

The incremental value of ambulatory blood pressure persists after controlling for methodological confounds: associations with carotid atherosclerosis in a healthy sample

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Background Ambulatory blood pressure assessments have been shown to be associated with subclinical and clinical endpoints even after controlling for the effects of clinic blood pressure.

Objective To examine the incremental validity of ambulatory over clinic blood pressures using equivalent time periods, equivalent numbers of observations, and comparable measurement instruments across both settings.

Design and Methods In this cross-sectional study of 216 healthy, community volunteers (ages 50–70 years), we compared three types of assessment in terms of their association with carotid artery atherosclerosis: manual clinic blood pressure (two readings, 10 min interval), automated clinic blood pressure (four readings, 2.5 h interval), and automated ambulatory blood pressure (four readings, 2.5 h interval) using the same type of automated device for the latter two conditions. These measurements were obtained during the morning hours on three separate occasions. Carotid intima–medial thickness and plaque were assessed, by ultrasound, as markers of atherosclerosis.

Results Greater ambulatory systolic and diastolic blood pressure were associated with increased intima–medial thickness and an increased prevalence of plaque (odds

ratios > 3.0), even after statistical adjustment for clinic blood pressure assessments and demographic covariates.

Conclusions We conclude that the independent utility of ambulatory over clinic blood pressure cannot be attributed to methodological issues that have traditionally confounded these comparisons. These findings highlight the potential importance of behavioral and lifestyle factors in contributing to the incremental value of ambulatory blood pressure. *J Hypertens* 20:1535–1541 © 2002 Lippincott Williams & Wilkins.

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Introduction

Over the past 20 years, accumulating data from cross-sectional, prospective and intervention studies have supported the importance of ambulatory blood pressure (ABP) as an independent marker of cardiovascular risk [1]. In numerous reports, ABP assessments have been shown to be associated with subclinical [2] and clinical endpoints [3] over and beyond the effects of clinic blood pressure (CBP).

Some have hypothesized that the incremental value of ambulatory measures may derive from their generalizability to daily life; that is, ABP may be more likely to capture the effects on blood pressure of lifestyle and behavioral influences that cannot be observed in the

clinic [4]. The cumulative impact of such influences is presumably an important determinant of cardiovascular disease risk, according to this argument.

In addition to its generalizability, however, there are other measurement features associated with ABP that could also account for its differential utility. For example, in the literature cited, ambulatory measures are typically based upon the average of 20 or more observations over the course of a day, whereas clinic measures may be based upon as few as one to three blood pressure assessments collected over the course of several minutes. The automated readings used as part of ABP measurement may also be more standardized and less prone to reader bias when compared with

clinic assessments [5]. Measurement standardization and use of multiple observations are both associated with enhanced reliability; therefore, each of these practices could plausibly contribute to the enhanced prognostic value of ABP. If the advantages of ABP measurement could be entirely accounted for by methodological factors, however, this would raise questions about the essential importance of assessing blood pressure outside the clinic.

A small number of studies have attempted to eliminate the methodological advantages of ABP relative to CBP assessments, by enhancing the number of blood pressure readings or the number of days of measurement in the clinic [5–8]. Most of these studies show some increase in the predictive power of clinic measures, as expected, when these methodological refinements are adopted. The prognostic importance of ABP is not necessarily diminished under these circumstances, however, if it continues to be an independent correlate of disease endpoints. To our knowledge, only one report [8] has examined changes in the prognostic value of ABP when methodological differences between clinic and ambulatory methods are reduced. Moreover, none of the existing studies in this area has compared the value of ambulatory and clinic readings using the same type of measurement device, the same number of observations, and the same intervals of measurement.

The current investigation is an extension of previous work, evaluating the relative importance of ABP and CBP in a sample of healthy, unmedicated community volunteers. We hypothesized that ABP should continue to be an independent correlate of target-organ damage after controlling for CBP, even when the assessment interval and number of observations associated with each of the two measurement settings are equivalent, and when similar measurement devices are used in each case. If our data are found to be consistent with this hypothesis, this may suggest that part of the value of ABP can be attributed to its generalizability (i.e. its ability to capture cardiovascular activity during representative daily activities), in addition to these more superficial methodological characteristics.

Methods

Participants

Participants were recruited as part of a larger study, the Pittsburgh Healthy Heart Project, examining the predictors of subclinical cardiovascular disease progression in asymptomatic, community-dwelling older adults. The study received the approval of the Institutional Review Board at the University of Pittsburgh and participants were paid \$200 for completion of this portion of the investigation.

Recruitment strategies involved targeted mailings, radio

and television announcements, and billboards, flyers and pamphlets distributed in the Pittsburgh metropolitan area. Major inclusion criteria were age (50–70 years) and menopausal status (women were required to be postmenopausal for at least 6 months). Participants were excluded if they reported a history of chronic medical disorders (including symptomatic coronary heart disease or stroke), current (within the past year) pharmacological treatment for high blood pressure or hypercholesterolemia, current use of medication with autonomic effects, and excessive alcohol consumption (i.e. five or more drinks at least three times a week). Patients with diabetes who were receiving insulin were excluded, as were persons with clinic systolic blood pressure (SBP) > 180 mmHg or clinic diastolic blood pressure (DBP) > 110 mmHg. We also excluded obese participants whose arm girth prohibited reliable microphone detection of Korotkoff sounds.

We enrolled in the study 464 individuals, who provided written consent to participate. Of these, 216 were eligible for the present report, by virtue of continued retention and eligibility ($n = 367$), and complete data required for this report. We excluded individuals who did not have four valid ambulatory blood pressure assessments during their first 2.5 h of ambulatory monitoring ($n = 107$), those for whom one or more of the required CBP ($n = 1$) or automated clinic readings ($n = 39$) were missing, and those who were missing any carotid ultrasound data ($n = 4$).

Among the group of 216 participants, 103 (48%) were women and 31 (14%) were non-white. The group was somewhat better educated, on average, than the local population, with 23% (50/216) reporting a high school education or less and 51% (110/216) holding a bachelor's or higher degree. Sixty-three (29%) were hypertensive, by manual clinic manometry (SBP \geq 140 mmHg, DBP \geq 90 mmHg, or both).

Measures

Manual clinic pressures (initial visit)

The initial study visit included a medical history interview and blood pressure screening; blood was withdrawn for assessment of glucose, lipids, and other risk factors (data not reported here). Participants were asked to abstain from food or caffeine for 12 h before the visit. They arrived at the laboratory for an early morning session, and they were seated for at least 30 min before the CBP assessments. In accordance with American Heart Association guidelines [9], three seated manual blood pressure readings were initiated, at 2 min intervals, by a trained research nurse. A standard mercury sphygmomanometer was used (Vital Signs Model 63154; Country Technology, Gays Mills, Wisconsin, USA) and Korotkoff phases I and V were assessed for determining SBP and DBP. The term

‘manual clinic pressures’ refers to the average of the last two readings taken at this visit.

Automated ambulatory pressures (1-month visit)

Approximately 1 month after the initial visit (median of 28 days, range 3–196 days), participants were trained to use an automated ABP monitor (Accutracker DX; Suntech, Raleigh, North Carolina, USA) along with a computerized self-report diary (not described further). Cuff and microphone placement were altered, as necessary, to minimize discrepancies between manual and automated calibration readings. An appropriate microphone position was outlined on the arm, using a semi-permanent marker. After a feedback session on the day after training, participants were instructed to wear the monitor during all waking hours over the following 3 days. Automated pressures were assessed every 45 min over this period.

For this report, measures of ‘automated ambulatory pressures’ were obtained by averaging the first four ABP readings taken during the first day of monitoring (2.5 h monitoring period; a weekday morning in all instances). Only individuals with no missing or invalid readings were included in the sample. Invalid readings involved: (a) weak Korotkoff sounds, microphone difficulties, or air leaks, using error codes provided by the manufacturer [10], (b) arm movement codes when accompanied by large fluctuations in blood pressure values (± 30 mmHg from previous reading or more than 3SD from the individual’s mean), and (c) non-physiologic values, using criteria described by Verdecchia *et al.* [11].

Automated clinic pressures (2-month visit)

Approximately 2 months after the initial visit (median of 59 days, range 12–223 days), the volunteers participated in a laboratory testing session. As with the initial visit, all testing took place in the early morning; participants were instructed to refrain from food, exercise and tobacco for at least 2 h, from caffeine for 4 h, and from medication with autonomic effects (e.g. cold medication) for at least 24 h before this session. Testing took place in a sound-attenuated and temperature-controlled chamber. Participants were seated in a Lumex chair (Grahamfield Inc., Atlanta, Georgia, USA), locked into the upright seated position, and equipped with head and body bolsters to standardize and maintain posture throughout each testing session.

Starting approximately 30 min after their arrival, participants were presented with a series of cognitive, psychomotor and speaking tasks, interspersed with five 10 min pre-task resting baseline periods and a 15 min recovery baseline at the end of the session. They were asked to sit quietly throughout; during the pre-task resting baselines, they were asked to direct their attention to a

standardized color display. Recorded instructions were presented periodically, but interaction with the experimental assistant, who sat in an adjacent observation room, was minimized by design.

The Accutracker DX monitor, modified to permit PC-initiated data acquisition, was used for blood pressure assessment. Cuff and microphone placement were altered, if necessary, to reduce error and minimize discrepancies from previous calibration results. Participants were also instrumented with three electrocardiogram sensors and leads for impedance cardiographic monitoring (data not described further).

Baseline blood pressure readings (taken every 90 s during each resting period) were the focus of this investigation. ‘Automated clinic pressures’ were obtained by averaging four of the blood pressure assessments, sampled at the end of each of four of the resting baseline periods. These four readings were separated by an average of 45 min and spanned a 2.5 h period, in a manner similar to the automated ambulatory readings.

Carotid ultrasound assessments (2.5-month visit)

Approximately 2.5 months after the initial visit (median of 69 days, range 14–218 days), participants attended an appointment with the ultrasound research laboratory affiliated with this project. B-mode ultrasound (Toshiba SSA-270A and SSA-140A scanners; Toshiba American Medical Systems, Tustin, California, USA) was used to identify the borders of the intima and medial layers of the left and right carotid arteries, using the intima–lumen interface and the media–adventitial interface as markers. Digitized images were displayed on a workstation monitor, and the distances between these interfaces were measured across the distal 1 cm of the common carotid artery (near and far walls), the carotid bulb (far wall), and the first 1 cm of the internal carotid (far wall). Using scans from the right and left carotids, this yielded a total of eight sets of images for measurement. Mean intima–media thickness (IMT) was calculated for each participant, using the mean interface distance within each of the eight segments and averaging these measures across segments. Plaque (in the internal, external and common carotid arteries) was defined as a distinct protrusion into the vessel lumen, with more than 50% greater thickness when compared with the surrounding area. Previous literature (e.g. [12]) supports the use of carotid ultrasound measures as markers of atherosclerosis and cardiovascular risk.

Data analysis

We examined the relationship between automated ABP measurement and carotid atherosclerosis in the context of four different regression models. Model 1 examined the effects of standard demographic covariates along with ABP in association with carotid measures. Model 2

included demographic covariates and manual CBP and ABP measurement; this model showed us to what extent the association between ABP and atherosclerosis may be independent of CBP. Model 3 included demographic covariates and automated CBP and ABP measurement; it revealed to what extent the incremental value of ABP may be reduced by holding constant differences in measurement methods across clinic and ambulatory settings. Model 4 included demographic covariates, manual CBP, and automated CBP and ABP measurement; this model was the most conservative, as it included adjustments for two different types of clinic measures taken on separate days.

Because the distribution of the mean IMT scores was positively skewed, this variable was subjected to a reciprocal transformation; resulting scores were multiplied by (-1) in order to facilitate interpretation (i.e. greater thickness being associated with larger scores). Plaque was rated for its presence or absence (0 = no plaque, 1 = one or more detectable plaques) in each individual. Separate analyses were run in each case for SBP and DBP and for each of the two sets of carotid measures (IMT and plaque).

Results

Manual CBP, automated CBP and automated ABP measurement

Table 1 presents the means and standard deviations for SBP and DBP in this sample, as assessed by manual clinic, automated clinic, and automated ambulatory methods. These three assessment methods produced reliably different results, with the manual clinic measures being largest, and the automated clinic measures being smallest in each case (repeated measures *F* values (*df* = 2, 430) > 40, *P* < 0.0001 for SBP and for DBP). Follow-up contrasts showed that ambulatory and manual clinic readings were statistically equivalent, whereas the automated clinic method produced readings that were significantly lower than either of the other two methods in each case (*P* < 0.0001 for each). Method differences and order effects were confounded in these analyses, insofar as the automated clinic readings were always taken last.

Although the three methods were associated with different mean values, results for each were moderately correlated, with Pearson *r* values ranging from 0.51 to 0.68.

Demographic influences on carotid atherosclerosis

Intima-medial thickness values ranged from 0.57 to 1.42 mm (median 0.81 mm) in this sample, and 42% presented with some detectable plaque in the carotid arteries. Carotid atherosclerosis measures were regressed on each of four major demographic variables: age (measured continuously), race (white or non-white), sex and educational attainment (scored 1-4), using multiple and logistic regression for IMT and plaque, respectively. For IMT, significant main effects emerged for age (*P* < 0.0001), sex (*P* = 0.003, men showing larger IMT than women) and education (*P* = 0.04), and there was also a significant race-by-sex interaction (*P* = 0.002), with men showing larger IMT than women among whites only (*P* < 0.0001). For the plaque measure, there were significant main effects for age (*P* = 0.02), in addition to significant age-by-sex (*P* = 0.02) and race-by-sex interactions (*P* = 0.01), with sex effects (more plaque among men) significant for older, but not for younger individuals, and race effects (more plaque among whites) significant for men and not for women. On the basis of these results, we used the four demographic variables and the race-by-sex interaction term as covariates for analyses involving IMT, and the four demographic variables along with the two significant interaction terms as covariates for analyses involving plaque.

Blood pressure and carotid atherosclerosis: simple correlations

All three measures of blood pressure were associated with mean IMT, with manual clinic measures showing the smallest effects (*r* = 0.14, *P* = 0.046 for SBP, *r* = -0.05, *P* > 0.10 for DBP), automated clinic measures showing somewhat larger correlations (*r* = 0.23, *P* = 0.0005 for SBP, *r* = 0.02, *P* > 0.10 for DBP), and automated ambulatory measures yielding the largest associations (*r* = 0.30, *P* < 0.0001 for SBP, *r* = 0.14, *P* = 0.04 for DBP). Correlations involving the automated ambulatory measures were significantly larger

Table 1 Mean blood pressure (BP) as assessed using manual clinic, automated clinic, and automated ambulatory methods (*n* = 216)

	Manual clinic*	Automated clinic†	Automated ambulatory‡
Systolic BP (mmHg)	129.91 ± 14.39	122.44 ± 12.82	129.12 ± 14.76
Diastolic BP (mmHg)	80.32 ± 9.10	73.54 ± 8.39	79.65 ± 8.13

Values are mean ± SD. *Based on the mean of two out of three readings taken by a Research Nurse during the initial laboratory visit. †Based on the mean of four readings taken by an automated device during the 2-month laboratory visit. ‡Based on the mean of four readings taken during a one-day period 1 month after the initial laboratory visit.

than those involving manual clinic readings in each case ($P < 0.01$ for each). The comparisons involving automated clinic and ambulatory pressures were not significantly different from each other, although, for DBP, the relationship between IMT and automated ABP was marginally larger than the association between IMT and automated clinic pressure ($P < 0.10$).

Associations between blood pressure measures and carotid plaque were somewhat smaller than those involving IMT; once again, however, the pattern of results showed that associations involving manual clinic measures were smallest ($r = 0.12$, $P = 0.09$ for SBP, $r = 0.02$, $P > 0.10$ for DBP), that automated clinic measures showed stronger results ($r = 0.17$, $P = 0.01$ for SBP, $r = 0.06$, $P > 0.10$ for DBP), and that the automated ambulatory measures produced the largest associations with measures of plaque ($r = 0.21$, $P = 0.002$ for SBP, $r = 0.10$, $P > 0.10$ for DBP). In the case of plaque, none of these method-related differences reached statistical significance.

Incremental effects of ambulatory blood pressure

Model 1

In regression models adjusted for the demographic covariates, measures of ambulatory SBP were significantly associated with IMT and plaque, and ambulatory DBP was significantly associated with IMT (Table 2).

Model 2

In models adjusted for demographic covariates along with manual clinic pressures, both sets of ambulatory measures were significantly associated both with IMT and with plaque (Table 2). Interestingly, associations involving clinic SBP measures were not significant in any of these models after adjustment was made for

Table 2 Carotid intima–medial thickness (IMT) and plaque regressed on automated ambulatory systolic (SBP) and diastolic (DBP) blood pressures, with statistical adjustments for demographic factors, manual clinic blood pressure, and automated clinic blood pressure

	Ambulatory blood pressure			
	Model 1 [†]	Model 2 ^{††}	Model 3 [‡]	Model 4 [§]
Carotid IMT ^a				
SBP $R^2\Delta$	0.06****	0.06****	0.03***	0.04***
DBP $R^2\Delta$	0.01**	0.04***	0.03***	0.04***
Plaque ^b				
SBP χ^2	7.18***	7.84***	4.45**	5.77**
DBP χ^2	2.60	4.22**	2.29	3.00*

[†]Multiple and logistic regression models adjusting for demographic variables only. ^{††}Adjusting for demographic variables and manual clinic blood pressure (BP) measures. [‡]Adjusting for demographic variables and automated clinic BP measures. [§]Adjusting for demographic variables, manual clinic, and automated clinic BP measures. ^aIncremental variance accounted for by ambulatory blood pressure (ABP) in multiple regression models. ^b χ^2 for incremental variance accounted for by ABP in logistic regression models. * $P < 0.10$, ** $P < 0.05$, *** $P < 0.01$, **** $P < 0.0001$, compared with models without ABP.

demographic and ambulatory measures; clinic DBP remained a significant independent predictor of IMT.

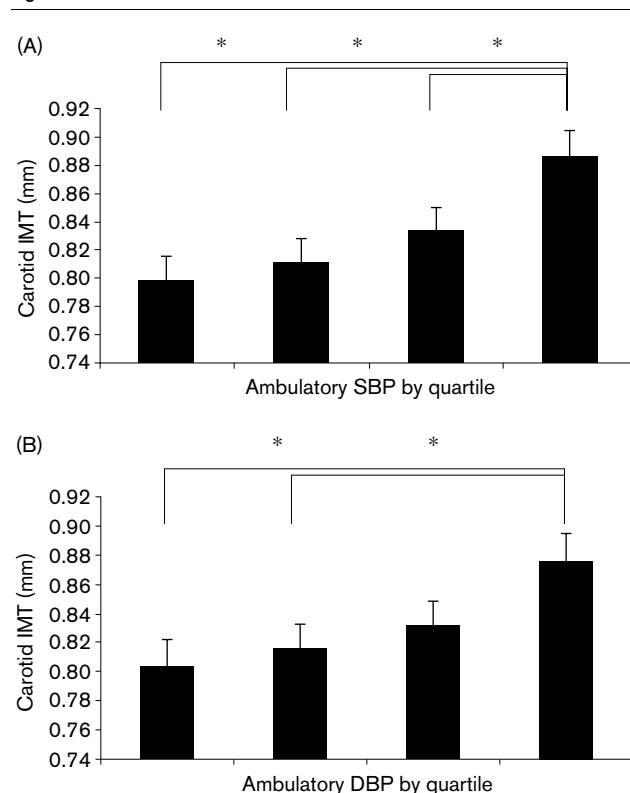
Model 3

When automated rather than manual clinic measures were entered along with demographic covariates, once again, both ABP measures remained significantly associated with IMT, and ambulatory SBP remained significant for plaque (Table 2). In contrast, none of the automated clinic measures was significant after adjustment was made for demographic and ABP assessments.

Model 4

Ambulatory blood pressure assessments were significantly associated with IMT, even after adjustment for demographic covariates and measures of manual and automated CBP (Table 2). In each of these models, ambulatory measures explained 4% of the variance after covariate adjustment. These incremental effects appeared to be strongest among those in the top quartile of ABP, for whom carotid IMT (in untransformed units) was 9% (for DBP) to 11% (for SBP) greater than for those in the lowest quartile of ambulatory pressures (Fig. 1).

Fig. 1



Association between (A) ambulatory systolic blood pressure (SBP) and ambulatory diastolic blood pressure (DBP) (B) by quartile, and carotid intima–medial thickness (IMT), after statistical adjustment for demographic covariates and two measures of clinic SBP and DBP.

In the case of plaque also, ambulatory SBP measures remained significant even in the context of demographic and both CBP covariates (Table 2). In this adjusted model, those in the top quartile of ambulatory SBP showed a significantly increased risk for carotid atherosclerotic plaque, by logistic regression, with the odds of plaque being 4.7 times greater in this group (28 (51.9%) with plaque and 26 without) than among those in the bottom quartile of the distribution (14 (25.5%) with plaque and 41 without; $\chi^2 = 7.69$, confidence interval 1.57–14.05, $P = 0.006$). Although ambulatory DBP, as a continuous measure, was not significantly associated with plaque, the odds of plaque was nevertheless 3.2 times greater among those in the highest quartile (26 (48.2%) with and 28 without plaque) as compared with the lowest quartile (19 (35.2%) with and 35 without plaque), using this covariate-adjusted model ($\chi^2 = 4.84$, confidence interval 1.14–9.03, $P = 0.028$).

Manual clinic measures were also significantly associated with IMT after demographic measures and both of the automated assessments were included as covariates, explaining 1.5% (SBP) and 2% (DBP) of the variance in these models. In contrast, automated clinic measures were not incrementally significant, and neither of the clinic measures was independently associated with plaque.

Discussion

We examined the relative value of ABP and CBP as correlates of subclinical disease, holding constant a number of extraneous measurement factors that have confounded these associations in previous studies. We showed that ABP was an independent correlate of ultrasound measures of atherosclerosis after controlling for CBP, and that this association remained significant even after methodological differences between clinic and ambulatory measures had been ruled out as an explanation for this effect. Our results appeared to hold when we used ABP either as a correlate of carotid IMT, or as a correlate of observable plaque in the carotid arteries. Those in the top quartile of ABP appeared to be most likely to show significant signs of carotid atherosclerosis, a finding that persisted even after adjustment was made for demographic confounders and for measures of CBP assessed on two different days. Associations involving ABP accounted for more independent variance than did manual clinic measures in all cases, and automated clinic measures showed incremental validity in only one of four comparisons after adjustment for ambulatory assessments.

Previous investigators have speculated that ambulatory measurement is incrementally useful, in part, because it allows us to capture the effects of psychological demands (e.g. the effects of exposure to a stressful work environment) in a manner that is not possible

when blood pressure is assessed in the clinic [4]. According to this hypothesis, such measures might be especially useful among individuals who live under demanding circumstances, or among those who are physiologically reactive when faced with mental or physical stress [13]. Because exaggerated physiological responding may plausibly either result from or contribute to atherosclerosis, no causal inferences may be drawn from this cross-sectional report. Future research should examine, in greater specificity, the interplay between personal and environmental influences that may account for the utility of ABP.

One potential limitation of this study involves the use of an atypical measurement strategy (automated measurement) for one of the assessments of CBP. Although the procedure for automated clinic readings used in this report was designed for another purpose, these measures were collected in a standardized fashion (and therefore were presumably free from observer bias) and were collected with the same type of instrument as was used in the field setting.

Automated clinic measures were taken during rest periods that were interspersed with cognitive tasks, another feature that makes this measurement strategy atypical. Insofar as these measures followed mental activity, however, this feature of the automated clinic measures might be seen as conservative, arguably reducing some of the distinctiveness of the ambulatory assessments with which they were compared (as the latter were also taken during periods that may have followed mental or physical effort). In any case, the automated clinic pressures seemed to be as valid as the manual clinic assessments, in terms of the magnitude of their unadjusted correlations with carotid disease.

Our volunteer group was not strictly representative in this study; moreover, missing data and withdrawals from the study further reduced the available sample size for this report. It is possible that a more representative group would have demonstrated a different pattern of results, although there is no *a priori* reason to expect differences in the incremental value of ABP as a function of education or other sample characteristics.

Correlations involving ABP were relatively small in this study, accounting, at most, for 9% of the variance in IMT ($r = 0.30$ with ambulatory SBP measures). After covariate adjustment, ABP accounted, at most, for only 6% of the variance in carotid IMT. These effects, although small, were larger than the observed associations with manual CBP measures in this study. It should also be noted that these results, based upon four ambulatory readings per person, are conservative estimates of the value of ABP measurement, a method which can easily yield more than 20 readings per day,

with a presumed increase in incremental utility over longer sampling intervals. This study was also conservative in another respect, as the majority of the participants were normotensive; previous evidence suggests that ambulatory methods may be associated with larger effects among hypertensive individuals [14]. Despite these conservative methods, our data suggest that the odds of the presence of detectable plaque may triple or quadruple among those with high ambulatory pressures, illustrating the clinical significance of this approach.

This study is the first to compare the utility of CBP and ABP when measurement practices and observations are held constant, and it is also one of the largest samples reported in the literature. Our data support the importance of blood pressure monitoring in the natural environment, suggesting that ABP measurement may be useful, both because it provides more measures and because the measures it provides afford us important new information not obtained in the clinic setting. Future work should continue to consider the importance of controlling for the methodological differences that may confound comparisons between measures of ambulatory and clinic blood pressure. Further research should also explore the determinants of ABP [15] and the factors that account for its unique importance as a correlate of cardiovascular risk.

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