CLINICAL SCIENCE

A comparison between sphygmomanometer-based and ambulatory blood pressure monitoring in acute salt loading and depletion protocol

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INTRODUCTION: Ambulatory blood pressure monitors have been used in salt loading and depletion protocols. However, the agreement between measurements made using ambulatory blood pressure monitors and those made with the sphygmomanometer has not been evaluated.

OBJECTIVE: The objective of this study was to compare the concordance of the two methods of blood pressure measurements in protocols of acute salt loading and depletion.

METHOD: Systolic blood pressure was measured using a sphygmomanometer at the completion of salt infusion (2 L NaCl 0.9%, 4 h) and salt depletion (furosemide, 120mg/day, p.o.) in 18 volunteers. Using the Pearson correlation coefficient (ρ), these readings were compared with the mean systolic blood pressure measured using the ambulatory blood pressure monitoring device during the following periods: 4 h of saline infusion and 12 h of salt depletion; 4 h of saline infusion and the last 6 h of salt depletion; 12 h of salt loading and the last 6 h of depletion; 12 h of salt loading and 12 h of depletion. Salt sensitivity was defined by a difference in the systolic blood pressure between salt loading and salt depletion greater than 10 mmHg when measured with the sphygmomanometer, and the Kappa analysis of concordance (K) was used with a significance level of $P<0.05$.

RESULTS: Only the blood pressure readings obtained using the ambulatory blood pressure device during 4 h of intravenous NaCl and during 12 h of salt depletion showed a high correlation with the variation in the systolic blood pressure measured by the sphygmomanometer, with a full agreement with the salt sensitivity classification ($\rho = 0.71$; $P = 0.001$ and $K = 1$).

CONCLUSION: In acute salt loading and depletion protocols, an ambulatory blood pressure monitoring device should be used to record the blood pressure during the 4-h interval of salt infusion and 12-h interval of salt depletion.

KEYWORDS: Blood Pressure; Blood Pressure Monitoring; Salt Sensitivity Methodology; Salt Loading; Salt Depletion.

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INTRODUCTION

Salt sensitivity (SS) is a heterogeneous phenomenon characterized by a significant increase in blood pressure (BP) in response to changes in dietary salt intake or by experimental intravenous salt overload followed by furosemide-induced salt depletion.[1] Although multiple mechanisms are involved in the BP response to the variation in sodium intake, an evident change in the renal tubular transport of sodium occurs in salt-sensitive individuals (S individuals).[2] In salt-resistant individuals (R individuals), a change from a low-sodium diet (70 mmol/day) to a high-sodium diet (185 mmol/day) is accompanied by a significant reduction of sodium reabsorption by the proximal tubules. In contrast, S individuals experience a significant increase in BP and a blunted inhibition of proximal tubular sodium transport. In addition, ''S normotensive individuals'' respond to a salt load with an increased glomerular filtration rate in an attempt to compensate for the inability to block the tubular sodium reabsorption.[3] The same response pattern is usually observed in ''S hypertensive individuals.''[4] Epidemiological studies have indicated a clear relationship between salt sensitivity individuals and the development of cardiac hypertrophy and glomerular damage.[5-8] In experimental

studies with rats, salt loading promotes the expression of factors related to the deposition of extracellular matrix in the mesangium, such as TGF-β, independent of changes in BP.[9] Moreover, in humans, microalbuminuria is observed in hypertensive individuals with an S pattern.[10,11] The presence of SS also affects the response to antihypertensive drugs, such as diuretics and angiotensin-converting enzyme inhibitors.[12] Although clinically relevant, the identification of S individuals involves exaggerated sodium consumption followed by salt depletion with the use of low-salt diets or diuretics. Although some authors have indicated better reproducibility using alternate chronic exposure to low- or high-salt diets,[13] the model of acute salt loading and depletion initially proposed by Weinberger et al.[1] is widely accepted for the identification of S individuals. In this model, volunteers are subjected to intravenous loading of 2 L of isotonic saline over a period of 4 h, and at the end of this process, BP is measured using the conventional sphygmomanometer (CS). On the next day, the volunteers are subjected to a low-salt diet (10 mmol/day) followed by three doses of oral furosemide, and CS BP is again measured at the end of this period. A difference greater than 10 mmHg between the two periods indicates the presence of SS. Because of the extensively documented various factors that interfere with the CS measurement of BP, some authors have recommended the use of the ABPM device as the best tool for assessing the BP in acute salt loading and depletion protocols.[14] However, there is no consensus about the ideal time intervals of measurements, and there is no clear evaluation of the agreement between the two methods of BP measurement in this context. Moreover, blood pressure measurements obtained by the Ambulatory Blood Pressure Monitoring (ABPM) are usually lower than those obtained using the CS. This could influence the determination of SS, leading to an incorrect classification. Thus, the main objective of the present study was to compare the concordance of two different methods of BP measurements in protocols of acute salt loading and depleting, including an evaluation of the different time intervals of BP measurements with the use of an ABPM device.

METHODS

Eighteen healthy, normotensive volunteers aged 18 to 43 years with clinical and biochemical parameters (hepatic, renal and hematologic function) within normal limits were selected for the study. The protocol was approved by the Institutional Research Ethics Committee, and the volunteers gave written informed consent to participate. The subjects were instructed to consume a diet containing a standard amount of sodium (180 mmol/day) five days before the beginning of the acute protocol. Adherence to the diet was monitored by the measurement of the 24-h urine sodium on the fifth standard diet day. On the day of acute protocol, after an overnight fast, the volunteers were asked to come to the Clinical Research Unit where they stayed for two days. Starting at 8:00 am on the first day, 2 L of 0.9% isotonic saline solution were infused into a peripheral vein over a period of 4 h. An ABPM device (Spacelabs model 90207, Washington, USA) was installed in each participant's non-dominant arm and programmed to measure BP at 10-minute intervals for the first 12 h. At the end of the saline infusion, BP was measured with a previously calibrated mercury sphygmomanometer, and the mean value of three measurements was calculated. On the second day of the experimental period, volunteers consumed a low-salt diet (10 mmol/day) and received three 40-mg doses of oral furosemide at 8:00 a.m., 10:00 a.m. and 2:00 p.m. The ABPM device was again installed according to the parameters described above, and the CS BP was measured at the end of salt depletion (8:00 p.m.). The patients were classified as S individuals when the difference in the CS Systolic BP (SBP) measurements between the salt loading and salt depletion periods was >10 mmHg ($\Delta SBP_{diu\text{-}salt}$). The CS BP measurements were compared to the means obtained using the ABPM in the following combinations: SBP between the 4 h of saline infusion and the 12 h of salt depletion ($\Delta SBP_{4\text{-}12}$); between the 4 h of saline infusion and the last 6 h of salt depletion ($\Delta SBP_{4\text{-}6}$); between the 12 h of the salt-loading period and the last 6 h of depletion ($\Delta SBP_{12\text{-}6}$); and between the 12 h of the salt-loading period and the 12 h of salt depletion ($\Delta SBP_{12\text{-}12}$). In addition to BP, blood and urine samples were obtained at the end of the saline infusion (12:00 p.m. of day 1) and at the end of the protocol (8:00 p.m. of day 2) for the determination of sodium, creatinine, plasma renin activity and aldosterone. Sodium and creatinine analyses were performed using a standard method. Plasma renin activity and aldosterone were determined by radioimmunoassay (DiaSorin, Minnesota, USA). Fractional sodium excretion (FENa) was determined using the following formula: (UNa x Pcr/Ucr x PNa) ×100, where UNa, PNa, Ucr and Pcr are the concentrations of urine sodium (mMol), urine creatinine (mg/dL), plasma sodium (mMol) and plasma creatinine (mg/dL), respectively.

Data were reported as means ± SEM and were compared using a paired t-test or ANOVA for repeated measures, followed by a Bonferroni post-test. The correlations between FENa and the variation in renin and aldosterone activity and SBP (CS or ABPM) were determined using the Pearson correlation, and the concordance between the CS and ABPM measurements during the various time intervals studied for the identification of S individuals was determined using the Kappa (κ) coefficient.[15] The reference criterion used for S individual classification was arbitrarily chosen as $\Delta SBP_{diu\text{-}salt}$ >10 mmHg. The comparison between the ABPM SBP during the different intervals and the CS SBP was performed using the Pearson correlation coefficient (ρ). The level of significance was set at $P<0.05$ for all analyses. SAS/STAT software (Version 9.0, SAS institute, USA) was used all statistical calculations.

RESULTS

This study included 18 volunteers (10 men and 8 women) who were self-reportedly white and were on average 29±2 years old. All of the subjects were normotensive (the SBP and Diastolic BP (DBP) were 115±3 mmHg and 73±2 mmHg, respectively) and none were obese (BMI of 25.2±0.9 kg/m^2). The volunteers were divided into S ($\Delta SBP_{diu\text{-}salt}$ >10 mmHg) and R groups, and their main clinical characteristics are presented in Table 1. There was no difference between the S and R groups in nutritional status, age or daily salt consumption. As expected, the S group showed a greater reduction of $\Delta SBP_{diu\text{-}salt}$ compared to the R group (-21.4±3.0 mmHg *vs.* -5.0±1.2 mmHg, P = 0.0006). However, compared with the use of the CS, we observed a smaller fall in ΔSBP in the S group between the salt loading and depletion periods with use of the ABPM (-21.4±3.0 mmHg *vs.* -12.4±0.8 mmHg; P = 0.007). Figure 1

Table 1 - Clinical characteristics of the volunteers included in the study protocol. Data are reported as means ± SEM, with the number of volunteers in parentheses.

	R (11)	S (7)	P value
Age (years)	28±2	30±3	0.85
Women (%)	45%	43%	0.99
BMI (kg/m^2)	24±1	26±1	0.19
Waist circumference (cm)	87±3	91±4	0.32
Office SBP (mmHg)	112±4	120±5	0.27
Office DBP (mmHg)	71±2	74±3	0.47
Na_u 24 h (mEq/L)	140±17	126±16	0.85
Creatinine clearance (ml/min)	103±1	102±2	0.65
$\Delta SBP_{diu\text{-}salt}$	-5.0±1.2	-21.4±3.0	**0.0006**
$\Delta SBP_{4\text{-}12}$	-3.9±1.3	-12.4±0.8**	**0.0006**

**P = 0.007 $\Delta SBP_{diu\text{-}salt}$ *vs.* $\Delta SBP_{4\text{-}12}$

illustrates the behavior of CS BP during the periods of salt loading and depletion. Salt loading increased the SBP and DBP ($P<0.05$) only in the S group. Also, only the S group experienced a decrease in the SBP and DBP with the furosemide-induced salt depletion ($P<0.05$). Figure 1 shows the behavior of the tubular sodium transport inferred by FENa. Both R and S volunteers presented elevated FENa during salt loading ($P<0.01$) compared with FENa baseline values. However, only the R group experienced a significant increase in FENa after furosemide administration when compared with the salt loading ($P<0.05$). Table 2 illustrates that there was no significant difference in the variation of the response of the renin-angiotensin-aldosterone system between the R and S groups, as measured in terms of the plasma renin activity and the plasma aldosterone values between the phases of salt loading and depletion. Table 2 also shows the behavior of the excreted sodium load during salt loading and depletion. A significant increase in the excreted sodium load was observed after salt loading, which was maintained during the phase of furosemide use, although there were no significant differences between the R and S groups.

There was a significant correlation between the SBP and DBP measurements made using the ABPM and those made using the CS during the phases of salt loading and depletion for all the periods analyzed. However, the Pearson correlation coefficient (ρ) for the different time periods showed various results; the best correlations were observed between

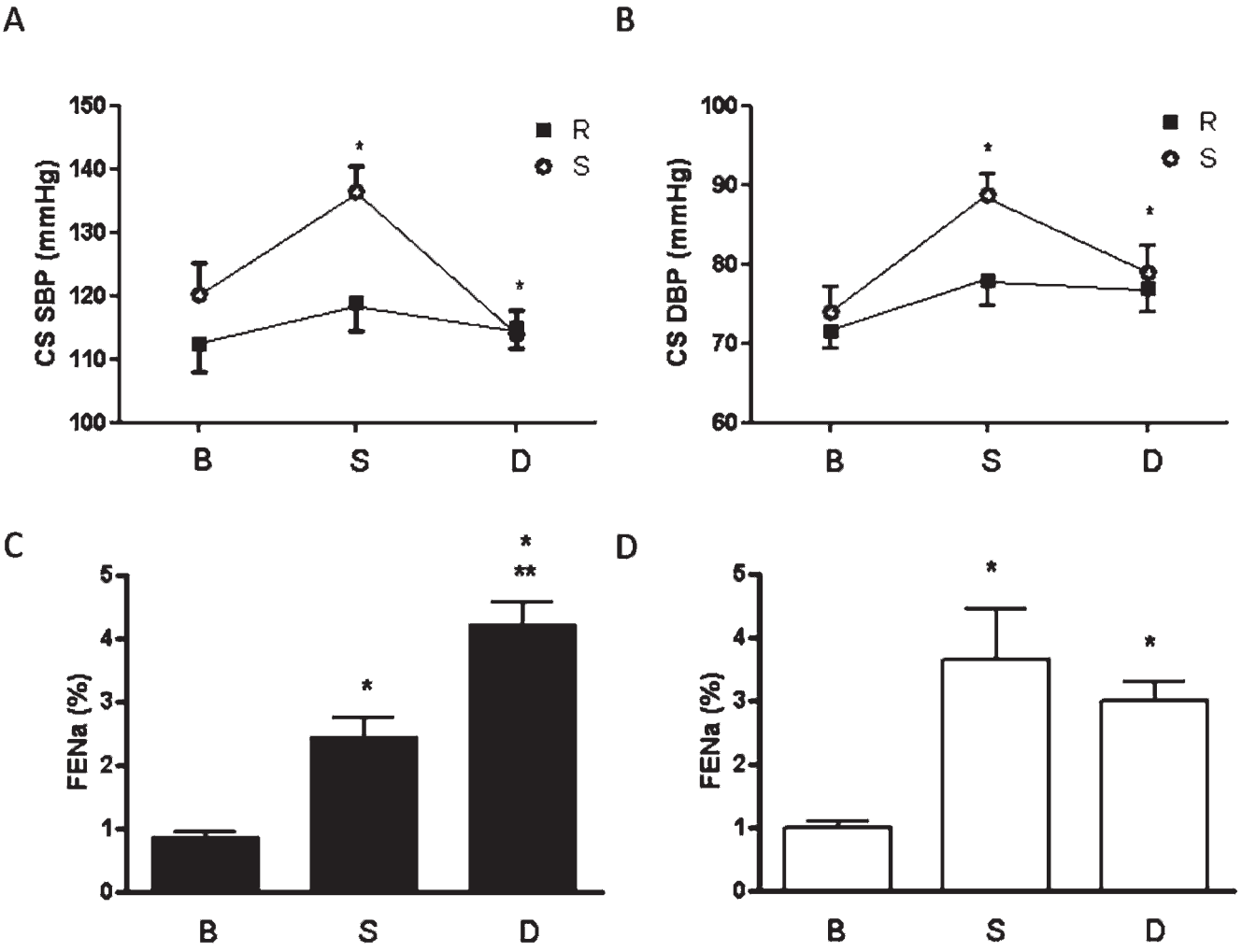

Figure 1 - CS SBP (A, upper panel left) and DBP (B, upper panel right) during the baseline (B) and periods of salt loading (S) and depletion (D). There was a significant increase in BP with salt loading ($P<0.05$) and a decrease in BP with furosemide-induced salt depletion ($P<0.05$) only in the S group. The lower panel shows FENa at baseline (B) and during periods of salt loading (S) and depletion (D) for the R group (black bars, C) and S group (white bars, D). Data are expressed as means ± SE; * = $P<0.01$ *vs.* baseline; ** $P<0.05$ S *vs.* D.

Table 2 - Behavior of fractional excretion of sodium (FENa%), urinary sodium excretion (UNa, mMol/h), plasma renin activity (PRA, ng/ml/h) and plasma aldosterone (pg/mL) during acute sodium loading and depletion. Data are reported as means ± SEM.

	R			S		
	Baseline	Salt	Diuretic	Baseline	Salt	Diuretic
FENa (%)	0.9±0.3	2.4±0.3*	4.2±0.4*#	1.0±0.1	3.6±0.8*	3.0±0.3*
UNa (mMol/h)	7.5±0.8	31.5±3.4*	31.9±2.6*	8.4±1.1	46.0±9.5*	31.1±5.5*
PRA (ng/mL/h)	-	0.9±0.2	7.2±2.3#	-	0.7±0.2	5.1±3.0#
Aldosterone (pg/mL)	-	44.8±7.4	206.4±27.0#	-	70.5±18.3	236.1±46.7#

*P<0.05 for the salt and diuretic periods compared with the baseline period; P<0.05 for salt *vs.* diuretic.

the CS SBP and the mean of the ABPM SBP measurements made during the 4 h of intravenous NaCl infusion and the mean of the ABPM SBP measurements made during the 12 h of the salt depletion with furosemide ($\Delta SBP_{4\text{-}12}$, $\rho = 0.71$). Figure 2 shows the correlation observed between the CS SBP and DBP and the mean ABPM BP during the phase of salt loading (4 h) and depletion with furosemide (12 h).

Table 3 shows the values of concordance (*K*) for the classification of S and R using $\Delta SBP_{diu\text{-}salt} > 10$ mmHg as the reference cut-off value. The same cut-off value was arbitrarily selected for ABPM. Full concordance ($K = 1$) with CS SBP was observed only when the criterion for classification was based on the ABPM BP measurements during the 4 to 12-h period ($\Delta SBP_{4\text{-}12}$).

DISCUSSION

The objective of this study was to compare the concordance of two different methods of BP measurement in protocols of acute salt loading and depletion, including an

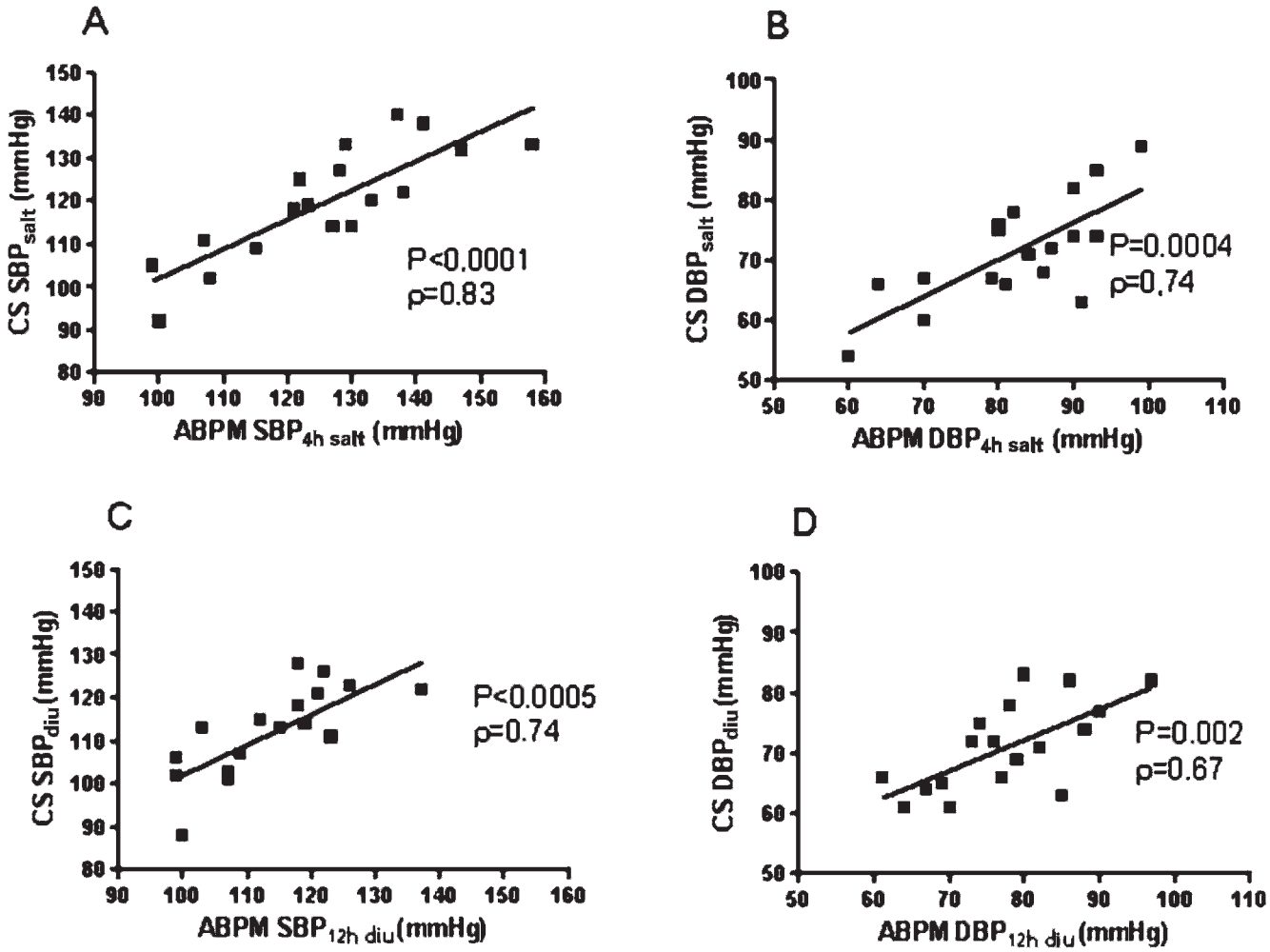

Figure 2 - Pearson correlation coefficients (ρ) between CS SBP and DBP, with mean BP measured by ABPM during the phase of salt loading (4 h, upper panel A and B) and of salt depletion with furosemide (12 h, lower panels C and D).

Table 3 - Pearson correlation coefficient (ρ) between the variation in CS $\Delta SBP_{diu\text{-}salt}$ in a salt loading and depletion maneuver and the mean variation in SBP obtained by ABPM according to intervals of measurement (see text for details).

	P value	Pearson ρ
$\Delta SBP_{diu\text{-}salt}$ *vs.* $\Delta SBP_{4\text{-}12}$	0.001	0.71
$\Delta SBP_{diu\text{-}salt}$ *vs.* $\Delta SBP_{12\text{-}12}$	0.02	0.53
$\Delta SBP_{diu\text{-}salt}$ *vs.* $\Delta SBP_{4\text{-}6}$	0.007	0.61
$\Delta SBP_{diu\text{-}salt}$ *vs.* $\Delta SBP_{12\text{-}6}$	0.07	0.44

evaluation of different time intervals of BP measurements with the use of an ABPM device. Our data showed that the classification of individuals as S or R, based on the measurement of the difference in SBP between the periods of salt loading and depletion using ABPM, varied according to the time interval of BP measurement. The greatest concordance between the $\Delta SBP_{diu\text{-}salt}$ using the CS method defined by Weinberger and an ABPM device to measure BP was the interval of $\Delta SBP_{4\text{-}12}$.

The CS $\Delta SBP_{diu\text{-}salt}$ was used here as the ''gold standard'' because this type of measurement has been extensively studied in previous protocols[1,8] and has been shown to be correlated with humoral markers, particularly the renin-angiotensin-aldosterone system. Furthermore, it was shown to be an independent risk factor for cardiovascular death. In this context, Weinberg et al. [8] conducted a 27-year follow-up study of a cohort of 430 normotensive individuals subjected to the acute salt loading and depletion protocol. They found that the presence of S individuals detected by this method was accompanied by an increase in cardiovascular mortality compared with R individuals.

Previous studies have suggested that the identification of S individuals can be more accurate by manipulating the sodium content of an individual's diet.[6,14] However, these protocols rely on compliance with a specific diet, which results in difficult technical execution. Another relevant point for the comparison of these two methodologies is the concordance of the classification as S individuals and R individuals when the same volunteer was subjected to the two methods in a sequential manner. Weinberg et al. reported agreement between acute salt loading protocols when dietary sodium manipulations were performed over prolonged periods of time.[16] However, other studies have not had the same results and have reported a weak concordance between the two methods.[14,17]

The BP measurement method may also generate an important bias of the criterion for subject classification as S individuals and R individuals. However, few studies have compared the different methods of BP measurement for this purpose. In a study of dietary salt intervention, the ABPM measurements were more accurate than the use of office BP measurement for the classification of S individuals and R individuals an observation that was suggested to be due to the larger number of measurements obtained with the ABPM, which may have involved a lower chance of error.[13]

Table 4 - Kappa correlation (95% CI) between the variation in CS $\Delta SBP_{diu\text{-}salt}$ in a salt loading and depletion protocol and the mean variation in SBP obtained by ABPM according to intervals of measurement (see text for details).

	k	95%CI
$\Delta SBP_{diu\text{-}salt}$ *vs.* $\Delta SBP_{4\text{-}12}$	1	_
$\Delta SBP_{diu\text{-}salt}$ *vs.* $\Delta SBP_{12\text{-}12}$	0.48	(0.09 – 0.86)
$\Delta SBP_{diu\text{-}salt}$ *vs.* $\Delta SBP_{4\text{-}6}$	0.66	(0.31 – 1.00)
$\Delta SBP_{diu\text{-}salt}$ *vs.* $\Delta SBP_{12\text{-}6}$	0.26	(-0.19 – 0.71)

The present study contributes to the definition of the best time interval for BP measurements when using the ABPM device in protocols of acute salt loading and salt depletion. Our data show that the time interval of BP measurements had a clear influence on the designation of S and R individuals, with the CS BP used as the standard. Analysis of the Pearson coefficient (Table 2) showed that the measurements made between the periods of 4 and 12 h, which corresponded to the peak of salt load (during the 4 h of intravenous NaCl infusion) of the first day, and the measurements obtained during the daytime of the second day were best correlated with the variation of CS SBP between the two periods.[1] The same table also shows a poor correlation between the SBP measurements corresponding to 12 h of daytime salt loading and those corresponding to 12 h of daytime salt depletion, particularly those most frequently used in this protocol.[18] The analysis of concordance (*K*) supported the Pearson univariate analysis, showing full agreement between the measurements of $\Delta SBP_{4\text{-}12}$ and Δ $SBP_{diu\text{-}salt}$. Despite this agreement, there was a significant difference in the ΔSBP values obtained by the two methods, with greater amplitude and dispersal of the CS measurements compared with the ABPM measurements.

The results of this study do have limitations because the sample size was small (18 individuals). Also, the ΔSBP value >10 mmHg was arbitrarily established for the classification of S. However, the ABPM BP measurements were usually lower values than those obtained with the CS, an observation that may modify the cut-off for the classification of S individuals on the basis of ABPM. Because the variation in SBP between the phases of salt loading and depletion follows a Gaussian distribution, a new study with a larger number of participants is necessary to determine the best ABPM cut-off value to distinguish R and S individuals. However, such limitations do not invalidate the observation that the best interval for measuring BP with the ABPM is $\Delta SBP_{4\text{-}12}$.

In conclusion, the present study shows that the use of ABPM in protocols of acute salt loading and depletion should involve measurements at 10-minute intervals, with a recording of the 4-h interval of acute intravenous salt infusion and the 12-h interval of salt depletion with furosemide and setting the cut-off value for the classification of S at $\Delta SBP_{4\text{-}12}$ >10 mmHg.

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