A reliable index for the prognostic significance of blood pressure variability

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Objectives **This study presents a reliable index inspired by the total variability concept of real analysis in mathematics, called average real variability (ARV), for the prognostic significance of blood pressure variability (BPV) overcoming the pitfalls of the commonly used standard deviation (SD).**

Background **Recent studies have suggested that an increase in BPV is associated with an increase in subsequent cardiovascular events/complications. However, there are other studies where the cited association was not found or was lost in the presence of other well-known risk factors. An explanation for these apparently contradictory results may be the selection of the variability index used (SD).**

Methods **Ambulatory blood pressure monitoring in 312 subjects aged $\geq$ 55 years. Logistic regression models and survival methods were used to establish the prognostic significance of awake systolic BPV: in particular, (i) the performance of ARV versus SD, and (ii) the value of BPV relative to other well-known risk factors.**

Results **The analyses using the ARV index show a statistically significant relative risk equal to 4.548 ($P = 0.006$) for the group with high BPV with respect to the low BPV group (reference level); in contrast, the corresponding relative risk associated to the SD index was not statistically significant. Furthermore, ARV exhibited a similar predictive value to systolic blood pressure.**

Conclusions **The proposed ARV index is a more reliable representation of time series variability than SD and may be less sensitive to the relative low sampling frequency of the ambulatory blood pressure monitoring devices. The results suggest that ARV adds prognostic value to the ABPM and could prompt the use of therapeutic measures to control BPV. *J Hypertens* 23:505–511 © 2005 Lippincott Williams & Wilkins.**

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Introduction

Several studies [1–9] have suggested that an increase of blood pressure variability (BPV) is associated with an increase in subsequent cardiovascular events (CE)/complications. However, there are other studies where the cited association was not found [10–12] or was lost in the presence of other well-known risk factors [13,14]. An explanation for these apparently contradictory results may be the selection of the index [standard deviation (SD)] used for quantifying variability [15–17].

This study presents a reliable index inspired by the total variability concept [18] of real analysis in mathematics called average real variability (ARV) for establishing the prognostic significance of BPV. The prognostic significance of the proposed BPV index when compared with the SD index is established using data from the ambulatory blood pressure monitoring (ABPM) of a population in the city of Maracaibo, Venezuela. The value of BPV as a single predictor relative to other well-known risk factors is also discussed.

Methods

ARV index

The proposed index is calculated using the following formula:

$$ARV = \frac{1}{N-1}\sum_{k=1}^{N-1}|BP_{k+1} - BP_k|$$

where N denotes the number of valid blood pressure (BP) measurements in the ABPM data corresponding to a given subject.

Subjects

The subjects took part in a longitudinal study, the Maracaibo Aging Study [19] conducted from October

1998 to June 2001 (2.83 years) by the Center for Cardiovascular Diseases of the University of Zulia, in Maracaibo, Venezuela. The study included all the individuals with ABPM and 70% or higher valid measurements, and without important concomitant diseases. The initial evaluation included office BP, ABPM and laboratory tests (cholesterol and triglycerides). The 312 subjects selected had the following characteristics: age $\geq$ 55 years, mean age = 66.9 years, 63% women, 71% office hypertension, 39% ambulatory hypertension [20], and 29% white-coat hypertension [21]; note that the patients with ambulatory hypertension include those with and without simultaneous white-coat hypertension. Additional characteristics include: 52% smoking status (current and former), 14% under antihypertensive medication (β-blockers, calcium channel blockers, α-blockers, angiotensin-converting enzyme inhibitors, antihypertensive of central action and diuretics) and 22% obese. The follow-up period for each of the individual had a mean value of 1.86 years and ended with a non-fatal CE or with the arrival of the termination date of the study. Informed consent was obtained from every participant and the study protocol was approved by the ethics committee of the Center.

Cardiovascular events under consideration

The CE under consideration were coronary artery disease, stroke and congestive heart failure. Coronary artery disease was defined by any of the following: myocardial infarction diagnosed on the basis of at least two of three standard criteria (typical chest pain, electrocardiographic QRS changes, and positive ischemia serum markers) or angina pectoris defined by chest pain, cardiac catheterism showing hemodynamic significant obstructions or revascularization procedures. Stroke was diagnosed on the basis of rapid onset of localizing neurological deficit lasting $\geq$ 24 h in the absence of any other disease (or lasting $<$ 24 h for transient ischemic attack). Congestive heart failure was diagnosed using McKee criteria [22–24].

Ambulatory blood pressure monitoring

All subjects underwent 24-h ABPM with a fully automatic device (SpaceLabs 90207) that met the criteria of the Association for the Advancement of Medical Instrumentation [25,26]. Readings during awake time (0600–2259 h) were obtained every 15 min, an interval that is positively correlated with the BP measure beat to beat in rest [27], and every 30 min for the sleeping period (2300–0559 h). Systolic readings values greater than 260 mmHg or lower than 70 mmHg as well as diastolic readings greater than 150 mmHg or lower than 40 mmHg were discarded. Participants were told to carry on with their normal daily activities during measurements. The study focuses on the systolic blood pressure (SBP) measurements obtained during the awake period (mean of 83% of valid measurements).

Statistical methods

The association of CE events and BPV measured by ARV and SD, as well as the value of BPV as a predictor when compared with other well-known risk factors were explored using logistic regression models with goodness of fit calculated using the Hosmer–Lemeshow test, and survival semi-parametric (Cox proportional hazards model) and non-parametric (Kaplan–Meier) methods. A global comparison of the survival curves obtained with the Kaplan–Meier method using the Log-Rank test is also included. A value of $P < 0.05$ was established for statistical significance.

Results

ARV versus SD

The subjects were grouped (tertile analysis) based on their awake systolic BPV calculated using both ARV and SD. The groups were labeled as exhibiting low, medium and high variability. The clinical characteristics of the participants in each of the groups corresponding to the ARV and SD cases are summarized in Tables 1 and 2, respectively. During the follow-up, 31 subjects developed non-fatal CE (15 coronary artery disease, five stroke, and 11 congestive heart failure), which represents an event rate of 5.38 per 100 patient-years; similar results to those obtained by Sander *et al.* [8] where only transient ischemic attacks, myocardial infarctions and strokes were considered. The estimated risks (rate of events per 100 patient-years) associated with the different groups were calculated and are displayed in Figure 1. Note that when the ARV index is used the estimated risks of having a CE increases monotonically with BPV. In fact, the group with high BPV has four times higher risk than that corresponding to the low BPV group. In contrast, when the SD index is used the groups with medium and high BPV have similar risk values.

A logistic regression model for CE among the three groups was established using SD and ARV indices. In both cases, the hypothesis of adopting the logistic regression models was not rejected (Hosmer–Lemeshow test). When using the SD index the odds ratio (OR) obtained with an increment in the level of BPV was 1.241 and was not statistically significant ($P = 0.355$, confidence interval = 0.784–1.963). In contrast, the analysis using the ARV index showed an OR equal to 2.119 and statistically significant ($P = 0.003$, confidence interval = 1.276–3.519).

A survival analysis using both parametric (Cox proportional hazard regression model) and non-parametric (Kaplan–Meier) methods was also conducted. Using the group with low BPV as a reference, Table 3 presents the relative risk (RR), the statistical significance, and associated confidence intervals for the groups with medium and high BPV corresponding to the ARV and SD indices.

Table 1 Clinical characteristics of participants in groupings based on awake systolic blood pressure (SBP) variability: average real variability (mmHg)

Variable	Low variability (5.39–8.27)	Medium variability (8.28–9.83)	High variability (9.86–15.09)	*P*
Number of subjects	104	104	104	
Cardiovascular event	4	10	17	
Age (years)	64.77	65.94	70.02	0.000*
Ambulatory blood pressure monitoring (mmHg)				
Awake SBP	125.53	133.79	142.9	0.000*
Asleep SBP	119.16	125.72	136.3	0.000*
24-h SBP	124.28	132.26	141.6	0.000*
Awake DBP	75.22	79.1	79.83	0.008*
Asleep DBP	68.93	72.23	73.14	0.025*
24-h DBP	73.98	77.78	78.52	0.007*
Heart rate (beats/min)				
Awake	75.89	77.72	80.44	0.009*
Asleep	64.68	67.16	69.69	0.001*
24 h	73.73	75.68	78.33	0.005*
Smoking status (%)				
Current	39.42	33.65	38.46	NS†
Former	10.57	17.3	12.5	NS†
Never	50	49.03	49.03	NS†
Hypertension (%)				
Office	62.5	72.12	78.85	0.009†
Ambulatory	25	38.46	51.92	0.000†
White-coat	33.65	29.81	23.08	NS†
Cholesterol (mg/dl)	209.89	213.11	210.34	NS*
Triglycerides (mg/dl)	136.02	152.56	147.8	NS*
Men (%)	32.69	46.15	32.69	NS†
Antyhypertensive medication (%)	9.62	19.23	13.46	NS†
Obesity (%)	29.81	14.42	21.15	NS†

DBP, diastolic blood pressure; NS, not significant. *Analysis of variance. †χ^2 test. $P < 0.05$.

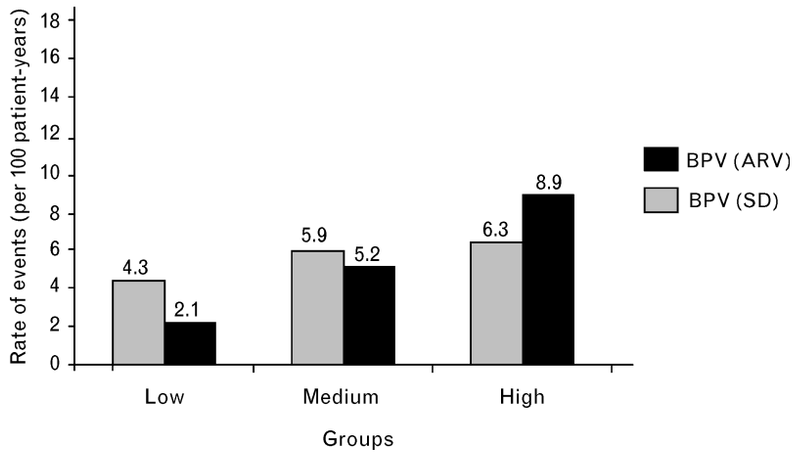
With reference to Table 3 for the SD index, a significant increment of RR in the groups with medium and high BPV is not observed. The results obtained using the ARV index (Table 3) were more supportive of the prognostic significance of BPV, with the RR monotonically higher for the groups with medium and high BPV; for the last group the value of RR was statistically significant ($P = 0.018$).

Table 2 Clinical characteristics of participants in groupings based on awake systolic blood pressure (SBP) variability: standard deviation (mmHg)

Variable	Low variability (5.92–11.96)	Medium variability (11.97–15.19)	High variability (15.22–26.29)	*P*
Number of subjects	104	104	104	
Cardiovascular event	8	11	12	
Age (years)	63.66	66.39	70.67	0.000*
Ambulatory blood pressure monitoring (mmHg)				
Awake SBP	126.32	133.38	142.54	0.000*
Asleep SBP	120.35	125.42	135.42	0.000*
24-h SBP	125.13	131.87	141.13	0.000*
Awake DBP	75.64	78.13	80.38	0.005*
Asleep DBP	69.85	70.71	73.74	0.018*
24-h DBP	74.48	76.7	79.1	0.005*
Heart rate (beats/min)				
Awake	77.51	78.95	77.59	NS*
Asleep	66.87	68.08	66.57	NS*
24 h	75.41	76.86	75.46	NS*
Smoking status (%)				
Current	35.57	34.61	41.34	NS†
Former	15.38	19.23	5.76	0,04†
Never	49.03	46.15	52.88	NS†
Hypertension (%)				
Office	65.38	65.38	82.69	0.008†
Ambulatory	30.77	29.81	54.81	0.000†
White-coat	31.73	32.69	22.12	NS†
Cholesterol (mg/dl)	207.95	216.26	208.76	NS*
Triglycerides (mg/dl)	140.65	141.31	155.02	NS*
Men (%)	36.54	39.42	35.58	NS†
Antyhypertensive medication (%)	8.65	15.38	18.27	0.04+†
Obesity (%)	29.81	16.35	19.23	NS†

DBP, diastolic blood pressure; NS, not significant. *Analysis of variance. †χ^2 test. $P < 0.05$.

Fig. 1



Risks for cardiovascular events according to their blood pressure variability (BPV) level. ARV, average real variability; SD, standard deviation.

Figures 2 and 3 depict the survival curves calculated using the Kaplan–Meier method for the aforementioned groups considering ARV and SD as variability indices, respectively. The survival curves corresponding to the ARV index (Fig. 2) are clearly differentiated; in contrast, those associated with the SD index (Fig. 3) exhibit similar values for the medium and high BPV groups.

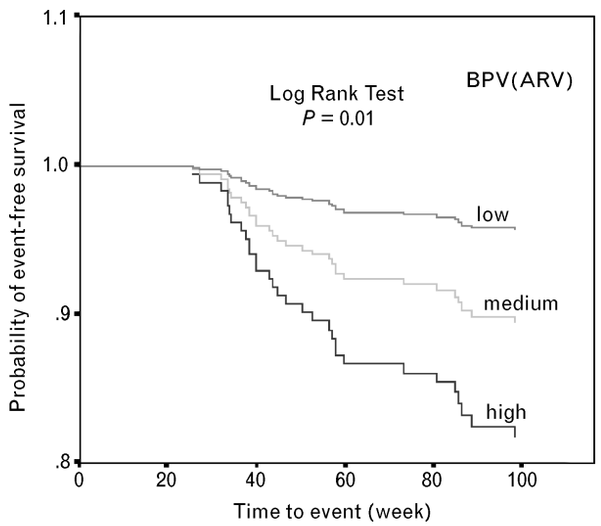
The Log-Rank test results for the global comparison of the survival curves show that the risks among the groups are statistically different ($P = 0.010$) when using the ARV index, while the opposite occurs in the case of SD ($P = 0.648$).

With the purpose of obtaining a better comparison between ARV and SD, both indexes were standardized (dividing among their standard deviation) [28]; the variables must be normalized so that the corresponding coefficients are comparable, both providing the change

Table 3 Cox proportional hazard regression model results

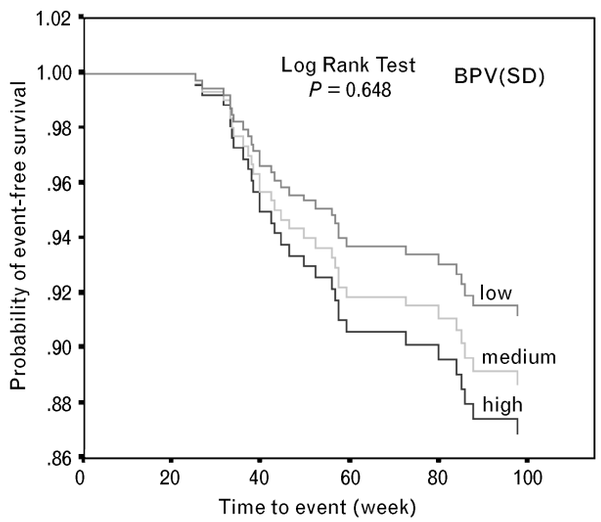
Blood pressure variability	Relative risk	95% confidence interval	*P*
Average real variability			
Medium	2.524	0.791–8.050	0.117
High	4.548	1.530–13.521	0.018
Standad deviation			
Medium	1.299	0.522–3.231	0.537
High	1.565	0.623–3.732	0.355

Fig. 2



Event-free survival curves by groups according to blood pressure variability level measured using average real variability [BPV(ARV)].

Fig. 3



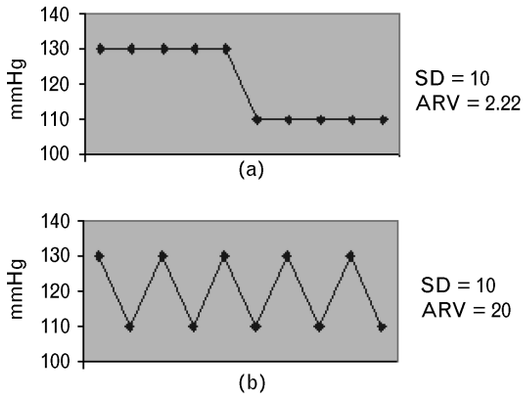
Event-free survival curves by groups according to blood pressure variability level measured using standard deviation [BPV(SD)].

Table 4 Cox proportional hazard regression model results for selected risk factors

	Relative risk	95% confidence interval	*P*
Awake BPV(ARV)	1.283	1.080–1.523	0.004
24-h BPV(ARV)	1.281	1.071–1.531	0.006
24-h systolic blood pressure	1.022	1.002–1.043	0.027
Night/day diastolic ratio	1.033	0.997–1.070	0.072
Night/day systolic ratio	1.036	0.996–1.079	0.077
24-h diastolic blood pressure	1.016	0.984–1.048	0.329
Triglycerides	1.001	0.998–1.004	0.344
Asleep BPV(ARV)	1.034	0.934–1.144	0.512
24-h heart rate	1.011	0.976–1.047	0.526
Smoking status	0.811	0.400–1.646	0.563
Awake BPV(SD)	1.027	0.935–1.127	0.572
Body mass index	1.016	0.957–1.080	0.591
Cholesterol	0.999	0.994–1.004	0.807
Age	1.004	0.965–1.045	0.823
Asleep BPV(SD)	1.008	0.915–1.110	0.868
24-h BPV(SD)	0.998	0.902–1.104	0.979

BPV, blood pressure variability; ARV, average real variability; SD, standard deviation.

Fig. 4



Blood pressure variability for two distinct blood pressure signals. ARV, average real variability; SD, standard deviation.

of OR per unit change in their standard deviation. Using the logistic regression model for each index the OR obtained was 1.618 ($P = 0.007$, confidence interval = 1.137–2.305) for the standardized ARV and 1.118 ($P = 0.546$, confidence interval = 0.777–1.609) for the standardized SD. The difference in the OR (1.62 versus 1.12) shows the superiority of the ARV index as a risk factor. A similar model including standardized SD and ARV determines that in the presence of ARV ($P = 0.003$), the SD leaves the model since it is not significant ($P = 0.172$). When the Cox model is used, similar results are obtained; for the standardized ARV and SD, the RR was 1.611 ($P = 0.004$) and 1.103 ($P = 0.571$), respectively.

BPV versus other well-known risk factors

The difference of the mean values of the risk factors under consideration in the groups with and without CE was calculated. These differences were statistically significant ($P < 0.05$) for awake and 24-h ARV, asleep and 24-h SBP. Table 4 displays the RR (Cox model) associated with the individual risk factors under consideration; while observing the *P* values note that, in both cases, BPV(ARV) and SBP were the single most significant factors, and that BPV(SD) was not statistically significant for all the settings (awake BPV, 24-h BPV, asleep BPV). Furthermore, the significance of BPV was established using the Cox model (Table 5) in the presence of the other most significant individual risk factor (SBP). The addition of awake BPV(ARV) to the model with SBP as the only factor results in a statistically significant ($P = 0.034$) difference of the −2 log likelihood statistic. When the added factor is awake BPV(SD), the cited difference is not statistically significant ($P = 0.393$). Similar results were obtained when the logistic regression model was used.

Table 5 Values of −2 log likehood for the Cox proportional hazard regression model

	−2 log likelihood	Reduction	*P*
None	346.394		
SBP	341.890	4.504	0.033
ARV	338.762	7.632	0.005
SD	346.081	0.313	0.575
SBP + ARV	337.656	4.234	0.034
SBP + SD	472.630	0.747	0.393

SBP, systolic blood pressure; ARV, average real variability; SD, standard deviation.

The predictive value of ARV in the presence of other well-known risk factors is assessed. The Cox proportional hazard regression model BPV(ARV) is adjusted using awake BPV(ARV), gender, age, use of antihypertensive medication, smoking status, cholesterol, and triglyceride levels, 24-h SBP, DBP, heart rate (HR), night/day systolic ratio (NDSR) [29], night/day diastolic ratio (NDDR), and body mass index (BMI). The RR associated with the BPV(ARV) was found to be equal to 1.253 and still statistically significant ($P = 0.04$, confidence interval = 1.010–1.556). Under this scenario, the logistic regression model estimates an OR equal to 1.278 and is also statistically significant ($P = 0.041$, confidence interval = 1.010–1.616).

Discussion

BP measurements for variability studies typically come from reliable, non-invasive ABPM, and the variability is commonly quantified as SD. This variability index has a notorious pitfall; it only reflects the dispersion of BP measurements around a single value (the mean) not accounting for the order in which the BP measurements were obtained. As a result, two subjects with significantly different BP measurement sets could have the same SD value (Fig. 4). With reference to Figure 4a, note that the signal has significantly lower variability than the other (Fig. 4b); however, the SD values in both cases are the same. Hence, the SD index may not properly reflect the data variability. Note that ARV essentially averages the absolute differences of consecutive measurements. As illustrated in Figure 4, the ARV index, contrary to the

SD, is sensitive to the individual BP measurement order. A figure similar to Figure 4 was reported by De Boer *et al.* [15].

The present study has shown that: (i) proper selection of the variability index is critical to assessing the value of BPV as a risk factor and could explain apparently contradictory results previously reported; and (ii) given the nature of the ABPM data, a time series variability index such as ARV should be used.

ARV versus SD

The main finding of the present study is that the prognostic significance of BPV is affected by the variability selection index, and the fact that the commonly used SD may not properly reflect the time series nature of the ABPM data and may be more sensitive to the sampling frequency of the ABPM device [30]. A reliable variability index for prognostic studies called ARV is proposed to substitute the commonly used but potentially ineffective SD index.

Using a population-based study of 312 subjects, the relative performance of the ARV and SD indices for establishing the association of BPV and CE was assessed. A statistically significant association of increasing levels of BPV and risk measures (i.e. RR and OR) was found when the ARV index was used. In contrast, the use of SD as a variability index does not confirm this association. Similar results were obtained when the survival curves for the groups identified according to their level of BPV were compared. When using the SD index the risks associated with each of the groups cannot be considered significantly different. In contrast, when using the ARV index the Log-Rank test establishes that the null hypothesis is rejected and that the risks are significantly different among the groups.

Among the authors that found association between BPV and CE/complications using the SD, Kikuya *et al.* [7] report a non-monotonic relationship between BPV and CV; specifically, the group with the lowest BPV does not have the lowest RR. Sanders *et al.* [8] show the relationship of BPV and early carotid atherosclerosis, and CE, but the findings could be challenged considering they divided the subjects into only two groups based on their BPV values. In addition, Veerman *et al.* [3] also found a relationship between BPV and left ventricular mass but the study was limited to only 33 subjects.

In addition to the SD index not reflecting the time series nature of the BP signal, a possible explanation for some of the cited inconsistencies in the predictive value of SD can be related to the relative low sampling frequency of the ABPM devices [30]; in particular, considering the results of studies that used intra-arterial, beat-by-beat ABPM [1,2].

BPV versus other well-known risk factors

The present study also compares the prognostic significance of short-term systolic BPV with other selected risk factors such as BMI, gender, age, smoking status, cholesterol, triglycerides, and 24-h SBP, DBP, HR, NDSR, and NDDR. The results show that the differences in the mean values corresponding to the risk factors BPV and SBP were statistically significant ($P < 0.05$). Using the OR (logistic regression model) and RR (Cox model) as risk measures, BPV(ARV) and SBP were found to be the single most significant factors.

Considering that the SBP is widely accepted as a fundamental factor (also confirmed in this study) in the prognosis of CE, the BPV significance was assessed by the ARV index regardless of the regression model used (Cox and logistic regression). The BPV(SD) factor failed to be statistically significant in the presence of SBP, which confirms the importance of selecting a reliable variability index such as the one proposed in this work.

Previous studies assessing the prognostic value of BPV(SD) in a multivariate analysis considering other risk factors have been inconclusive; this can be attributed not only to the fact that the SD index does not capture the time series nature of the BP signal, but also to the relative low sampling frequency at which the ABPM measurements are taken [30]. For example, Verdecchia *et al.* [13] using a Cox model did not found BPV (calculated using SD) statistically significant in the presence of factors such as age, previous CE, diabetes mellitus, SBP and DBP. Similarly, in the Roman *et al.* [14] study, awake and sleep time BPV(SD) were not found statistically significant in a multivariate regression model analysis for left ventricular mass when also considering age, age^2, gender, SBP, DBP, serum cholesterol, smoking habit, and previous use of antihypertensive medication. In contrast, in the present study using Cox and logistic regression models alternative risk measures (RR and OR) associated with BPV(ARV) were statistically significant even in the simultaneous presence of factors such as gender, age, use of antihypertensive medication, smoking status, cholesterol, triglyceride levels, and 24-h SBP, DBP, HR, NDSR, NDDR, and BMI.

Future work will, in the context of the ongoing longitudinal study Maracaibo Aging Study [19], further evaluate BPV (calculated using ARV) as a risk factor, estimate limits for normal BPV values obtained at standard sampling rates of ABPM devices, and construct models for the prediction of CE based on ARV and other well-known risk factors.

Conclusions

The present study presents a reliable variability index called the ARV that overcomes deficiencies of the commonly used SD. The SD index does not reflect the time

series nature of the BP signal, and may be more sensitive to the relatively low sampling frequency of the ABPM devices.

The ARV index is a more faithful representation of time series variability and should be used for establishing the prognostic significance of BPV and other time series of interest (e.g. heart rate variability). When the ARV variability index is used, BPV and SBP were found to be the single most statistically significant risk factors. The results suggest ARV adds prognostic value to the ABPM and could prompt the use of therapeutic measures to control BPV.

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