ORIGINAL ARTICLE

Ambulatory Blood Pressure Variability Increases Over a 10-Year Follow-Up in Community-Dwelling Older People

Claire McDonald,[1,2] Mark S. Pearce,[3] Joanna Wincenciak,[4] Simon R.J. Kerr,[1,2] and Julia L. Newton[1,2]

BACKGROUND
Greater ambulatory blood pressure variability (ABPV) is associated with end-organ damage and increased mortality. Age-related changes in the cardiovascular and autonomic nervous systems make age-associated increases in ABPV likely. Cross-sectional studies support this hypothesis, showing greater ABPV among older compared to younger adults. The only longitudinal study to examine changes in ABPV, however, found ABPV decreased over 5 years follow-up. This unexpected observation probably reflected the highly selected nature of the study participants.

METHODS
In this longitudinal study, we assessed changes in ABPV over 10 years in a community-cohort of older people. In addition, we examined the extent to which ABPV was predicted by demographics, cardiovascular risk factors, and medication. Clinical examination and 24-hour ambulatory blood pressure monitoring were carried out at baseline and at 10 years follow-up in 83 people, median age 70 years. ABPV was calculated using SD and coefficient of variation (Cv). Three time periods were examined: daytime, nighttime, and 24 hours.

RESULTS
Daytime and 24-hour, systolic and diastolic, SD, and Cv were significantly greater at follow-up than at baseline ($P < 0.001$ in all cases). Mean BP did not change.

CONCLUSIONS
Multilevel modeling showed follow-up interval had a significant, positive effect on SD and Cv ($P < 0.004$), independent of age, sex, and medication.

ABPV *increased* over a 10-year follow-up despite stable mean BP. ABPV may therefore be an additional target for treatment in older people. Future studies should examine what degree of ABPV is harmful and if control of ABPV reduces adverse outcome.

Keywords: aging; ambulatory blood pressure variability; blood pressure monitoring; hypertension; longitudinal study.

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Ambulatory blood pressure monitors (ABPMs) record mean blood pressure (BP) and BP variability. Current UK guidelines recommend routine use of ABPM in the diagnosis of hypertension.[1,2] Mean ambulatory BP is a well-recognized predictor of cardiovascular and all-cause mortality.[3–8] More recently it has been recognized that ambulatory BP variability (ABPV) also carries important prognostic information independent of mean BP. Increased ABPV is associated with: carotid artery damage, progression of small vessel disease, cognitive decline, left ventricular hypertrophy, increased cardiovascular events, and increased all-cause mortality.[9–17]

It is now widely accepted that mean systolic BP increases with age. However few studies have examined how ABPV changes as people get older. A small number of cross-sectional studies have found that ABPV is higher in older adults compared to younger adults.[10,18,19] This is in keeping with previous studies that have shown that increased ABPV is associated with decreased baroreceptor sensitivity[20–23] and that baroreceptor sensitivity decreases with age.[24,25] It is, therefore, surprising that the only longitudinal study to examine ABPV found ABPV decreased over a 5-year follow-up.[26]

Great strides have been made in controlling mean BP. Mean BP and BP variability are correlated but it is not clear if control of mean BP inevitably stabilizes BP variability. Recent studies have suggested that calcium channel blockers and diuretics have greater impact on ABPV compared to other antihypertensive classes and animal studies have shown that reduction in ABPV to be associated with decreased end-organ damage.[27–29]

These data suggest that monitoring and controlling ABPV maybe an additional method of moderating cardiovascular risk. It is therefore important to understand how ABPV changes overtime, its relationship to change in mean BP and if there are antihypertensive class effects on ABPV.

We hypothesize that age-related changes in the cardiovascular and autonomic nervous systems, resulting in decreased baroreflex sensitivity and increased neurocardiovascular instability, will result in increased ABPV over time and that Goldstein's unexpected findings reflected an unrepresentative exceptionally healthy older population.[26]

[1]Institute of Cellular Medicine, Newcastle University, Newcastle, UK; [2]Newcastle Hospitals NHS Foundation Trust, Newcastle, UK; [3]Institute of Health & Society, Newcastle University, Newcastle, UK; [4]Institute of Neuroscience, Newcastle University, Newcastle, UK.

This longitudinal study aimed to assess changes in ABPV over a 10-year follow-up and examined if these changes were associated with mean BP or prescribed antihypertensive medication.

METHODS

Between April 2002 and October 2003, 353 community-dwelling people aged 65 years and older took part in the first phase of a longitudinal study examining neurocardiovascular function in older people. Participants were recruited from a single general practice in the North of England. Persons living in residential care were excluded. Full details of recruitment have been previously described elsewhere.[30]

Participants were followed-up at 2, 5 and 10 years. Clinical examination and ambulatory BP monitoring was only included in the baseline assessment, in 2002, and the 2012 assessment.

Ambulatory blood pressure monitoring

Consenting participants were fitted with a 24-hour BP monitor (Spacelabs 90207; Spacelabs Medical, Redmond, WA). An appropriate sized cuff was fitted to the nondominant arm. Subjects were instructed to relax their arm when the cuff was inflating. Monitors were programmed to take a BP recording every 30 minutes during the day (7 AM to 10 PM) and every hour overnight (10 PM to 7 AM). If the monitor failed to obtain a BP recording on the first attempt, it would automatically retry the measurement 2 minutes later.

Three time periods were examined: daytime (10 AM to 8 PM), nighttime (midnight to 6 AM), and the full 24-hour period.[31] Only studies with at least 16 recordings within 24 hours were included in the analysis. Studies with 10 or more daytime recordings were deemed suitable for daytime analysis and studies with 5 or more nighttime recordings were deemed suitable for nocturnal analysis.[31]

Mean systolic and diastolic BP were calculated for each time period. BP variability was calculated using the SD of the mean BPs. The coefficient of variation (Cv) of BP (SD/mean BP) was also calculated for each time period.

Clinical assessment

Past medical history was obtained by direct interview of subjects. Particular attention was paid to presence or absence of cardiovascular disease and risk factors. If participants were unsure of their past medical history, general practice medical notes were reviewed.

Participants were asked to bring a list of all medications they were taking with them to the assessment. Use of cardioactive medication was defined as using any antihypertensive medication, diuretic, anti-anginal, or anti-arrhythmic. Height and weight were recorded and body mass index was calculated.

Follow-up examination

In 2011, surviving participants were invited to take part in a follow-up study if they remained registered with the participating general practice and had not withdrawn from the study at the 2-year or 5-year follow-up assessments. Ten-year follow-up included; clinical assessment and ambulatory BP, measured as described at baseline.

Ethical approval

Ethical approval for the baseline study was provided by the County Durham and Darlington Local Research Ethics Committee. Ethical approval for the follow-up study was granted by the National Research Ethics Service Committee North East-Newcastle and North Tyneside One. All participants gave written informed consent.

Analysis

Data were analyzed using Statistical Package for Social Science (SPSS) version 19 and R[32] with *lme4*[33] and *lmerTest*[34] packages. For all tests, the level of statistical significance was set at <0.05.

Categorical data are displayed as frequency and percentage. Chi square and Fisher's exact tests were used, as appropriate, to test for differences in the distribution of categorical data.

Normally distributed, continuous data are displayed using mean and SD. Nonparametric data are displayed using median and interquartile range. Normally distributed data from 2 unrelated samples were compared using the Student's *t*-test for independent samples. Repeated measures from 2 related samples were compared using paired *t*-tests.

Multilevel modeling with test sessions grouped by participant was used to examine if BP variability was affected by session independent of age, sex, medication, and mean BP. The models included a random intercept term by participant.

RESULTS

Study participants

At baseline, 338 participants underwent ambulatory BP monitoring. At follow-up 104 of these participants consented to participation in the study, 83 of whom underwent successful repeat ambulatory BP monitoring. Figure 1 shows the details of recruitment. Participants lost to follow-up (either due to death or withdrawal from the study) were significantly older than participants who took part in the follow-up examination (median (interquartile range) 74 (69–78) vs. 70 (67–73), $P < 0.001$]. Prevalence of ischemic heart disease, diabetes, hypertension, use of tobacco, and use of antihypertensive medication at baseline did not significantly differ between groups (Table 1). Class of antihypertensive medication prescribed did not differ between groups (Supplementary Table 1). Participants lost to follow-up had significantly greater 24-hour and nighttime mean systolic BP, daytime systolic BP variability, and diastolic variability compared to those participating in the follow-up examination (Table 1).

Median numbers of ABPM readings during the 24-hour period at baseline and follow-up was 37 (range 20–40)

and 35 (range 18–40) respectively. For the daytime period median number of readings at baseline and follow-up were 19 (range 10–20) and 18 (range 10–20) respectively and for the nighttime period the median number was 6 (range 5–6) at both baseline and follow-up.
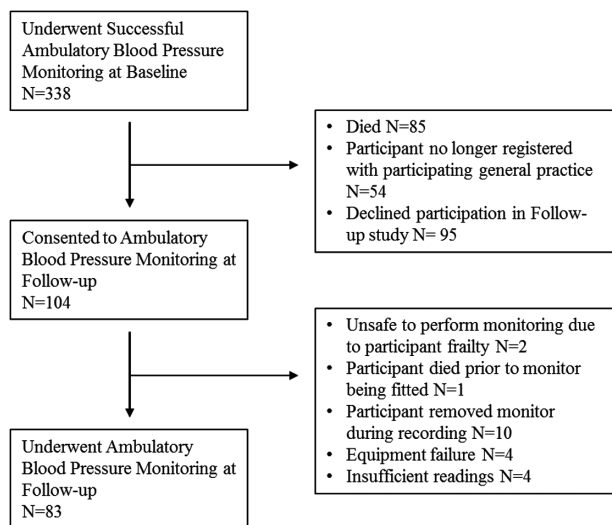

Figure 1. Flow chart demonstrating recruitment.

Changes in ambulatory blood pressure over time

Data from the 83 participants with BP recordings at baseline and follow-up were analyzed. Mean BP did not significantly differ between baseline and follow-up for any of the time periods examined (Table 2). Twenty-four-hour and daytime systolic and diastolic BP SD were significantly greater at follow-up than at baseline (Table 3). Similarly, 24-hour and daytime systolic and diastolic Cv were significantly greater at follow-up compared to baseline (Table 3). None of the nighttime measures of variability significantly differed between baseline and follow-up.

Changes in comorbidities and use of medication over follow-up

Comorbidities and medication use at baseline and follow-up were compared for the 83 individuals who underwent ABPM at both examinations. There was a significant increase in the number of individuals reporting a past medical history of hypertension at follow-up compared to baseline (60% vs. 37% respectively, $P = 0.005$). Similarly, the number of individuals diagnosed as diabetic had increased (2% vs. 15%, $P = 0.001$).

The percentage of patients taking antihypertensive medication increased from 46% at baseline to 69% at follow-up ($P = 0.003$). Examining use of individual antihypertensive

Table 1. Comparison of baseline characteristics for follow-up participants and those lost to follow up

Dependent variable	Lost to follow-up *N* = 255	Follow-up participants *N* = 83	*P*
Age (median (IQR))	74.0 (69.0, 78.0)	70.0 (67.0, 73.0)	**<0.001**
BMI (median (IQR))	26.2 (24.0, 28.9)	26.8 (24.7, 296)	0.159
Pack years (median (IQR))	4.0 (0, 25.0)	3.5 (0, 21.8)	0.791
Male (frequency (%))	144 (56)	46 (56)	0.867
IHD (frequency (%))	69 (27)	16 (20)	0.156
Hypertension (frequency (%))	123 (48)	37 (45)	0.562
Diabetes (frequency (%))	21 (8)	2 (2)	0.067
Antihypertensive med (frequency (%))	119 (78)	38 (46)	0.889
Baseline 24hr mean SBP (mean ± SD)	130.49 ± 13.98	126.40 ± 14.27	**0.021**
Baseline 24hr mean DBP (mean ± SD)	71.98 ± 7.30	72.18 ± 9.67	0.861
Baseline 24hr SD SBP (mean ± SD)	13.95 ± 3.75	12.95 ± 3.29	**0.032**
Baseline 24hr SD DBP (mean ± SD)	9.68 ± 2.23	9.34 ± 2.37	0.227
Baseline day SBP (mean ± SD)	135.15 ± 14.40	131.35 ± 16.06	**0.043**
Baseline day DBP (mean ± SD)	75.73 ± 7.95	76.46 ± 10.91	0.581
Baseline day SD SBP (mean ± SD)	12.55 ± 4.22	11.24 ± 3.40	**0.010**
Baseline day SD DBP (mean ± SD)	8.36 ± 2.39	7.71 ± 2.24	**0.032**
Baseline night mean SBP (mean ± SD)	120.27 ± 16.09	115.55 ± 13.04	**0.012**
Baseline night mean DBP (mean ± SD)	64.34 ± 8.32	63.55 ± 8.69	0.483
Baseline night SD SBP (mean ± SD)	9.31 ± 3.85	8.51 ± 3.68	0.107
Baseline night SD DBP (mean ± SD)	7.13 ± 3.07	6.73 ± 2.77	0.303

Normally distributed data compared using Student's *T*-test. Nonparametric data compared using Mann–Whitney *U*-test. Chi square test and Fisher's exact test used for categorical data. Bold values indicate *P*-value <0.05.

Abbreviations: IQR, interquartile range; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; IHD, ischemic heart disease.

Table 2. Comparison of mean BP at baseline and follow-up

| | | Entire follow-up cohort | | | | Participants not taking cardioactive medication | | |
| | | Baseline | Follow-up | | | Baseline | Follow-up | |
Dependent variable	N	Mean ± SD	Mean ± SD	P	N	Mean ± SD	Mean ± SD	P
24hr mean systolic pressure	83	126.40±14.27	123.69±11.80	0.139	19	119.68±11.59	126.63±13.00	**0.004**
24hr mean diastolic pressure	83	72 .18±9.67	71.92±8.24	0.820	19	69.68±9.47	72.79±9.84	0.082
Day mean systolic pressure	76	131.18±16.16	127.71±12.25	0.060	17	125.35±11.26	133.53±12.74	**0.005**
Day mean diastolic pressure	76	77.96±11.05	75.18±8.33	0.120	17	74.88±10.25	77.94±9.00	0.126
Night mean systolic pressure	65	116.20±13.31	113.85±13.37	0.290	13	108.17±11.58	113.58±10.92	**0.008**
Night mean diastolic pressure	65	63.72±9.16	64.05±8.95	0.733	13	59.25±7.53	62.42±6.43	0.093

Paired *T*-tests used to compare mean BP at baseline and follow-up. Analysis shown for participants who had ABPM recordings at baseline and follow-up and a subset of patients who were not prescribed any cardioactive mediation at baseline or follow-up. Bold values indicate *P*-value <0.05.

Table 3. Comparison of BP variability at baseline and follow-up

| | | Entire follow-up cohort | | | | Participants not taking cardioactive medication | | |
| | | Baseline | Follow-up | | | Baseline | Follow-up | |
Dependent variable	N	Mean ± SD	Mean ± SD	P	N	Mean	Mean	P
24hr SD SBP	83	12.95±3.29	15.07±4.48	**<0.001**	19	12.08±2.11	15.22±4.20	**0.011**
24hr SD DBP	83	9.34±2.36	10.70±3.62	**0.001**	19	9.09±1.48	11.46±3.08	**0.003**
24hr Cv SBP	83	0.10±0.02	0.12±0.04	**0.002**	19	0.10±0.02	0.12±0.03	**0.031**
24hr Cv DBP	83	0.13±0.03	0.15±0.05	**0.008**	19	0.13±0.03	0.16±0.05	**0.012**
Day SD SBP	76	11.03±3.22	14.02±4.97	**<0.001**	17	10.31±2.67	14.46±4.91	**<0.001**
Day SD DBP	76	7.68±2.28	9.83±4.20	**<0.001**	17	6.88±1.73	10.72±4.05	**0.002**
Day Cv SBP	76	0.08±0.03	0.11±0.04	**<0.001**	17	0.08±0.02	0.10±0.03	**0.018**
Day Cv DBP	76	0.10±0.03	0.13±0.05	**<0.001**	17	0.09±0.03	0.14±0.05	**0.004**
Night SD SBP	65	8.64±3.79	10.65±10.47	0.488	13	8.87±3.77	8.29±3.91	0.644
Night SD DBP	65	6.79±2.85	7.96±6.68	0.175	13	6.43±2.34	7.54±3.50	0.272
Night Cv SBP	65	0.07±0.03	0.09±0.10	0.115	13	0.08±0.03	0.07±0.03	0.431
Night Cv DBP	65	0.11±0.05	0.13±0.11	0.182	13	0.11±0.04	0.12±0.06	0.501

Paired *T*-tests used to compare BP variability at baseline and follow-up. Analysis shown for participants who had ABPM recordings at baseline and follow-up and a subset of patients who were not prescribed any cardioactive mediation at baseline or follow-up. Bold values indicate *P*-value <0.05.

Abbreviations: Cv, coefficient of variation; DBP, diastolic blood pressure; SBP, systolic blood pressure.

medication classes showed that there was a significant increase in the number of participants prescribed calcium channel blockers (14% vs. 30% (*P* = 0.015)), angiotensin 2 receptor blockers (4% vs. 17% (*P* = 0.005)) and diuretics (17% vs. 36% (*P* = 0.005)). Use of angiotensin converting enzyme inhibitors (29% vs. 13% (*P* = 0.013)) and beta-blockers (24% vs. 17% (*P* = 0.183)) had decreased.

To examine if increased use of cardioactive medication may account for the increase in ABPV, a subgroup of 19 patients not taking cardioactive medication at baseline or at follow-up were examined. These patients had no history of cardiovascular disease or diabetes. Twenty-four-hour and daytime systolic and diastolic BP SD were significantly greater at follow-up than at baseline in this subgroup (Table 3). Similarly, the Cv significantly increased between baseline and follow-up

(Table 3). Twenty-four-hour, daytime, and nighttime mean systolic BP were also significantly greater at follow-up than at baseline in this subgroup (Table 2)

Predictors of ABPM variables

Finally multilevel modeling was used to examine if association between session and BP variability was independent of potential confounders. The initial model included; age at baseline, sex, use of antihypertensive medication, mean BP, and follow-up interval represented by months between ABPM recordings. An interaction term sex × months between recordings was also added to the model to examine if the effect differed for men and women. Results are shown in (Table 4). Follow-up interval had a significant, positive effect on the

Table 4. Multilevel modeling examining association between interval between examinations and BP variability

Model	Dependent variable	Significant fixed effects	B	SE	DF	T	P
Model 1	24hr SD SBP	24hr mean SBP	0.056	0.0218	166	2.575	0.012
		Years since baseline	0.590	0.0759	87	7.775	<0.001
Model 2	24hr SD DBP	24hr mean DBP	0.095	0.0323	166	−1.867	<0.004
		Years since baseline	0.270	0.0903	166	2.984	<0.004
Model 3	24hr Cv SBP	Years since baseline	2.812e − 03	6.409e − 04	84	4.386	<0.001
Model 4	24hr Cv DBP	Years since baseline	3.082e − 03	9.015e − 04	84	3.419	<0.001
		Age at baseline	1.770e − 03	8.228e − 04	82	2.151	0.03
Model 5	Day SD SBP	Years since baseline	0.460	0.096	86	4.779	<0.001
		Daytime mean SBP	0.054	0.024	155	2.248	0.026
Model 6	Day SD DBP	Years since baseline	0.289	0.079	89	3.654	<0.001
		Daytime mean DBP	0.094	0.028	139	3.296	0.001
Model 7	Day Cv SBP	Years since baseline	3.212e − 03	7.700e − 04	84	4.172	<0.001
Model 8	Day Cv DBP	Years since baseline	3.786e − 03	1.026e − 03	86	3.689	<0.001

Linear mixed effects models examining relationship between years, between assessments, and blood pressure variability. In all models fixed effects entered were; age at baseline, sex, use of antihypertensive medication, years between baseline and follow-up assessment and interaction term sex × years since baseline. As random effects, we had intercepts for subjects. *P*-values were obtained by maximum likelihood *t*-tests. This table shows the terms in each model significantly associated with BP variability measure as defined in column 2.

Abbreviations: DBP, diastolic blood pressure; SBP, systolic blood pressure; Cv, coefficient of variation.

24-hour and daytime BP variability, measured by BP SD, independent of participant age, sex, and use of antihypertensive medication. The interaction between sex and follow-up interval was of borderline significance in models of 24-hour and daytime systolic SD (*P* = 0.078 and *P* = 0.055 respectively), suggesting a trend toward greater BP variability in women.

The analysis was repeated with Cv as the dependent variable and age at baseline, sex, use of antihypertensive medication, follow-up interval and sex × follow-up interval an interaction term. Follow-up interval was a significant and positive predictor of 24 hour and daytime but not nighttime Cv.

The models were rerun adding body mass index, history of diabetes, alcohol consumption, and smoking history (in pack/years) to the model as predictors. None of these variables were significant predictors of BP variability and did not alter the fit of the model (data not shown).

Analysis was also repeated substituting number of antihypertensive medications for use of antihypertensive medication. This did not significantly alter the model or significant predictors.

Finally, analysis was run with use of individual antihypertensive medication (ace inhibitor, ARB, alpha-blocker, beta antagonist, diuretic, and calcium channel blocker) replacing use of any hypertensive medication. Follow-up interval remained a significant predictor of BP variability measure as either SD or Cv. Individual medication classes did not have a significant effect on BP variability (Supplementary Table 2).

DISCUSSION

In this study, we have shown that 24-hour and daytime ABPV (measured as SD or Cv) increased among community-dwelling older people over a 10-year follow-up interval, whereas mean BP did not significantly change. Over recent decades, great strides have been made in controlling mean BP. It is therefore interesting to find, that even when mean BP is stable, BP variability increases. BP variability has been identified as a risk factor for cardiovascular disease and mortality independent of the mean BP.[9–17] To date, very little attention has been paid to monitoring or controlling ABPV and it remains unknown what degree of BP variability is harmful.

It has been suggested that ABPV may be an additional target for treatment over and above mean BP.[35] Animal model shows that control of BP variability is associated with reduced end-organ disease.[36] In this study use of antihypertensive medication was not associated with BP variability, nor were specific antihypertensive classes associated with BP variability. Previous studies have shown that calcium channel blockers and diuretics have greater effect on BP variability compared to other antihypertensive.[27–29] Failure to reproduce this finding here may reflect type 2 error resulting from the relatively small number of participants taking each class of medication.

Our observation that BP variability increases over a 10-year follow-up is in contrast to the findings of Goldstein *et al.* who reported that ABPV among older people decreased over a 5-year follow-up.[26] Goldstein *et al.*'s cohort was highly selected and was unrepresentative of the general older population. Participants with a history of hypertension, obesity, impaired cognitive abnormalities, or psychiatric disorders were excluded from the Goldstein study. In contrast, the population examined here was more typical of the general older population. It must still, however, be acknowledged that there was high attrition in this study. The individuals participating in the follow-up study were, in general, younger, with

lower mean BP and lower BP variability than participants lost to follow-up, suggesting follow-up participant may represent a selected cohort at lower cardiovascular risk.

Although our findings are not in keeping with Goldstein *et al.*'s findings, they are in keeping with cross-sectional studies showing a relationship between age and ABPV.[10,18,19] Sakakura *et al.* compared BP variability among a group of 101 younger elderly (aged 61–79) and 101 older elderly (aged ≥80). BP variability was significantly greater among the older group compared to the "young elderly."[10] Cicconetti *et al.* found that BP variability is greater among older hypertensive patients compared to younger hypertensive patients and that age and BP variability were significantly correlated in men and women.[19]

It is not surprising that BP variability increases with age. Increased ABPV is associated with decreased baroreceptor sensitivity and arterial compliance.[20–23] Both baroreceptor sensitivity and arterial compliance decrease with age.[24,25] Interestingly nocturnal BP variability did not significantly change. This may reflect type II error. Only 65 individuals met the criteria for inclusion in the nocturnal analysis (≥5 ABP readings) compared to the 76 who met the criteria for daytime analysis. Alternatively the greater increase in daytime BP variability compared to nighttime variability may reflect BP lability in response to physical and mental exertion during waking hours. At both time points BP variability was greater during the daytime than at nighttime. Conditions associated with exaggerated changes in BP in response to day-to-day activities, e.g., orthostatic hypotension and postprandial hypotension all become more common in later life.[30,37,38] Age has also been associated with greater BP variability in response to mental stress.[39] It is possible, that these fluctuations in BP in response to normal activities of daily living have greater influence on daytime ABPV than nocturnal ABPV.

Although ABPV increased over 10 years, mean BP did not significantly change over the follow-up period. The stability of mean systolic or diastolic BP over the 10-year follow-up period is interesting. Most studies using casual or ambulatory BP monitoring show an increase in BP with increasing age. The absence of an increase in mean BP in this cohort may reflect changes in the management of hypertension over the last 10 years, including; better detection of hypertension, increasing use of antihypertensive medication, and tighter BP control among older hypertensive patients. At baseline, the most up-to-date UK hypertension guidelines recommended antihypertensive drug therapy for all individuals with sustained BP >160/100 and treatment of individual with BP >140/90 according to target organ damage and 10-year coronary heart disease risk.[40] Low dose thiazide diuretics and beta-blockers were the preferred first-line antihypertensives. Over the intervening 10 years, between the baseline and follow-up assessment, there have been significant changes to the UK guidelines on the management of hypertension. The 2011 National Institute for Health and Care Excellence hypertension guidelines advocated widespread use of ABPM to confirm hypertension in all individuals with office BP >140/90.[2] Calcium channel blockers and thiazide-like diuretics are now recommended as first-line management for people aged above 55. In addition, the guidelines

recommend that individuals aged above 80 years are offered the same antihypertensive drug treatment as people aged 55–80.[2] These changes are reflected in the changes to prescribing patterns observed in this study. This move toward more accurate diagnosis of hypertension and tighter control of BP in all age groups may account for failure of this study to reproduce the increase in mean BP observed in other studies. Mean BP did increase among the 19 individuals not taking cardioactive medication, supporting the suggestion, that the lack of a significant increase in mean BP among the wider study population may be due to the increased use of effective antihypertensive medication.

A number of limitations should be acknowledged. This was a *post hoc* analysis from a large study designed to look at a number of aspects of neurocardiovascular function in older people. Attrition over the 10-year follow-up was high. This resulted in a relatively small follow-up sample that was younger and fitter at baseline compared to the original cohort. The small follow-up population may have resulted in type 2 error particularly when examining the influence of medication class on BP variability where the numbers in each group were small. Conversely the selection bias of younger fitter individuals may have led to an underestimation of changes in ABPV as ABPV would be expected to increase more in participants with greater burden of cardiovascular disease.

One of the challenges of comparing ambulatory BP studies is the variety of methodologies used to collect BP data. In this study, we used fixed periods for daytime and nighttime. This method meant data from morning and late evening periods were not included in the analysis of daytime and nighttime data. It could be argued that such methods risk excluding important contributions to BP variability such as the morning surge. However, using narrow fixed time periods avoids errors due to inaccuracies in patients' diaries and differences in patients wake sleep patterns associated with age. The use of fixed day/night windows is now recommended.[41]

Debate has long existed on the number of recordings required for satisfactory ABPM recordings. Since the inception of this study in 2002, international efforts have been made to standardize ABPM protocols. In 2013, the European Society of Cardiology (ESC) released a position paper suggesting BP readings should be made at 30-minute intervals and that recordings required at least 20 valid daytime readings (0900 to 2100) and 7 valid nighttime readings (0100 to 0600).[41] Although the shorter daytime window used in this study and the decision to record BP hourly overnight meant our protocol did not quite reach current ESC criteria, the majority of participants had 18 or more daytime recordings and 6 or more nocturnal recordings at both assessments. Suggesting that although the studies original criteria only demanded a 50% successful inflation rate the vast majority of patients had well above the 70% successful inflation rate suggested by the recently published ESC guidelines.[41]

It should also be noted that if hypertension was diagnosed on baseline ambulatory BP monitoring it was essential for ethical reasons that the participants general practitioner was informed and BP monitored and treated as appropriate. It is therefore possible that changes in mean BP and BP variability are not representative of those seen in an unmonitored

population. However, since 2004, general practitioners in the UK have been financially incentivized to identify and effectively manage hypertension in their patients. It is, therefore, likely that the monitoring of BP that participants received as a result of participating in this study is not too different from that offered to the general population.

The underlying mechanisms causing ABPV to increase over time were not examined in this study. Future work will examine the contribution of baroreceptor sensitivity, arterial stiffening and response to physical and mental stress.

These limitations aside, this study is the first to *observe* that ABPV *increased* over a 10-year follow-up. This was despite stable mean BP and independent of medication. These findings are important as increased ABPV is associated with adverse cardiovascular outcomes and has recently been suggested as an additional target for treatments aimed at reducing cardiovascular risk.[35] If ABPV is to become a target for treatment, further studies are needed to determine how different antihypertensive classes effect ABPV and what degree of ABPV should be considered harmful.

SUPPLEMENTARY MATERIAL

Supplementary materials are available at *American Journal of Hypertension* (http://ajh.oxfordjournals.org).

DISCLOSURE

The authors declared no conflict of interest.

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