

ORIGINAL ARTICLE

How many measurements are needed to provide reliable information in terms of the ambulatory arterial stiffness index? the Ohasama study

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The aim of this study was to investigate how frequent ambulatory blood pressure (ABP) readings need to be obtained to reproduce the ambulatory arterial stiffness index (AASI) and pulse pressure (PP) without loss of information. We compared concordance from full and reduced ABP recordings. We recorded 24-h ABP at 30-min intervals in 1542 residents of Ohasama, Japan (baseline age, 40–93 years; 63.4% women). We randomly excluded up to 16 readings per recording or we selected readings at fixed 1- or 2-h intervals. Using full recordings as reference, we computed for the reduced recordings repeatability coefficient by Bland and Altman's approach. By Cox regression, we also calculated multivariate-adjusted hazard ratios for cardiovascular mortality. The median number of ABP readings per recording was 46. Randomly excluding more readings reduced the concordance of AASI, but not PP. Selecting blood pressure readings at 1- or 2-h intervals produced mean values of AASI and PP, which significantly differed from those in full recordings. During follow-up (median, 13.3 years) 126 cardiovascular deaths occurred. Across quartiles, AASI significantly predicted cardiovascular mortality in a U-shaped manner. AASI lost its prognostic significance when the number of randomly excluded readings increased from 8 to 16 or when the interval between readings was 1 h or longer. Compared with PP, AASI is less reproducible when the number of readings in ABP decreases, but this does not affect the predictive accuracy of AASI for cardiovascular mortality, until the median number of readings per ABP recording is less than ~35.

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INTRODUCTION

We previously defined the ambulatory arterial stiffness index (AASI) as unity minus the regression slope of diastolic on systolic blood pressure, as measured at the brachial artery by ambulatory monitoring.^{1,2} AASI reflects the dynamic relation between systolic and diastolic blood pressure during the day. Conceptually consistent with a hypothesis put forward in 1914,³ the stiffer the arterial tree, the closer the regression slope and AASI are to zero and unity, respectively. We validated AASI in terms of established indexes of arterial stiffness.¹ Several studies^{2,4–8} demonstrated significant association of AASI with signs of target organ damage^{4,7} or with the incidence of cardiovascular mortality⁸ and morbidity^{2,5,6} in

hypertensive patients,^{7,8} or in population samples randomly recruited in Western Europe⁵ and Japan.⁶

In the aforementioned studies,^{1,2,4–8} the interval between programmed blood pressure readings ranged from 15 (see refs 4, 5, 7 and 8) to 30 (see refs 2 and 6) minutes during daytime and from 20 (see ref 7) to 45 (see ref 1) minutes during nighttime. None of the studies addressed the issue how many blood pressure readings are required to calculate in a reproducible manner AASI from 24-h ambulatory readings. To answer this question, we analyzed the Ohasama database⁹ randomly excluding a stepwise increasing number of blood pressure readings from each individual ambulatory blood pressure (ABP) recording according to the approach originally

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described by Di Rienzo *et al.*¹⁰ We also addressed the prognostic accuracy with full and reduced recordings.

METHODS

Study population

The Institutional Review Boards of Tohoku University School of Medicine and the Department of Health of the Ohasama Municipal Government approved the study. All participants gave informed written consent. From 1988 until 1994, we contacted all 2716 subjects aged 40 years or more and living in three of four Ohasama districts. Subjects who were not at home during the normal working hours of the study nurses ($n=575$) and those hospitalized ($n=121$) or incapacitated ($n=31$) were not eligible.¹¹ Of the remaining 1989 residents, 1552 (78.0%) participated in the baseline examinations and were followed up. We excluded 10 subjects from this analysis because their ABP recording included less than 8 or 4 h during the awake and asleep periods, respectively. Thus, the number of participants statistically analyzed totaled 1542.^{6,11}

ABP measurement

We programmed validated ABPM-630 recorders (Nippon Colin, Komaki, Japan)¹² to obtain oscillometric blood pressure reading at 30-min intervals throughout the whole day. On monitoring days, participants noted the hour of awakening and going to sleep. According to the diary, 'daytime' and 'nighttime' were determined as the awakening and sleeping periods of the subject, respectively. In agreement with current guidelines,¹³ we defined ambulatory hypertension as an awake blood pressure of at least 135 mm Hg systolic or 85 mm Hg diastolic, or use of antihypertensive drugs. From 24-h recordings edited according to previously published criteria,¹⁴ we computed for each participant the regression slope of diastolic on systolic blood pressure.^{1,2} We did not force the regression line through the origin (intercept=0) because during diastole when flow drops to zero, such phenomenon does not occur for blood pressure.¹⁵ We defined AASI as one minus the regression slope. In addition, from individual ABP recordings and from the same readings as used for AASI, we computed pulse pressure (PP) as the difference between the 24-h systolic and diastolic blood pressure and mean arterial pressure as 24-h diastolic blood pressure plus one-third of the PP.

We first computed AASI and PP, using all available blood pressure readings in each individual recording. Next, we recalculated AASI and PP for each subject randomly excluding from 2 to 16 ABP readings. Finally, we also computed AASI and PP only using ABP readings at fixed 1- or 2-h intervals. Dipping was a night-to-day ratio of systolic blood pressure less than 0.90.¹⁶

Other measurements

At baseline, trained nurses measured anthropometric characteristics. Body mass index was weight in kilograms divided by height in meters squared. The study nurses administered a standardized questionnaire, inquiring into each subject's medical history, intake of medications, and smoking and drinking habits.

We followed cardiovascular mortality (ICD-10 codes 'I') until 31 December 2004.⁶ We ascertained vital status from the Ohasama residents' registration cards, which are the basis for the distribution of social security benefits. We obtained the causes of death from the National Japanese Mortality Registry. We verified the diagnoses reported on the death certificates against the medical records of Ohasama hospital, where over 90% of the Ohasama inhabitants undergo regular health check-ups.

Statistical analysis

For statistical analysis, we used SAS software, version 9.1 (SAS Institute, Cary, NC, USA). We compared means and proportions by the standard normal z -test for large samples and the χ^2 -statistic, respectively.

We randomly reduced the number of recordings in two reiterating steps. First, we randomly excluded two reading from each recording, using the SURVEYSELECT procedure, as implemented in the SAS package. Next, we computed each participant's AASI and PP from the reduced recording. To exclude more readings in a random manner, we repeated the two steps, always starting from the full recording, but using different seeds in the SURVEYSELECT procedure. Thus, we computed AASI and PP always from the same set

of ambulatory readings. The exclusion of a larger number of readings was truly random and not cumulative to the reduction in recordings with fewer readings excluded.

We determined agreement between the ambulatory parameters from original and reduced recordings, using Bland and Altman's¹⁷ approach and Pearson's correlation coefficients. The repeatability coefficient (RC) was defined as twice the standard deviation (s.d.) of the within-subject differences between the parameters from original and reduced recordings.¹⁷ The relative RC was RC expressed as a percentage of the maximal variability of the parameter under study.¹⁸ Maximal variability was four times the s.d. for the between-subjects variation in AASI or PP in the full recordings. RC allows comparing concordance across different definitions of AASI and PP. Higher values of RC and RCC indicate worse concordance.

We also evaluated the consistency of AASI and PP, as determined from original and reduced recordings in the prediction of cardiovascular mortality. We calculated hazard ratios by multiple Cox regression comparing the risk in each quartile of AASI or PP with the overall risk in the whole cohort. We used the deviation from mean coding¹⁹ because, as previously described,⁶ the association of cardiovascular mortality with AASI and PP was curvilinear. This approach also allows computation of confidence intervals for the hazard ratio in each quartile without definition of an arbitrary reference group. We adjusted the hazard ratios for baseline characteristics, including sex, age, mean arterial pressure, body mass index, current and past smoking, and drinking habits, diabetes mellitus, and a history of cardiovascular disease.

RESULTS

Baseline characteristics of the subjects

The 1542 participants included 977 (63.4%) women and 760 (49.3%) patients with ambulatory hypertension, of whom 473 (62.2%) were taking antihypertensive drugs. Mean age (\pm s.d.) was 61.7 ± 10.7 years. AASI averaged 0.46 ± 0.10 units and PP averaged 51.3 ± 7.4 mm Hg. The 24-h blood pressure was 123.2 ± 13.0 mm Hg systolic, and 72.0 ± 7.7 mm Hg diastolic. Height averaged 151.9 ± 8.8 cm, weight 54.6 ± 9.2 kg and body mass index 23.6 ± 3.1 kg m⁻². At enrollment, 319 men (56.6%) were current smokers and 251 (62.4%) reported intake of alcohol. Among women these numbers were 14 (1.4%) and 28 (3.3%), respectively. The average level of serum total cholesterol was 4.99 ± 0.88 mmol l⁻¹. Of the study participants, 268 had diabetes mellitus (17.4%) and 98 had history of previous cardiovascular disease (6.4%).

Agreement of AASI and PP by reducing the number of readings

The number of readings available per recording for the calculation of AASI and PP averaged 44.6. The 95th, 75th, 50th, 25th, 10th, 5th and first percentile values were 52, 48, 46, 42, 38, 36 and 30, respectively.

Random exclusion of 2–16 readings from the ambulatory recordings did not consistently change the average value of AASI (Table 1), but increased RC and RCC from 0.040 to 0.113 and from 10.2 to 29.3%, respectively, indicating worsening concordance with more readings omitted from analysis. The corresponding correlation coefficients expressing concordance of AASI between the full, that is, one reading every 30 min and randomly reduced recordings range dropped from 0.98 to 0.87. The fixedly reduced recordings produced average values of AASI, which significantly differed from those in the full recordings. Fixedly spacing the interval between readings by 1 and 2 h increased RC and RCC to 0.119 and 0.213, and to 30.5 and 54.7%, respectively. The corresponding Pearson's correlation coefficients were 0.85 and 0.65.

Random exclusion of readings from ambulatory recordings did not significantly change the average value of PP (Table 2), whereas the fixedly reduced recordings produced average PP values, which were significantly higher than those in the full recordings were. However, for PP, both the random and fixed exclusion of readings had little influence on RC, RCC and the correlation coefficients.

Table 1 Agreement of AASI between full^a and reduced recordings

Readings	AASI (units)	$\Delta \pm s.d.$ (units)	RC (units)	RRC (%)	r
All readings ^a	0.457 ± 0.097				
<i>Random exclusion of readings</i>					
2 readings	0.456 ± 0.098	-0.0013 ± 0.0199	0.04	10.2	0.98
4 readings	0.457 ± 0.100	-0.0003 ± 0.0217	0.04	11.2	0.98
8 readings	0.456 ± 0.103	-0.0006 ± 0.0330	0.07	17.0	0.95
16 readings	0.459 ± 0.115	0.0018 ± 0.0564	0.11	29.0	0.87
<i>Non-random selection of readings</i>					
One reading per hour	0.454 ± 0.113	-0.0035 ± 0.0593	0.12	30.5	0.85
One reading per 2 h	0.447 ± 0.139	-0.0101 ± 0.1065	0.21	54.7	0.65

Abbreviations: AASI, ambulatory arterial stiffness index; RC, repeatability coefficient; RRC, relative repeatability coefficient.

^aOne reading per 30 min. Plus-minus values are mean ± s.d. Mean difference (Δ) was computed as AASI from reduced recording minus AASI from full recordings. RC, RRC and *r* indicate the repeatability coefficient, the relative repeatability coefficient and Pearson's correlation coefficient. For further clarification, see Methods and reference.

Table 2 Agreement of 24-h Pulse Pressure (PP) between full^a and reduced recordings

Readings	PP (mm Hg)	$\Delta \pm s.d.$ (mm Hg)	RC (mm Hg)	RRC (%)	r
All readings ^a	51.29 ± 7.41				
<i>Random exclusion of readings</i>					
2 readings	51.27 ± 7.41	-0.0143 ± 0.3719	0.74	2.5	1.00
4 readings	51.28 ± 7.42	-0.0095 ± 0.5010	1.00	3.4	1.00
8 readings	51.28 ± 7.43	-0.0073 ± 0.7556	1.51	5.1	0.99
16 readings	51.35 ± 7.51	0.0589 ± 1.2021	2.40	8.1	0.99
<i>Non-random selection of readings</i>					
One reading per hour	51.41 ± 7.49	0.1194 ± 1.2161	2.43	8.2	0.99
One reading per 2 h	51.72 ± 7.74	0.4267 ± 2.0848	4.17	14.1	0.96

Abbreviations: RC, repeatability coefficient; RRC, relative repeatability coefficient.

^aOne reading per 30 min. Plus-minus values are mean ± s.d. Mean difference (Δ) was computed as PP from reduced recording minus PP from full recordings. RC, RRC and *r* indicate the repeatability coefficient, the relative repeatability coefficient and Pearson's correlation coefficient. For further clarification, see Methods and reference.

Analysis of cardiovascular mortality

During follow-up (median, 13.3 years; 5–95th percentile interval, 4.7–16.3 years), 19 024 person-years accrued. Of 345 deaths, 126 (36.5%) were cardiovascular, including 63 strokes and 59 cardiac deaths.

Using full recordings, that is, one reading every 30 min, the multivariate-adjusted hazard ratios for cardiovascular death significantly deviated from those in the whole population in an U-shaped manner for AASI (Table 3), whereas for PP none of the hazard ratios significantly departed from the overall risk (Table 4), after adjustment for 24-h mean arterial pressure and other covariates. Next, we computed hazards ratios from reduced recordings. When we randomly excluded readings, the multivariate-adjusted hazard ratios of cardiovascular mortality with AASI lost significance, when the

number of excluded readings increased from 8 to 16 (Table 3) or when the interval between readings was 1 h or longer.

Sensitivity analyses

In sensitivity analyses, using all available readings, we evaluated whether dipping status and antihypertensive treatment affected estimates of AASI and PP. Both AASI (0.493 ± 0.107 vs. 0.438 ± 0.086 units) and PP (52.8 ± 8.1 vs. 50.5 ± 6.9 mm Hg) were slightly but significantly ($P < 0.0001$) higher in 526 non-dippers compared with 1016 dippers. AASI was similar in 473 treated patients and 1069 untreated subjects (0.463 ± 0.095 vs. 0.454 ± 0.098; $P = 0.12$), whereas PP was significantly higher in the former group (54.0 ± 8.2 vs. 50.1 ± 7.3 mm Hg; $P < 0.0001$). However, estimates of RC and RRC, as reported in Tables 1 and 2 for AASI and PP, respectively, were not materially different between dippers and non-dippers or between treated and untreated patients (data not shown).

DISCUSSION

We studied the concordance of AASI and PP, whereas excluding a stepwise increasing number of blood pressure readings from ABP recordings, according to the approach originally described by Di Rienzo *et al.*¹⁰ In addition, we evaluated to what extent AASI from full and reduced recordings predicted cardiovascular mortality. In middle-aged and older subjects recruited from a Japanese population, AASI, a measure of the dynamic relation between diastolic and systolic blood pressure throughout the day,^{1,2} could be reproducibly computed from ambulatory recordings with readings programmed at 30-min intervals, until more than eight readings were randomly omitted. Similarly, AASI remained a significant predictor of cardiovascular mortality until more than eight readings were randomly excluded. On the other hand, AASI computed from recordings with the interval between readings set at 1 or 2 h lost its prognostic value. Estimates of mean PP were also significantly affected by the random exclusion of more than eight readings or by using an interval between readings of 1 or 2 h. However, relative RC of PP in the reduced compared with the full recordings never increased above 15%, whereas for AASI RRC already exceeded the 15% threshold after the random exclusion of eight readings.

To our knowledge, there are currently no published data on the number of measurements required for AASI. When comparing our current results for PP with the literature, one should realize that as Di Rienzo *et al.*,¹⁰ we evaluated concordance from reduced vs. full recordings, which is different from assessing concordance from repeat (test-retest) measurements. Di Rienzo *et al.* recorded blood pressure intra-arterially in 20 hypertensive patients and compared estimates from continuous beat-to-beat recordings with those from intermittent measurements at interval. When the interval between the intermittent measurement was 30 min or shorter, estimates of the 24-h systolic and diastolic blood pressure means were within 1 mm Hg of those based on beat-to-beat recordings.¹⁰ At 1-h intervals, the 24-h systolic and diastolic differences were 2–3 mm Hg.¹⁰ Di Rienzo *et al.*¹⁰ did not report on PP, but from the results on systolic and diastolic pressure one may infer that up to 30-min intervals estimates of 24-h PP would be within 2 mm Hg of those from continuous recordings, a result in-line with our current findings. Thijs *et al.*¹⁸ studied 97 normotensive volunteers, aged 23–84 years, who underwent ambulatory monitoring with readings programmed at 7.5-min intervals from 0800 to 2000 h and at 15-min intervals for the remainder of the day. If only the readings at 30-min or 1-h intervals were considered, estimates of PP were within 0.5 mm Hg of those derived from the full recordings.

Table 3 Adjusted Hazard Ratios for cardiovascular mortality by quartiles of AASI derived From full^a and reduced recordings

Readings	AASI quartile limits, unit			
	< 0.38	0.39–0.45	0.45–0.51	> 0.52
All readings ^a	1.40 (1.01–1.95) [†]	0.82 (0.59–1.15)	0.64 (0.46–0.91) [†]	1.35 (1.03–1.78) [†]
<i>Random exclusion of readings</i>				
2 readings	1.35 (0.97–1.89) [†]	0.86 (0.62–1.19)	0.68 (0.49–0.95) [†]	1.27 (0.96–1.67)
4 readings	1.30 (0.93–1.82)	0.88 (0.63–1.24)	0.64 (0.45–0.89) [†]	1.37 (1.04–1.80) [†]
8 readings	1.18 (0.84–1.65)	0.88 (0.63–1.23)	0.71 (0.51–0.99) [†]	1.37 (1.04–1.79) [†]
16 readings	1.31 (0.95–1.82)	0.80 (0.56–1.13)	0.84 (0.61–1.16)	1.13 (0.85–1.49)
<i>Non-random selection of readings</i>				
One reading per hour	0.99 (0.70–1.40)	1.03 (0.74–1.42)	0.80 (0.58–1.12)	1.23 (0.93–1.62)
One reading per 2 h	0.87 (0.60–1.26)	0.92 (0.66–1.27)	0.88 (0.63–1.22)	1.44 (1.09–1.89) [†]

Abbreviation: AASI, ambulatory arterial stiffness index.

^aOne reading per 30 min. The hazard ratios (95% confidence interval) express the risk in each quartile vs. the overall risk in the whole study population. All hazard ratios were adjusted for sex, age, body mass index, 24-h mean arterial pressure, past and current smoking and drinking, diabetes mellitus, and a history of cardiovascular disease. Significance of the hazard ratios: [†] $P < 0.05$.

Table 4 Adjusted Hazard Ratios for cardiovascular mortality by quartiles of PP derived from full^a and reduced recordings

Readings	PP quartile limits (mm Hg)			
	< 45.8	45.8–50.2	50.2–55.6	> 55.6
All readings ^a	0.90 (0.53–1.52)	1.08 (0.73–1.60)	0.81 (0.57–1.16)	1.26 (0.87–1.83)
<i>Random exclusion of readings</i>				
2 readings	0.78 (0.45–1.33)	1.36 (0.93–1.99)	0.69 (0.47–1.01)	1.37 (0.95–1.98)
4 readings	1.06 (0.65–1.74)	0.99 (0.66–1.48)	0.71 (0.49–1.02)	1.35 (0.93–1.95)
8 readings	0.86 (0.51–1.45)	1.08 (0.73–1.59)	0.77 (0.54–1.12)	1.39 (0.97–2.00)
16 readings	0.81 (0.48–1.35)	1.09 (0.74–1.61)	0.88 (0.62–1.25)	1.29 (0.90–1.85)
<i>Non-random selection of readings</i>				
One reading per hour	0.91 (0.54–1.53)	1.01 (0.69–1.49)	0.84 (0.89–1.19)	1.30 (0.91–1.87)
One reading per 2 h	0.99 (0.61–1.62)	0.98 (0.66–1.45)	0.77 (0.53–1.11)	1.34 (0.95–1.89)

^aOne reading per 30 min. The hazard ratios (95% confidence interval) express the risk in each quartile vs. the overall risk in the whole study population. All hazard ratios were adjusted for sex, age, body mass index, 24-h mean arterial pressure, past and current smoking and drinking, diabetes mellitus and a history of cardiovascular disease.

Our current results show that estimates of PP are less vulnerable to an increasing interval between successive ambulatory readings than AASI. This is not surprising. Previous studies clarified that the 24-h systolic and diastolic blood pressures are highly reproducible, even if the number of readings are reduced to one every 30 min¹⁰ or to 1 per hour.¹⁸ In Thijs *et al.*¹⁸ study, the relative RC for 24-h blood pressure in recordings with only 1-hourly readings compared with the full recordings was 9% systolic and 12% diastolic. For the night-to-day blood pressure difference, RCC was 23% systolic and 30% diastolic. For all variables that involved computation of statistical parameters from whole-day recordings, estimates of RCC for a 1-h interval between readings vs. full recordings were consistently higher than 30% with values up to 80%. PP is the simple difference between the average systolic and diastolic blood pressure over 24h, which are measurements with high concordance in reduced recordings. In contrast, AASI is a parameter derived by linear regression from individual readings in one person's ambulatory recordings. Individual blood pressure readings in ambulatory recordings are not reproducible.

In this study, up to eight readings could be randomly excluded from ABP recordings with readings programmed at 30-min intervals before AASI started to lose its prognostic significance, whereas PP did not

predict cardiovascular death neither in full, nor in reduced recordings. The Dublin Outcome Study involved 11 291 patients, who over a median follow-up of 5.3 years experienced 566 cardiovascular deaths, including 151 from stroke and 358 from cardiac disorders.² Before and after adjustment for other cardiovascular risk factors, AASI and PP significantly predicted total cardiovascular mortality.² AASI was a stronger predictor than PP for stroke (mutually adjusted relative hazard ratios for 1 s.d. increase, 1.21 ($P=0.02$) vs. 1.04 ($P=0.66$)) with the opposite trend for cardiac mortality (1.03 ($P=0.63$) vs. 1.21 ($P=0.002$)).² In the Ohasama population stroke represents 50% of cardiovascular mortality,⁶ whereas in the Irish patients this proportion was 26.7%.² The AASI, not PP, predicted cardiovascular mortality in the Ohasama cohort was therefore in-line with previous findings.^{2,6} Aortic pulse-wave velocity, in the experts' view the gold standard to measure arterial stiffness,²⁰ is a strong predictor of outcome over and beyond classical risk factors. We recently assessed the independent contributions of aortic pulse-wave velocity and AASI to the stratification of cardiovascular risk in a Danish cohort sample.²¹ In multivariate-adjusted Cox regression models including both indexes,²¹ AASI (standardized hazard ratio, 1.68; $P=0.01$) but not aortic pulse-wave velocity (0.91; $P=0.62$) predicted stroke, whereas the opposite was true for the composite of

all cardiovascular events (aortic pulse-wave velocity, 1.15; $P=0.03$ and AASI, 1.04; $P=0.68$).

This study must be interpreted within the context of its potential limitations. First, we programmed our ABP readings at a constant interval during the day and night for 30 min.² However, from the current results as well as from those published before,^{10,18} it is unlikely that a shorter interval between consecutive measurements in the full recordings, of for instance 15 min, would have had a bearing on the present conclusions. Second, middle-aged and older women made up the majority of the Ohasama cohort. Furthermore, only subjects who were at home during normal working hours were included in the study. This might to some extent limit the generalizability of our findings. On the other hand, the proportion of patients on antihypertensive drug treatment was lower in our population study than in cohorts of hypertensive patients.² Finally, we studied only mortality and we cannot extrapolate our current results to the combination of fatal and non-fatal outcomes.

In conclusion, compared with PP, AASI is less reproducible when the number of readings in ABP decreases, but this does not affect the predictive accuracy of AASI for cardiovascular mortality, until the median number of readings per ABP recording becomes less than ~35.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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