Reproducibility of Blood Pressure Response to Hydrochlorothiazide

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Few studies have investigated the reproducibility of responses to antihypertensive therapies. The purpose of this study was to assess the reproducibility of the blood pressure response to a thiazide diuretic, a preferred initial treatment for hypertension. Twenty-two subjects who underwent monotherapy with hydrochlorothiazide as part of a study to identify predictors of blood pressure response agreed to undergo the same protocol a second time, 26.6±11.8 (range, 4–52) months after their first participation. The mean systolic and diastolic blood pressure responses to hydrochlorothiazide did not differ significantly between the first and second participation (systolic response, –14.2±16.4 mm Hg vs. –16.0±16.5 mm Hg; diastolic response, –7.1±11.8 mm Hg vs. –6.6±8.6 mm Hg), and these responses were significantly correlated between the two trials (systolic response, r=*0.61 and* p<*0.01; diastolic response,* r=*0.64 and* p<*0.01). However, both the direction and magnitude of responses for individual subjects varied considerably, with the limits of agreement between the first and second participations (i.e., 2 standard deviations above and below the mean difference between responses) ranging from 27.4 mm Hg to –23.8 mm Hg for systolic blood pressure response and from 17.4 mm Hg to –18.4 mm Hg for diastolic blood pressure response. These results show that the average systolic and diastolic blood pressure responses to hydrochlorothiazide for a group of subjects are reproducible; however, the responses for individual subjects are unpredictable.(J Clin Hypertens. 2002;4:408–412)* ©2002 *Le Jacq Communications, Inc.*

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Manuscript received June 19, 2001;
revised October 2, 2001;
accepted December 27, 2001

The sixth report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC VI) recommends that the medical history elicited from patients with documented hypertension should include the results of previous antihypertensive therapies.[1] This recommendation may be based, in part, on the premise that if a particular antihypertensive drug was effective in the past, it will be so in the future—in other words, that its antihypertensive effect will be reproducible. However, only a few studies have investigated the reproducibility of response to antihypertensive therapies.

The purpose of this study was to assess the reproducibility of the blood pressure response to a thiazide diuretic. To accomplish this, we re-recruited a group of participants who had received hydrochlorothiazide as monotherapy in a previous study[2] to undergo the same treatment a second time.

METHODS

Eleven hypertensive non-Hispanic white adults from Rochester, MN (five women and six men) and eleven hypertensive African American adults (six women and five men) from Atlanta, GA participated in this investigation. They were among a group of individuals who had undergone monotherapy with hydrochlorothiazide as part of a study to identify predictors of blood

pressure response.[2] Twenty-two subjects agreed to undergo the same protocol a second time, 26.6±11.8 (range, 4–52) months after their first participation. Each participant was required to review and sign the written consent form again. All procedures involving human subjects were approved by the institutional review boards of the Mayo Clinic and Emory University and were performed in accordance with institutional guidelines.

The study protocol has been described previously.[2] In brief, subjects had to be in good health with blood pressure of <180/<110 mm Hg and have no evidence of secondary hypertension, renal or liver dysfunction, serious heart disease, diabetes, gout, or sulfa allergy. Subjects had their previous antihypertensive medications withdrawn and were instructed in a diet designed to provide a standard sodium intake of 2 mmol per kg body weight per day. They were seen every 2 weeks by the study nurse for blood pressure measurements and were included in the study if, after discontinuing previous antihypertensive drug therapies for at least 4 but no more than 8 weeks, their systolic blood pressure was <180 mm Hg and their diastolic blood pressure ranged from 90–109 mm Hg. After the drug-free period, subjects began taking 25 mg of hydrochlorothiazide orally each day for 4 weeks.

Blood pressure was recorded before withdrawal of antihypertensive medications (prestudy), at the end of the drug-free period prior to administration of hydrochlorothiazide (prediuretic), and after 4 weeks of hydrochlorothiazide (postdiuretic). At each visit, blood pressure was measured in the dominant arm with an appropriate-sized cuff, with a random-zero sphygmomanometer (Hawksley and Sons, Ltd., West Sussex, England). An initial reading was obtained after 5 minutes of quiet rest in the sitting position. Two additional readings, taken at 2-minute intervals, were recorded and their average was used as the blood pressure level for each visit. All readings were made between 7 a.m. and 9 a.m. The antihypertensive response was calculated as the difference between postdiuretic and prediuretic blood pressure levels.

Descriptive characteristics for the participants are presented as means±standard deviation. Group reproducibility of the prestudy, prediuretic, and postdiuretic blood pressure levels and of the blood pressure responses to hydrochlorothiazide were assessed by contrasting mean values between the first and second participation, using the Wilcoxon matched-pairs signed-rank test and by correlating the values of individual subjects, using Spearman's rank correlation coefficient. To assess the limits of agreement for individual subjects between measurements made in the first and second participations, the difference between measurements was plotted against their mean, as suggested by Bland and Altman.[3] Test statistics with $p<0.05$ were considered statistically significant.

RESULTS

At the first study participation, the mean age of the 22 subjects was 49.0±7.0 years, their mean body mass index was 31.3±6.1 kg/m^2, and their mean waist-to-hip ratio was 0.92±0.08. At the second participation, means for body mass index and waist-to-hip ratio were not significantly different and individual values were highly correlated

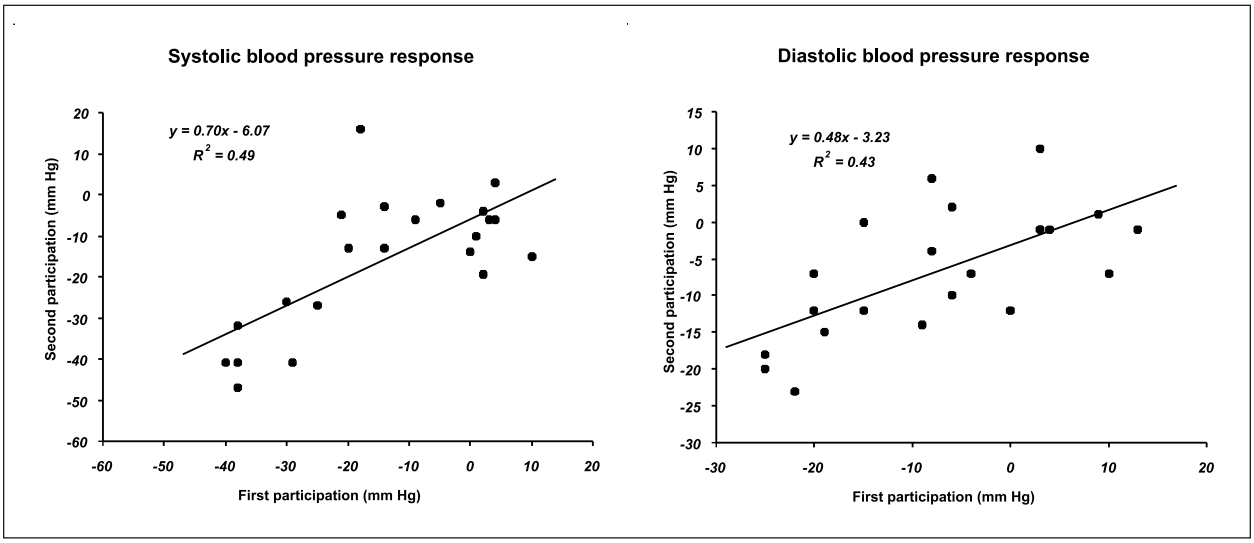

Figure 1. Plots of systolic and diastolic blood pressure responses at first and second participation

Table I. Reproducibility of Measurements			
	SYSTOLIC BLOOD PRESSURE		
	FIRST PARTICIPATION (MEANS±SD)	SECOND PARTICIPATION (MEANS±SD)	CORRELATION (*R*)
Prestudy	136.1±15.7	132.0±13.2 (NS)	0.49*
Prediuretic	143.4±13.8	146.1±14.8 (NS)	0.48*
Postdiuretic	129.1±13.5	130.0±18.2 (NS)	0.70‡
Response	−14.2±16.4	−16.0±16.5 (NS)	0.61†
	DIASTOLIC BLOOD PRESSURE		
Prestudy	88.5±9.3	87.1±8.7 (NS)	0.54†
Prediuretic	95.5±7.5	96.1±6.3 (NS)	0.04 (NS)
Postdiuretic	88.4±10.5	89.5±10.8 (NS)	0.83‡
Response	−7.1±11.8	−6.6±8.6 (NS)	0.64†
NS=not significant; *$p<0.05$; †$p<0.01$; ‡$p<0.001$			

between the first and second participation (r=0.96 and 0.95, respectively; $p<0.0001$ for both).

Mean levels of systolic and diastolic blood pressure (prestudy, prediuretic, and postdiuretic) and blood pressure responses to hydrochlorothiazide did not differ significantly between the first and second participations (Table I). In addition, blood pressure responses to hydrochlorothiazide were also significantly correlated between the first and second participations (Table I and Figure 1). However, despite the nonsignificant mean differences between the first and second responses, the "limits of agreement" for individual differences—defined by Bland and Altman[3] as the mean difference ±2 standard deviations—were broad (Table II and Figure 2).

DISCUSSION

To our knowledge, few studies have investigated the reproducibility of response to antihypertensive therapies. Zoccali and colleagues[4] found that reproducibility of the blood pressure response to 1 week of a low-sodium diet reimposed after an average interval of 3.4 months was "unsatisfactory." Chatellier and colleagues[5] conducted a single-blind trial of enalapril with two successive 10-day treatment periods, each consisting of 5 days of placebo followed by 5 days of enalapril. Reproducibility of the blood pressure response to enalapril was judged "moderate at best." In agreement with these investigations, our study shows that systolic and diastolic blood pressure responses to hydrochlorothiazide are, on average, significantly reproducible *for a group of*

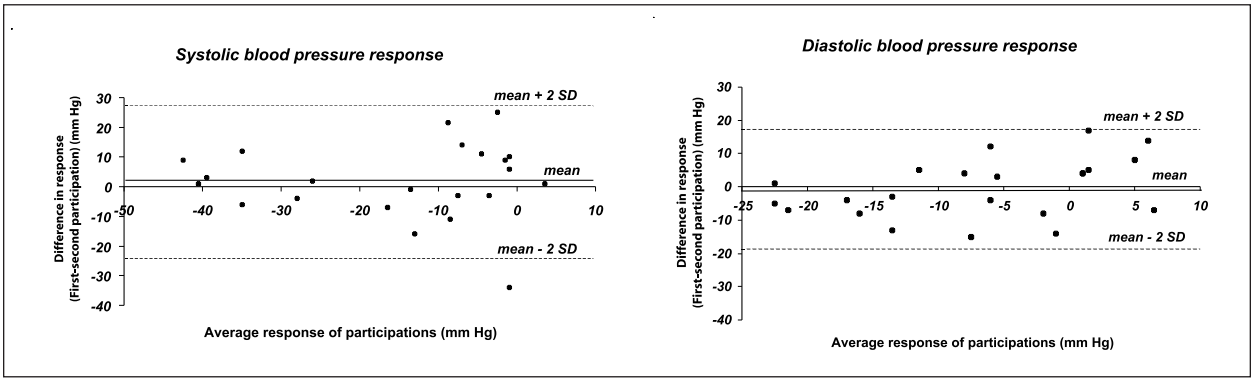

Figure 2. Reproducibility of systolic and diastolic blood pressure responses to hydrochlorothiazide, according to the method of Bland and Altman.[3] The average response was obtained by calculating the mean response of the first and second participations, and the difference was calculated as the blood pressure response at the first participation minus the second.

Table II. Agreement Between First and Second Participation According to the Method of Bland and Altman[3]		
	SYSTOLIC BLOOD PRESSURE	DIASTOLIC BLOOD PRESSURE
Prestudy		
Means±SD	4.1±15.2	1.4±8.6
Limits of agreement (means±2 SD)	34.4/−26.3	18.6/−15.8
Prediuretic		
Means±SD	−2.7±14.4	−0.6±8.9
Limits of agreement (means±2 SD)	26.1/−31.5	17.2/−18.5
Postdiuretic		
Means±SD	−0.9±12.6	−1.1±6.1
Limits of agreement (means±2 SD)	24.4/−26.2	11.0/−13.3
Response		
Means±SD	1.8±12.8	−0.5±8.9
Limits of agreement (means±2 SD)	27.4/−23.8	17.4/−18.4

subjects. However, responses *for individual subjects* varied widely between the first and second participation, making intraindividual agreement much less consistent.

Since clinicians treat individuals, rather than groups, they should understand that individual variability of blood pressure is greater than group variability and, consequently, the response of an individual patient may deviate considerably from the average response of a group of patients.[6,7] Previous studies have demonstrated considerable intraday and day-to-day variability in standardized office blood pressure measurements in individual subjects[7–10]; consequently, intraindividual variation is expected in the measured response to antihypertensive therapy, which reflects intraindividual variation in both the pre- and post-treatment measurements. In an effort to minimize such variability in the present study, blood pressures were measured in the same locations, at approximately the same time of the day, and by the same trained nurses. Although the interval between participations varied among subjects from 4–52 months, similar intraindividual variation has been reported in previous studies for blood pressure response, suggesting that this factor did not have a major influence on the observed intraindividual variation in the blood pressure response to hydrochlorothiazide. Other potential limitations of our study relate to the small number of study subjects; a potential selection bias, since not all the participants in the parent study participated in the repeatability trial; the imposition of a standardized diet; and a method of blood pressure measurement that differs from clinical practice. However, it appears that none of these factors increased group variability or decreased intraindividual variability in antihypertensive drug response in our study, relative to reports of previous studies.[6–10]

Reproducibility of the antihypertensive response to hydrochlorothiazide has important implications for clinical investigation as well as patient care. Studies to identify predictors of antihypertensive drug response can be successful only insofar as the drug response of interest is reproducible.[11] In particular, the difficulty in accurately phenotyping individual blood pressure response based on office measurements poses an obstacle to pharmacogenetic investigations. To elucidate the genetic architecture of interindividual differences in antihypertensive drug response will undoubtedly require alternative methods of blood pressure measurement, such as 24-hour blood pressure monitoring, which is characterized by less intraindividual variability and greater intraindividual repeatability than office blood pressure readings.[12] Moreover, eliciting and recording an individual patient's history of blood pressure response to previous antihypertensive medications, as suggested by the JNC VI,[1] appears to have limited utility in predicting future response to a retrial of the same antihypertensive drug therapy.

Acknowledgement: Source of support: US Public Health service grant R01-HL 53330 and funds from the Mayo Foundation.

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