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ORIGINAL ARTICLE

Between-visit reproducibility of inter-arm systolic blood pressure differences in treated hypertensive patients: the coconet study

Jang Young Kim[1], Eung Ju Kim[2], June Namgung[3], Byung-Ryul Cho[4], Chang-Wook Nam[5], Young-Kwon Kim[6] and Jeong Bae Park[7] on behalf of the CoCoNET study investigators

Inter-arm systolic blood pressure (BP) differences (sIADs) have recently been recognized as a risk factor for cardiovascular mortality. However, sIAD reproducibility remains unresolved from a controlled trial perspective. We evaluated the between-visit reproducibility of sIADs in hypertensive patients. We examined 1875 hypertensive participants aged 20 years and older (mean age: 62.3 years, 45.4% female) from nine primary clinics and 27 secondary and tertiary hospitals. The BPs in both arms were automatically and simultaneously measured in triplicate with a cuff-oscillometric BP device. BP measurements were obtained at baseline and at 3-month follow-up time points. Increased sIAD was defined as an absolute difference of $\geqslant 10$ mm Hg in the average systolic BPs between the left and right arms. The overall mean sIAD was 4.33 ± 4.17 mm Hg. The prevalences of increased sIAD at baseline and at the 3-month measurements were 7.6% and 7.1%, respectively. The intraclass correlation coefficient for the between-visit sIADs was 0.304 (95% confidence interval (CI) 0.262–0.344). The κ-value between the baseline and follow-up increased sIADs was 0.165 (95% CI 0.096–0.234). The percentage of patients who exhibited an increased sIAD at 3 months compared with the initially increased sIAD at baseline was 21.8%. The reproducibility of sIAD determination between baseline and the 3-month follow-up measurements lacked agreement in the hypertensive patients. Further studies should identify the relevant variables and characteristics of this poor reproducibility (CRIS number; KCT0001235).
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INTRODUCTION

Measuring blood pressure (BP) in both arms is a recently recommended hypertension guideline for initial patient visits.[1,2] Instances in which the BP is higher in one arm should subsequently be measured on subsequent visits for reference because low BP measurements in one arm may lead to erroneous treatment. Inter-arm BP differences, especially in systolic BP, are relatively common and range in frequency from 9.5 to 19.6%.[3–5] An inter-arm systolic BP difference (sIAD) is recognized as a risk factor for subclavian stenosis,[5,6] peripheral vascular disease,[5,6] high arterial stiffness,[5,7] increased left ventricular mass[5] and cardiovascular morbidity and mortality.[6,8,9]

Given the high prevalence of sIAD and its link to poor cardiovascular outcomes, it is essential to evaluate the prevalence and between-visit reproducibility of sIAD, so that effective treatment of hypertension can be administered.[10] Some studies performed at hypertension clinics have reported reproducible sIADs in US veterans with histories of obstructive arterial disease.[11,12] Other studies have highlighted the poor agreement of between-visit measurements in elderly and antihypertensive drug-treated patients.[12–14] Such discrepancies may be related to systemic errors in the inter-arm systolic measurements rather than to random variations in BP. Potential sources of variation include manual error during BP measurements[11,12] and variations in the measurements between the instruments used to simultaneously measure BP in each arm.[12–14] Moreover, some studies have been conducted in patients admitted to a hospital and whose unstable conditions may have influenced the BP readings and the reproducibility.[13,14]

[1]Division of Cardiology, Department of Internal Medicine, Yonsei University Wonju College of Medicine, Gangwon-do, Republic of Korea; [2]Division of Cardiology, Department of Medicine, Korea University Guro Hospital, Korea University College of Medicine, Seoul, Republic of Korea; [3]Division of Cardiology, Department of Internal Medicine, Ilsan Paik Hospital, Inje University College of Medicine, Goyang, Republic of Korea; [4]Division of Cardiology, Department of Internal Medicine, College of Medicine, Kangwon National University Hospital, Chuncheon, Republic of Korea; [5]Division of Cardiology, Department of Internal Medicine, Keimyung University Dongsan Medical Center, Daegu, Republic of Korea; [6]Division of Cardiology, Department of Internal Medicine, Dongguk University College of Medicine, Ilsan Hospital, Goyang, Republic of Korea and [7]Division of Cardiology, Department of Medicine, Cheil General Hospital, Dankook University, College of Medicine, Seoul, Republic of Korea
Correspondence: Professor JB Park, Division of Cardiology, Department of Medicine, Cheil General Hospital, Dankook University College of Medicine, 17, Seoae-ro 1-gil, Jung-gu, Seoul 100-380, Republic of Korea.
E-mail: mdparkjb@gmail.com
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We thus conducted a multicenter outpatient hypertension cohort study to evaluate sIAD reproducibility, as measured with automated, simultaneous triplicate measurements in both arms by using cuff-oscillometric BP devices.

METHODS

Subjects

The Cooperative Network Construction of Nationwide Clinical Trials (CoCoNet) study is a prospective cohort study that was undertaken to evaluate patient characteristics and treatment strategies for hypertension and related complications. Patients were enrolled from nine primary clinics and 27 hospitals (secondary or tertiary) from 1 September 2013 to 31 December, 2014. Hypertensive patients >20 years old who were taking antihypertensive medication or were newly diagnosed with hypertension on the basis of a BP ⩾ 140/90 mm Hg were included. The eligibility criteria were repeated measurements of BP at baseline and 3-month follow-up points. No subjects exhibited arrhythmia or chronic renal disease (serum creatinine > 2.0 mg dl^{-1}) at the time of examination. Antihypertensive treatments were directed by the doctor in charge, and no changes were made during the follow-up. This study was approved by the Institutional Review Board of Cheil General Hospital (IRB approval number: CGH-IRB-2013-33). Written informed consent was obtained from all patients.

BP measurements

BP was measured after patients had rested for at least 5 min in a quiet room. Sequential and simultaneous BP measurements were taken with an oscillometric device (Watch BP Office, Microlife Corportation, Taipei, Taiwan). This device is equipped with two linked cuffs that allow for both simultaneous and sequential measurements with the same device. Automated simultaneous BP measurements from each arm were taken in triplicate using the oscillometric device within a 2 min interval and then averaged. An sIAD was defined as a difference in the systolic BP averages of three simultaneous measurements between the left and right arms. An increased sIAD was usually defined by a difference of ⩾ 10 mm Hg for the average values.[3–5]

Data collection

At baseline and at 3-month examinations, the study participants completed a standardized medical history and lifestyle questionnaire and underwent a comprehensive health examination according to standard procedures. The smoking status was self-reported. Non-smokers were defined as participants who had smoked <100 cigarettes (<5 packs of cigarettes) in their lifetime. Current smokers were defined as participants who had smoked ⩾ 100 cigarettes in their lifetime and reported 'currently smoking' in the questionnaire. Diabetes mellitus was defined by the use of oral hypoglycemic agents or insulin, and newly diagnosed diabetes mellitus was determined on the basis of repeated results of fasting glucose levels ⩾ 126 mg dl^{-1} or HbA1c levels ⩾ 6.5%. Coronary artery disease was defined by patient histories of myocardial infarction or angina pectoris with compatible symptoms with or without angiographic results. Cerebrovascular events were also defined by patient histories of cerebral infarction or transient ischemic attack. Chronic kidney disease was confirmed when the estimated glomerular filtration rate was <60 ml min^{-1}. A >12 h fasting blood sample was drawn from each study participant. Routine blood chemistry tests were performed to determine the lipid profiles and renal functions. Harmonization of the laboratory findings was performed to coordinate the results from the different hospitals.[15]

Statistical analysis

The continuous variables are expressed as the means ± s.d. The categorical variables are described as the frequencies and percentages. BP measurements between the left and right arms were compared with Student's *t*-tests. We used the intraclass correlation coefficient to measure the test–retest reliability of the sIAD as a continuous variable at baseline and at 3 months. The intraclass correlation coefficient values were interpreted as follows: >0.75 was excellent; 0.40–0.75 was fair to good; and <0.40 was poor. The Bland–Altman approach was applied to examine the agreement between the measurements. Differences between the measurements of the sIADs were plotted against their means to display the level of agreement between the measurements. The agreement levels were assessed by using the mean differences and the s.d. of the differences to calculate the biases.

We used κ (kappa) to measure the inter-rater reliability of the categorization of increased IAD as below or above 10 mm Hg. We interpreted the κ-values as follows: >0.80 was very good; 0.61–0.80 was good; 0.41–0.60 was moderate; 0.21–0.40 was fair; and <0.21 was poor. SAS version 9.3 (SAS Institute, Cary, NC, USA) was used for all tests, and significance was defined at the level of $P<0.05$.

Table 1 Patient characteristics

	Total patients (n = *1875*)
Age (years)	62.3 ± 11.3
Sex (female %)	852 (45.4)
Body mass index (kg m^{-2})	26.0 ± 3.5
Systolic BP (mm Hg)	128.7 ± 14.3
Diastolic BP (mm Hg)	78.6 ± 9.9
Heart rate (pulse min^{-1})	69.6 ± 11.0
HbA1c (%)	6.4 ± 1.1
Glucose (mg dl^{-1})	119.5 ± 40.5
Creatinine (mg dl^{-1})	1.0 ± 0.7
Total cholesterol (mg dl^{-1})	173.3 ± 38.0
Coronary artery disease (*n*, %)	536 (28.6)
Diabetes mellitus (*n*, %)	495 (26.4)
Cerebrovascular disease (*n*, %)	111 (5.9)
Chronic kidney disease (*n*, %)	132 (7.0)
ACEI/ARB (*n*, %)	1323 (70.5)
Beta blocker (*n*, %)	713 (38.3)
Calcium channel blocker (*n*, %)	1126 (60.5)
Diuretics (*n*, %)	475 (25.5)

Abbreviations: ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; BP, blood pressure.

RESULTS

During the study period, 1875 patients (45.4% female) were eligible for inclusion. One-quarter of the patients were diabetic, and 20% had coronary artery disease. The mean age was 62.3 ± 11.3 years. The most common antihypertensive medications used were angiotensin receptor blockers and calcium channel antagonists (Table 1).

The mean BP values for the triplicate readings from each arm are displayed in Table 2. The left-arm mean systolic BP was consistently higher. The mean sIAD were 4.33 ± 4.17 mm Hg at baseline and 3.93 ± 3.87 at 3 months. The prevalence of sIAD was 7.6% at baseline and 7.1% at 3 months. The intraclass correlation coefficient for the between-visit sIAD measurement differences was 0.304 with a 95% confidence interval (CI) that ranged from 0.262 to 0.344. In the Bland–Altman plots, the majority of the differences in the means were within the limits of the CI (Figure 1). The middle horizontal red line indicates a mean difference of −0.437 mm Hg, and the other horizontal green lines indicate the 95% limits of agreement from −13.76 mm Hg to 12.89 mm Hg. The 95% limits of agreement are drawn at the mean difference plus or minus two times the s.d. of the differences. Some measurements were outside of the limit of agreement. In 1649 patients (87.9%), the sIAD persisted in the same range. The Cohen's κ-value between the baseline and follow-up among the increased sIAD patients was 0.165 (95% CI 0.096–0.234 mm Hg; Table 3). Figure 2 illustrates the likelihood of increased sIADs in the measurements at both time points. At baseline, 142 patients exhibited increased sIADs, whereas 1733 patients did not. At 3 months, 132 patients exhibited increased sIADs. Thirty-one (21.8%) of these patients overlapped with the baseline 142 sIAD patients, and 101

Table 2 Mean systolic BP in both arms from triplicate measurements

	SBP-left	*SBP-right*	*sIAD*[a]	P-*value*	*Increased sIAD (%)*
Baseline	128.74 ± 14.81	128.59 ± 14.38	4.33 ± 4.17	0.289	142 (7.6)
Follow-up	128.03 ± 13.56	127.45 ± 13.39	3.93 ± 3.87	<0.0001	133 (7.1)

Abbreviations: BP, blood pressure; DBP, diastolic blood pressure; SBP, systolic blood pressure differences; sIADs, inter-arm systolic blood pressure differences.
Increased sIAD was defined as ⩾10 mm Hg using the average of three simultaneous measurements of BP obtained in both arms.
[a]sIAD = |left SBP–right SBP|.

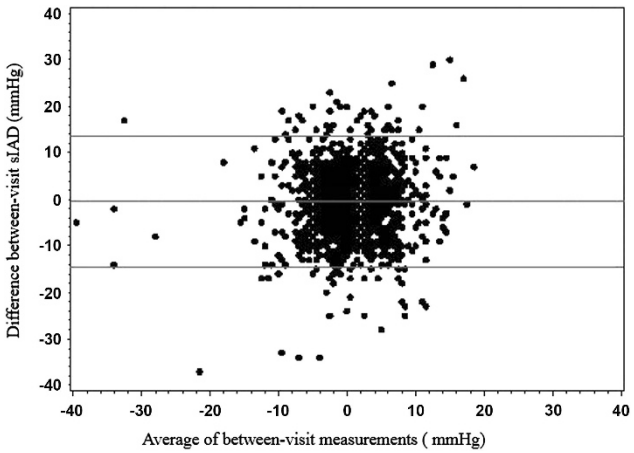

Figure 1 Bland–Altman plot of the sIAD between the baseline and follow-up visits (bias: −0.437 ± 6.798 (s.d.) mm Hg, 95% CI: −13.76 to 12.89 mm Hg). A full color version of this figure is available at *Hypertension Research* online.

Table 3 Categories of sIAD at baseline and follow-up measurements

	Increased sIAD	
	Second measurement ⩽ 10 mmHG	*Second measurement > 10 mm Hg*
First measurement, ⩽ 10 mm Hg	1618	101
First measurement, > 10 mm Hg	111	31
P-value	0.4922	

Abbreviations: BP, blood pressure; sIADs, inter-arm systolic blood pressure differences.
Cohen's κ-value was 0.165 (95% confidence interval 0.096–0.234).
sIAD and McNemar's test for paired samples.
Increased sIAD was defined as ⩾10 mm Hg using the average of three simultaneous measurements of BP obtained in both arms.

(5.8%) overlapped with the baseline 1733 sIAD-negative patients. The percentage of patients with increased sIADs at 3 months among the participants with increased sIAD at baseline was 21.8% (31 out of 142; Figure 2). In the subgroup analyses according to the presence or absence of diabetes mellitus, clinical cardiovascular disease and elderly status, the reproducibility of the sIAD between baseline and the 3-month follow-up measurements exhibited no significant interactions and poor agreement among all subgroups of hypertensive patients (data not shown).

DISCUSSION

We evaluated the between-visit reproducibility of the sIADs of this large hypertensive cohort. The reproducibility of the sIADs between

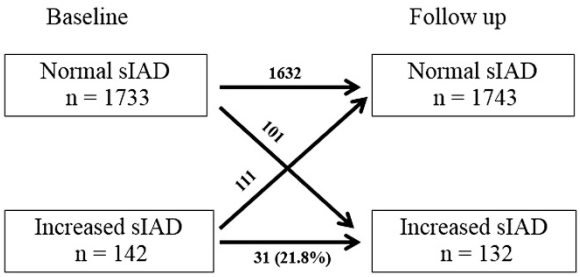

Figure 2 Graph of the proportion of patients with increased sIAD. Increased sIAD was defined as a difference ⩾10 mm Hg based on the average of triplicate simultaneous BP measurements obtained from both arms.

the baseline and 3-month points lacked credible agreement in the treated hypertensive patients. Thus, the low sIAD reproducibility between clinical visits raises concern regarding the diagnostic reliability of the sIAD value for treated hypertensive patients.

Although we lack a clear explanation for this poor agreement of the between-visit sIADs, one possibility is that the apparent sIADs in the hypertensive patients was simply the result of random variation due to the spontaneous variability in BP rather than to true differences or systemic measurement errors.[12] Eguchi *et al.*[12] have reported that clinically meaningful sIAD differences are reproducible only in cases of obstructive arterial disease. The other possible explanation is related to transient uneven stiffness of the aortic arch and the upper extremity artery. These differences may lead to temporal inter-arm BP differences.[16] Other confounding issues may have been the relatively long period of time between measurements (i.e., the 3-month interval) and any treatments or lifestyle modifications that may have been performed by the participants between visits. Agarwal *et al.*[11] have reported high between-visit IAD reproducibility in BP measurements collected within 1 week.

Our results suggest the value of reconsidering the current guidelines for hypertension, in which the use of the higher readings from multiple measurements from both arms is recommended.[1,2] The measurement of the sIAD is a simple and economical way to screen for peripheral artery disease in the ascending aorta and upper extremity arteries, but it is not always an indicator of pathology. In a milder form of hypertension without obstructive artery disease, a significant sIAD suggests a higher cardiovascular risk.[17] The absence of reproducibility of the sIAD compounded by the need for evidence for selecting the higher BP readings for better outcome prediction suggests that apparent differences as large as 10 mm Hg can be safely ignored.

The prevalence of sIAD in this study was relatively low (7.6%) compared with results from previous studies[3,4] but was in line with the 9.1% reported in a study of a Japanese cohort.[18] Together, these results may suggest that East Asians exhibit a relatively low prevalence of this condition compared with Western populations. One explanation is that the control BP levels might affect the relatively low prevalence of sIAD. Sun *et al.* have demonstrated that higher systolic BP influences

the higher sIAD of patients undergoing hypertensive therapy.[14] In this study, the systolic BPs of the right arm at baseline and at follow-up were 128.6 and 127.5 mm Hg, respectively. Well-controlled BP elicited a relatively low prevalence (Table 1).

The other possible explanation is related to the low measurement bias. We measured the BP with automated, simultaneous triplicate measurements in both arms using cuff-oscillometric BP devices, a method that is certainly the most accurate for diagnosing sIAD.[19] A recent meta-analysis has revealed a lower prevalence of an increase in sIAD when the BP measurements are performed more frequently and simultaneously.[3] This finding may explain the relatively low prevalence of sIAD observed herein compared with the results from previous studies.

Some limitations of our study should be considered. First, this study was restricted to hypertensive middle-aged and older Korean patients. Our findings may not be generalizable to other populations, particularly those of younger age, normotensive persons and those of other ethnicities. However, significant sIADs have also been observed in other races/ethnicities, thus suggesting that our observation of poor reproducibility may apply to other settings. Second, one potential bias in this study was the 3-month interval between the sIAD measurements. This study was part of an auxiliary research program within the CoCoNet study, a prospective cohort study undertaken to evaluate patient characteristics and treatment patterns for hypertension in real-world practice in multicenter hypertension clinics. Thus, we included a 3-month interval in the follow-up protocol. Potential lifestyle modifications and alterations in medications other than use of antihypertensive drugs by the participants between visits might have introduced potential biases to this study. However, the BP values were similar between time points, thus indicating that these factors may not have had considerable influence.

Given that the sIAD is recognized as a risk factor for cardiovascular mortality,[6,9] knowledge of the reproducibility of this measure at different time intervals is crucial. However, the results regarding reproducibility are not consistent and depend on the study design and the conditions involved.[10–14] The present study found that the reproducibility of between-visit sIADs was poor in hypertensive patients with drug interventions across a 3-month interval between measurements. Our study does not refute that an increased sIAD, along with other clinical indicators, may help identify severe atherosclerotic changes or identify patients with a high risk of hypertension. Instead, we highlight some key variables in the use of devices, patient cohorts, and the collection of measurement data that may guide further studies and improve sIAD evaluation. Therefore, the determination of significant sIAD and the cut-off value for significant sIAD are not confined to hypertension and hypertensive vascular diseases but also apply to other vascular diseases such as diabetes and kidney diseases. Further studies should identify the relevant variables that influence the sIAD, such as drugs or other interventions and the measurement device or method. Moreover, further studies also should assess differences in the clinical implication of BP differences between the upper-upper extremities and the upper-lower extremities.

In conclusion, the reproducibility of between-visit sIAD values is poor in hypertensive patients when the measurements are taken at 3-month intervals. Our study does not refute that increased sIAD, along with other clinical indicators, may aid in identifying severe atherosclerotic changes or patients with a high risk of hypertension. Moreover, we highlight some key variables regarding the use of devices, patient cohorts, and the collection of measurement data that may guide new studies and lead to improved approaches that rely on sIAD evaluations.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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