME and the STAR PLUS Research Grant provided by University of Naples Federico II and Compagnia di San Paolo.

Author contribution Study concept and design: LB, YR, PDSB, LR. Acquisition, analysis and interpretation of data: LB, MS, LR. They had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Drafting of the manuscript: LB, PDSB, LR. Critical revision of the manuscript for important intellectual content: YR, LM, BV, PDSB. All authors approved the final version to be published and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Funding The present work was performed in the context of the INSPIRE Program, a research platform supported by grants from the Region Occitanie/Pyrénées-Méditerranée (Reference number: 1901175) and the European Regional Development Fund (ERDF) (Project number: MP0022856).

Data availability The data that support the findings of this study are available from the corresponding author upon reasonable request.

Declarations

Conflict of interest The authors declare no competing interests.

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