

**NEW INSIGHTS FOR STATISTICAL ANALYSIS OF BLOOD PRESSURE RESPONSE TO RESISTANCE TRAINING IN ELDERLY HYPERTENSIVE WOMEN****NOVAS PERSPECTIVAS PARA A ANÁLISE ESTATÍSTICA DA RESPOSTA DA PRESSÃO ARTERIAL AO TREINAMENTO RESISTIDO EM MULHERES IDOSAS HIPERTENSAS****Dahan da Cunha Nascimento<sup>1,4</sup>, Cristiane Rocha Silva<sup>1</sup>, Denis Cesar Leite Vieira<sup>2,4</sup>, Brad Jon Schoenfeld<sup>3</sup> and Jonato Prestes<sup>1</sup>**<sup>1</sup>Universidade Católica de Brasília, Brasília-DF, Brasil.<sup>2</sup>Universidade de Brasília, Brasília-DF, Brasil.<sup>3</sup>Cuny Lehman College, Bronx-NY, United States of America.<sup>4</sup>Centro Universitário do Distrito Federal, Brasília-DF, Brasil.**RESUMO**

O objetivo principal do estudo foi apresentar procedimentos estatísticos para uma melhor interpretação dos dados sobre a responsividade, explicar como lidar com o efeito da regressão a média (RM) e descrever como determinar alterações clinicamente importantes na pressão arterial (PA) pelo cálculo da diferença clínica (DC). Vinte e sete mulheres idosas hipertensas foram incluídas e o treinamento resistido (TR) consistiu em um modelo linear periodizado. O TR durou 10 semanas, com duas sessões realizadas por semana. Os responsivos foram classificados com base nas diferenças da pressão arterial sistólica (PAS) entre os momentos T1 (primeiras 3 semanas) e T4 (semanas 9–10). As análises estatísticas no presente estudo foram realizadas utilizando a ANOVA de medidas repetidas, análise de covariância (ANCOVA) e modelo linear misto (MLM). Conclui-se que quando uma ANOVA de medidas repetidas é aplicada, os resultados mostram uma redução não significativa de -2,24 mmHg, mas a classificação dos participantes por responsividade fornece uma interpretação diferente dos resultados. Além disso, a PAS inicial foi o preditor mais potente da resposta pós-exercício da PAS, conforme analisado pela RM. Finalmente, as reduções de -2,24 mmHg não foram estatisticamente significativas e nem clinicamente importantes, mas caíram dentro do erro de medida.

**Palavras-chave:** Responsividade, Regressão a média, Erro padrão de medida, Diferença clínica, Pressão arterial.**ABSTRACT**

The main goal was to present statistical procedures for a better data interpretation of responsiveness, explain how to deal with RTM effect, and describe how to determine clinically important changes in BP from significant real difference (SRD). Twenty-seven hypertensive elderly women were included, and RT consisted of a periodized linear model. The RT lasted 10 weeks, with two sessions performed per week. Responders were classified on the basis of SBP differences between time-points T1 (first 3 weeks) and T4 (weeks 9–10). Statistical analyses were performed using One-Way Repeated Measures ANOVA, an analysis of covariance (ANCOVA), the linear mixed model (LMM) was used in the present study, and SRD was also calculated. In conclusion, when one-way repeated measure ANOVA was conducted to determine whether there was a statistically significant difference in SBP levels over the course of 10-week RT, results showed a non-significant reduction of -2.24 mmHg, while classifying subjects by responsiveness provides a different perspective of the results. Furthermore, initial SBP was the more powerful predictor of post-exercise SBP response, as analyzed by the regression to the mean effect. Finally, the reductions of -2.24 mmHg was not statistically significant nor clinically meaningful, but fell within the measurement error of the SBP measurements.

**Keywords:** Responsiveness, Regression to the mean, Standard error of measurement, Clinical difference, Blood pressure.**Introduction**

Exercise is beneficial for the control and prevention of hypertension in the elderly. In addition, it has been shown that traditional resistance training (RT) combined with aerobic training are effective in lowering blood pressure (BP) in elderly hypertensive women after 16 weeks<sup>1</sup>. Moreover, research indicates these benefits can be maintained for 4 and 14 weeks, respectively, following training cessation<sup>2,3</sup>. Those benefits promoted by the regular practice of RT might be explained by the changes on neural mechanisms, such as lower renal and muscle sympathetic nerve activity, lower norepinephrine spill-over, increment on heart rate

variability, and enhanced parasympathetic modulation that lower resting heart rate and blood pressure<sup>4</sup>.

Despite the reported beneficial effects of exercise in lowering BP levels, this variable naturally fluctuates based on factors such as emotional status, stress, antihypertensive medications, inaccuracies in the measurement process, and illness<sup>5</sup>. Thus, the greater BP variability during the study intervention, the greater the error measurement for individual BP scores. When taking this information into account, the apparently simple question: “Does experimental group BP reductions provided by interventions represent a statistical significant difference, a real difference, or a measurement error?” becomes rather complex.

The effects of exercise on blood pressure are normally represented by measures of central tendency (e.g. mean) when groups and time points are compared. This common practice is based on the premise that subjects will tend to present a similar response. However, in actuality subjects show a wide range of responses to an exercise intervention (a.k.a. “responsiveness”)<sup>6</sup>. Thus, analyzing data using group or time points means might induce Type III<sup>7,8</sup>. For the Type III error, the wrong question for the right answer is made. Essentially the Type III error, occurs when the statistician fails to do the best job and has not taken enough time (e.g. use of adequate statistical analyses) to question the research experiment<sup>8</sup>.

For the wrong question and misleading interpretation of a null hypothesis correctly rejected, researchers must be aware that BP reductions will occur for a small group of subjects. In addition, reductions in systolic blood pressure (SBP) will occur for subjects who show exceptionally large responses to training (a.k.a. “high responders”) when compared with individuals who show small responses to training (a.k.a. “low responders”). In this sense, looking at alternative statistical measures than just the group means and variability of data around the mean (e.g. standard deviation) might provide important insights as to inter-individual variation in training response<sup>9-14</sup>.

Another concern involving blood pressure response to exercise, is the regression to the mean (RTM). Variables as BP, that is associated with large within-subject variability over time, create the potential for a RTM effect<sup>15</sup>. A higher BP in the first measurement (e.g., at first week), will be likely be less extreme when measured again (e.g., at 10 week). Thus, classifying subjects as high and low responders to exercise will, in the great majority of cases, be RTM and random variation<sup>5,15</sup>. These findings emphasize the importance of including analysis of covariance (ANCOVA) into study design to deal with RTM as proposed by Barnett et al.<sup>16</sup>.

In addition, it is important to statistically determine if changes in SBP are real or influenced by error measurements<sup>6</sup>. The desired accuracy of BP error measurement in a study can be controlled by a complementary statistical analysis. Therefore, standard error of measurement (SEM)<sup>17</sup>, which controls the aggregate of factors that collectively affects the true value of the measurement, can be measured and the minimal important change or smallest real difference (SRD) can be calculated. The SRD determines what should be clinically important from what is known as the error of measurement<sup>18</sup>.

The application of these complementary statistical analyses to researchers in the field of BP and exercise interventions is relevant. Thus, the aim of the current study was to present statistical procedures for a better data interpretation of responsiveness, explain how to deal with RTM effect, and to describe how to determine clinically important changes in BP from SRD.

## Methods

To best illustrate concepts, we present real data from an experimental 10-week RT program, and the effect on SBP in hypertensive elderly women. This study was approved by

the Institutional Research Ethic Committee of Catholic University of Brasília (UCB) (protocol 45648115.8.0000.5650/2016). Each subject was fully informed about the risks and benefits associated with participation in the present study and gave their written informed consent to participate. Twenty-seven ( $n = 27$ ) hypertensive elderly women were included in this prospective exploratory study designed as a “pre-post”-intervention. All participants were recruited on a voluntary basis from the local community through posters and lectures about the study. Subject’s characteristics are presented in Table 1. According to the American College of Sports Medicine, subjects were considered *untrained* because they had no previous experience with resistance training (RT)<sup>19</sup>. Inclusion criteria for hypertensive subjects were as follows: women age  $\geq 60$  years and subjects who self-reported hypertension and had SBP and DBP below the threshold of hypertension stage 1 but were using antihypertensive medications<sup>20-22</sup>. Subjects were excluded if they had a history of heart failure, valvular or congenital disease, pacemaker implantation, osteo-articular disorders, if they were smokers, or were consuming alcohol.

**Table 1.** Subjects’ characteristics\*

Characteristics	High ( $N = 7$ )	Low ( $N = 20$ )	$p$ value
SBP, mmHg	126.04 $\pm$ 11.04 (115.83-136.26)	118.08 $\pm$ 9.09 (113.83-122.34)	0.12
DBP, mmHg	72.95 $\pm$ 6.47 (66.96-78.94)	69.02 $\pm$ 6.54 (65.96-72.08)	0.18
Heart rate, bpm	72.54 $\pm$ 15.61 (58.10-86.98)	72.02 $\pm$ 8.57 (68.01-76.04)	0.91
Age, years	69.14 $\pm$ 6.79 (62.86-75.42)	68.01 $\pm$ 5.23 (65.65-70.54)	0.67
Height, cm	1.52 $\pm$ 0.03 (1.49-1.54)	1.56 $\pm$ 0.06 (1.53-1.59)	0.09
Weight, kg	57.00 $\pm$ 5.64 (51.78-62.22)	71.22 $\pm$ 9.32 (68.85-75.58)	0.001
BMI, kg/m <sup>2</sup>	24.64 $\pm$ 2.49 (22.33-26.94)	29.01 $\pm$ 3.30 (27.55-30.65)	0.003
Leg press 10 RM, kg	33.14 $\pm$ 5.08 (28.44-37.84)	38.54 $\pm$ 6.84 (35.34-41.74)	0.06
Chest press 10 RM, kg	21.84 $\pm$ 3.96 (18.17-25.51)	22.49 $\pm$ 4.58 (20.34-24.63)	0.74
Leg extension 10 RM, kg	40.27 $\pm$ 11.85 (29.31-51.24)	39.34 $\pm$ 10.75 (34.31-44.38)	0.84
Low row 10 RM, kg	33.57 $\pm$ 3.77 (30.07-37.06)	34.75 $\pm$ 5.89 (31.99-37.50)	0.62
Leg curl 10 RM, kg	39.39 $\pm$ 9.01 (31.05-47.73)	39.98 $\pm$ 8.08 (36.20-43.76)	0.87

**Note:** SBP = systolic blood pressure, DBP = diastolic blood pressure, BMI = body mass index, RM = repetition maximum. \* Values are expressed as means, SD (standard deviation), and 95% confidence interval (CI)

**Source:** Authors

### Trial design

The strength of upper and low body was evaluated by ten-repetition maximum (10-RM) strength testing. After the 2-week familiarization period, subjects were tested for a 10-RM for the following exercises in this order: machine leg press, machine chest press, machine leg extension, machine low row, and machine leg curl (Righetto Fitness Equipment, Sao Paulo, Brazil) with 5 minutes rest between exercise tests. Subjects were advised to refrain from any exercise other than activities of daily living for at least 48 hours before 10-RM testing. In brief, subjects warmed-up on each exercise with 5-10 submaximal repetitions. Subjects performed 10 repetitions of increasing weight until reaching a valid 10-RM. Two minutes of rest was provided between attempts. All 10-RM tests were registered within two attempts.

Two experienced RT professionals supervised the tests. Furthermore, subjects were evaluated by an experienced physiotherapist before the 10-RM testing and study participation. Previous studies from our research group demonstrated a high test and retest reliability for this type of test  $r > 0.97$ <sup>1,11</sup>. All testing sessions were scheduled between the hours of 8:00 to 10:00 AM (morning class group) and 1:00 and 3:00 PM (afternoon class group). Before each training session, the correct use of hypertensive medications and the risks associated with non-use were reinforced<sup>23</sup>.

The RT consisted of a periodized linear model. The exercises performed were: machine leg press, machine chest press, machine leg extension, machine low row, and machine leg curl. The number of repetitions were reduced (maintaining the minimal zone established for each cycle) as the intensity increased over the course of the program. The periodization scheme was adapted from our previous research described in detail elsewhere<sup>24</sup>. The RT lasted 10 weeks, with two RT sessions performed per week, with a minimum of 24 h between sessions. All sessions were supervised by experienced RT professionals with a supervision ratio of 1:1 (coach to participant ratio) to favor greater strength gains<sup>25</sup> and for safety. Subjects were instructed to lift and lower loads at a constant velocity, taking ~2 seconds for the concentric (muscle shortening) and 2 seconds for the eccentric phase (muscle lengthening). In the first 3 weeks (T1) of the program, subjects performed three sets of 12–14 RM with a 60 s rest interval; from weeks 4–6 (T2), subjects performed three sets of 10–12 RM with a 80 s rest interval; from weeks 7–8 (T3), subjects performed three sets of 8–10 RM with a 100 s rest interval; and from weeks 9–10 (T4), subjects performed three sets of 6–8 RM with a 120 s rest interval. Loads were increased when subjects performed more than 3 repetitions in the third set beyond the prescribed RM zone.

#### *Hemodynamic measurements*

The SBP, diastolic BP (DBP) and heart rate were measured before each training session with an automatic oscillometric validated device (model Microlife BP 3BTO-A, Onbo Electronic, Widnau, Switzerland)<sup>26</sup>, consistent with the recommendations of the Guideline for the Prevention, Detection, Evaluation, and treatment of High Blood Pressure<sup>27,28</sup>. The measurements were performed after 10 minutes of seated rest in a quiet, temperature-controlled room, and cuff size was adapted to the arm circumference of each subject. All measurements of BP were taken between 8:00 and 10:00 a.m. (morning class group, 14 participants) and 1:00 and 3:00 p.m. (afternoon class group, 13 participants). Before measurements, subjects were advised to refrain from programmed exercise, and caffeine consumption.

#### *Participant sub-grouping*

Responders were classified on the basis of SBP differences between time-points T1 and T4. High responders were classified as a percent BP decline in the 25th percentile for the SBP. High responders were classified as systolic blood pressure decline  $\geq -6.83$  mmHg and low responders  $< -6.83$  mmHg. Furthermore, responsiveness was considered a “rare event” and no clinical or physiological criteria have been established to define high responders and low responders for SBP<sup>29</sup>. Although, different terms are used by previous research as, “high responders”, “responders” or even “adverse responders” to regular physical exercise<sup>6,9,11</sup>. In the present study, the terms high and low responders were used.

#### *Use of smallest real difference*

First, standard error of measurement was calculated by the square root of the mean square error term from the One-Way Repeated Measures ANOVA. This information can be found inside the output presented by statistical program SPSS (Table 2).

We next calculated the minimum difference (MD) to be considered real by the following formula<sup>17,18</sup>:

$$\text{(Equation 1). MD} = \text{SEM} \times 1.96 \times \sqrt{2},$$

The 1.96 value represents the z score associated with 95% IC. According to Weir<sup>17</sup>, the researcher might choose a different z score if a more liberal or conservative assessment is desired. The 80% confidence for BP is only suggested if 10-13 office measurements can be

made<sup>5</sup> with an accuracy about  $\pm 5$  mmHg of the ‘true’ blood pressure. Thus, a conservative assessment using 95% of confidence is recommended.

Using the data of Table 1, the SEM will be  $\sqrt{33.28} = 5.76$  mmHg. Thereafter, according to equation 1,  $MD = 5.76 \times 1.96 \times \sqrt{2} = 15.91$  mmHg.

Thus, a decline of at least 15.91 mmHg on BP needs to occur to be confident at the 95% level that a change in SBP reflects a real change and not a difference that is within the expected measurement error of the SBP values.

**Table 2.** One-way repeated measures ANOVA

Source		Type III Sum of Squares	df	Mean Square	F	Sig.
SBP	Sphericity Assumed	198.15	3	66.05	1.98	0.07
	Greenhouse-Geisser	198.15	2.85	66.42	1.98	0.07
	Huynh-Feldt	198.15	3.00	66.05	1.98	0.07
	Lower-bound	198.15	1.00	198.15	1.98	0.07
Error (SBP)	Sphericity Assumed	2596.57	78	<b>33.28 (MSE)</b>		
	Greenhouse-Geisser	2596.57	74.28	34.99		
	Huynh-Feldt	2596.57	78.00	33.28		
	Lower-bound	2596.57	26.00	99.86		

**Note:** SBP = systolic blood pressure; MSE = mean square error

**Source:** Authors

### Statistical analysis

Data were expressed as means and standard deviations. Shapiro-Wilk and Mauchly’s test were employed to check for normality and sphericity, respectively. Levene’s test was used to test homogeneity of variances. When the assumption of sphericity was not met, the significance of *F*-ratios was adjusted according to the Greenhouse-Geisser correction. Initially a repeated measures ANOVA was employed to verify the effects of training on hemodynamic changes<sup>30</sup>. This statistical analysis considered the data of all subjects.

An analysis of covariance (ANCOVA) controlling for pre-training SBP to verify its effects on SPB response post-training was employed to analyze the RTM effect<sup>16,31</sup>. Levene’s test was also applied for testing homogeneity of variances. When differences were identified, the Bonferroni post-hoc test was applied. An alpha level of  $\leq 0.05$  was considered significant, and *p* values were two-tailed. Considering a partial eta squared of 0.35, effect size of 0.74,  $\alpha$  error probability of 0.05, total sample size of 27 participants, number of groups (two groups), and covariates (one covariate), the power provided was 0.95% for this statistical analysis. The software G\*Power 3.1.6 was used to calculate the power.

Considering that sphericity condition is very difficult to justify, and it is very unlikely that the measurements taken between time points T1 to T4 will have the same degree of correlation. An analysis that can represent the average response value of the response at any time point in term of covariates such as treatment group (responsiveness), 10-week RT program, pre-training SBP values, and also account successfully for the observed pattern of dependences in those measurements. The linear mixed model (LMM) also called mixed effect model (MEM), random-regression models, multilevel models, hierarchical linear models, and empirical Bayes models<sup>32</sup> was used in the present study and can properly account for correlation between repeated measurements on the same subject and have greater flexibility to model time effects<sup>32,33</sup>. In addition, the LMM are expected to provide more accurate statistical inference than ANOVA, and have a power above 80%<sup>34</sup>.

We controlled for the influence of covariates (responsiveness, class time, 10-week RT program, and pre-training SBP values), that might predict post-training SBP changes. For the sake of brevity, we presented the *F* tests from the LMM results (type III Wald *F* tests with

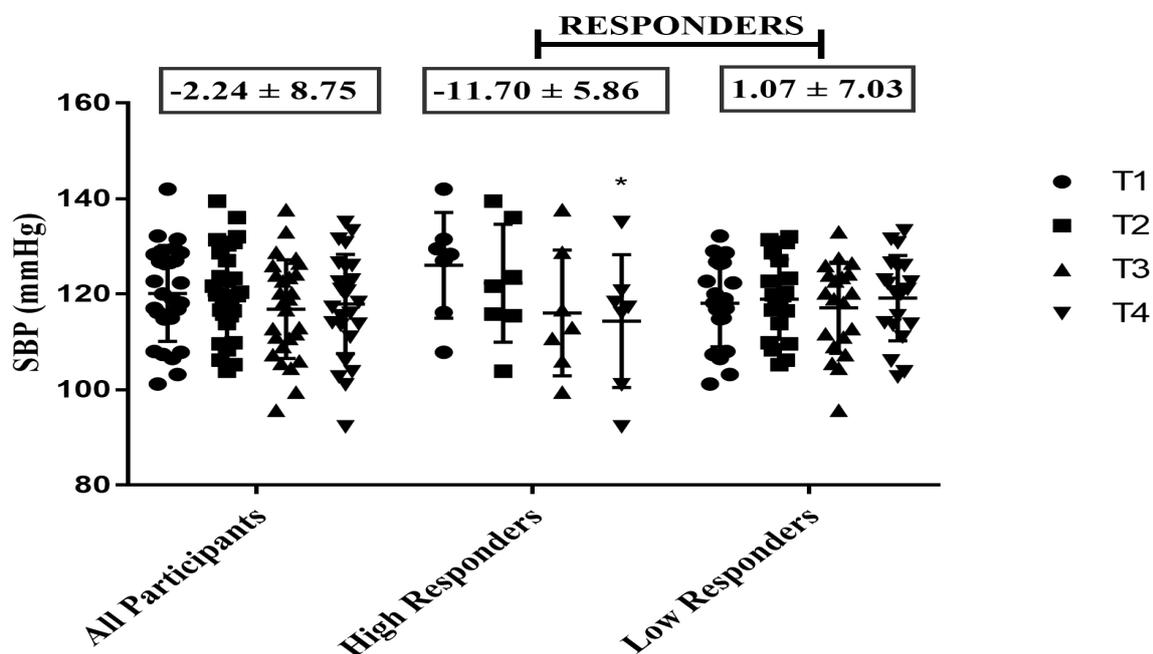
Kenward–Roger degrees of freedom approximation) and the parameters information in Table 5.

All analyses were conducted with SPSS version 18.0 (SPSS Inc., Chicago, USA). In addition, GraphPad Prism 6.0 software was also used for analysis (San Diego, California, USA).

## Results

### *All data analyzed*

A one-way repeated measure ANOVA was conducted to determine whether there was a statistically significant difference in SBP levels over the course of 10-week RT program. The RT intervention did not elicit statistically significant changes in SBP levels over time ( $F(3.00, 78.00) = 1.98, p = 0.071$ ). Figure 1.



**Figure 1.** Systolic blood pressure response

Note: \*significantly different from low responders at the same time point ( $p < 0.05$ ).

Source: Authors

### *Responsiveness analyzed*

After adjustment for pre-training SBP levels, there was a statistically significant difference in post-training SBP levels between groups ( $F(1.00, 24.00) = 13.17, p = 0.001$ ) after ANCOVA analyses. Post-hoc analysis was performed with a Bonferroni adjustment. Post-training SBP levels were statistically lower in the high vs low responders group (mean difference of  $-11.44$  (95% CI  $-17.95$  to  $-4.93$ ) mmHg,  $p = 0.001$ ). Table 3.

Considering that differences between groups were verified for BMI, after adjustment for pre-training BMI values, there was no statistically significant difference in post-training SBP levels between groups ( $F(1.00, 24.00) = 0.37, p = 0.544$ ).

**Table 3.** Adjusted and unadjusted intervention means and variability for post-training systolic blood pressure values with pre-training systolic blood pressure as a covariate

	Unadjusted			Adjusted	
	<i>N</i>	<i>M</i>	<i>SE</i>	<i>M</i>	<i>SE</i>
High responders	7	114.34	3.91	109.43*	2.66
Low responders	20	119.15	2.31	120.87	1.52

**Note:** N = number of participants, M = mean, SE = standard error. \* Significantly different from low responders ( $p \leq 0.001$ )

**Source:** Authors

*Smallest real difference*

After evaluating the SRD, only one participant from the high responders group presented a real change on SBP of -23.92 mmHg (Table 4). Other participants from the high responders group were within the error measurement ( $-9.66 \pm 2.54$  mmHg). Similarly, only one subject from the low responders group presented a real change in SBP of 24 mmHg (Table 4).

**Table 4.** Mean change score for SBP values according to the SRD

Systolic blood pressure	<i>n</i>	Mean change value (SD)
High Responders		
NSRD	6	-9,66 ± 2.54 mmHg
SRD	1	-23.92 mmHg
Low Responders		
NSRD	19	-0,17 ± 4.83 mmHg
SRD	1	24.83 mmHg

**Note:** SRD = smallest real difference, NSRD = no smallest real difference, SD = standard deviation

**Source:** Authors

After LMM was applied, we found a significant effect of pre-training SBP values ( $F(1,76) = 58.41, p = 0.001$ ) as predictive of post-training SBP changes. For other variables as class time ( $F(1,76) = 0.57, p = 0.450$ ), responsiveness ( $F(1,76) = 0.24, p = 0.624$ ), and 10-week RT program (with values, T2, T3, and T4),  $F(1,76) = 0.88, p = 0.350$ , no significant effects were observed. Table 5.

**Table 5.** Parametes estimates of the model (LMM, or MEM) to estimate post-training SBP changes

Parameters	Estimate	SE	<i>p</i>	95% CI
Class time	-1,66	2,95	0,57	-7.77 – 4.44
10-week RT program	-0,94	0,80	0,24	-2.56 – 0.67
Responsiveness	-1,21	3,32	0,71	-8.09 – 5.66
Pre-training SBP	0,67	0,11	0,00	0.42 – 0.91

**Note:** LMM = linear mixed model, RT = resistance traininig, SBP = systolic blood pressure, SE = standard error, CI = confidence interval, MEM = mixed effect model

**Source:** Authors

**Discussion**

In the above paragraphs, different statistical approaches has been discussed from an analytical, post hoc perspective, aiming at the identification of responders, how to verify the RTM effect, interpret the measurement error, and calculate the SRD effect.

If the mean of 27 participants is used to compare reductions in SBP between time points, results would show a statistically non-significant reduction of -2.24 mmHg (Figure 1). Hardy et al.<sup>35</sup> demonstrated that reductions of 2 mmHg in SBP were associated with reductions in the incidence of coronary artery disease, stroke, and heart failure events for

African and white Americans. Furthermore, Lawes et al.<sup>36</sup> demonstrated that a 10 mmHg reduction in SBP at mean age at baseline of 63 years was associated with a risk reduction in stroke of 31%. Nevertheless, the reductions of -2.24 mmHg observed in Figure 1 were neither statistically significant nor clinically meaningful, but fell within the measurement error of the SBP measurements.

Alternatively, classifying subjects by responsiveness (Figure 1) provides a different perspective on results. Seven elderly hypertensive women were deemed high responders and 20 participants as low responders. Differences between groups were identified; SBP on time point T4 were significantly lower for high responders when compared with low responders. These differences were only observed because the variability of scores around the mean were considered<sup>37</sup>. However, differences between time points reveals nothing about the clinical significance of findings or error measurement. This can be confirmed by the study from Nascimento et al.<sup>2</sup> who used an ANOVA of repeated measurements, and demonstrated a significant decline (-10 mmHg) on SBP at post-training, and detraining time points when compared with pre-training measurements in hypertensive elderly women. Nevertheless, important insights as to inter-individual variation in training response were missed by the authors. Furthermore, the significant differences between time points observed by Nascimento et al.<sup>2</sup> might reveal little about clinical significance of the findings or error measurement.

Thus, it is important to distinguish findings of statistical significance from what is clinically meaningful. Statistical significance is a statement about the likelihood of a result being due to random chance, but is not indicative of whether the finding is practically meaningful. On the other hand, the clinical meaningfulness of a finding has relevant implications for practical application regardless of whether the result is significant<sup>38</sup>.

Bouchard et al.<sup>9</sup> classified responsiveness by the measurement error of the trait. The parameter that captures the totality of these sources of variance in a trait is known as the technical error (TE). Thus, they defined the adverse responders or low responders as subjects in which the response was 2 X TE in a direction indicating a worsening of the risk factor. For the SBP, exercise training-induced increments of  $\geq 10$  mmHg.

The study from Moker et al.<sup>13</sup> did not use any statistical approach to determine the totality of technical error. Although, responders decreased SBP by -11.5 mmHg, whereas no responders increased SBP by 7.9 mmHg after training. We can conclude if changes in SBP were real or influenced by error measurements.

With regard to the aforementioned paragraphs, the results from the data used in the present study demonstrate that a change of at least 15.91 mmHg in SBP must occur to be confident at the 95% level that a change in SBP reflects a real change and not a difference that is within the expected measurement error of the SBP values. With this in mind, only one participant from the high responders group presented a real change on SBP of -23.92 mmHg (Table 4). Other participants from the high responders group were within the error measurement ( $-9.66 \pm 2.54$  mmHg). This implies that inter-individual variation response to exercise might cause a misleading interpretation.

Similarly, only one subject from the low responders group presented a real change in SBP of 24 mmHg (Table 4). This increase represents an adverse response to regular exercise. Adverse response is defined as an exercise-induced change that worsens a risk beyond measurement error and expected day-to-day variation<sup>9,13</sup>. So, classifying individuals by responsiveness represents an important tool for identifying individuals with unwanted responses and provides the ability to personalize exercise prescription<sup>9</sup>. Furthermore, there is evidence that, independent of the exercise modality (resistance training, aerobic training, concurrent training)<sup>13,37</sup>, an adverse response is not a rare event, but in fact a common occurrence<sup>9</sup>.

We also sought to assess the effect of RTM on SPB response. Analyses of covariance is one statistical method that have been proposed to estimate the RTM effect<sup>15</sup>. Using data from our study after adjustment for pre-training SBP levels, there was a statistically significant difference in post-intervention SBP levels between groups ( $F(1.00, 24.00) = 13.17$ ,  $p = 0.001$ ). In addition, after LMM, pre-training SBP was predictive of post-training SBP changes. High and low responders changed SBP from T1 to T4 by  $-11.70 \pm 5.86$  mmHg ( $-9.00\%$ ) and  $1.07 \pm 7.03$  mmHg ( $1.10\%$ ), respectively. Thus, responsiveness is a common occurrence as presented in previous research<sup>11,12,29,39</sup> or might be a RTM effect?

The focus of the present study is to demonstrate that determining the existence of change in BP and exercise research is a complex undertaking. However, several considerations regarding the control of other variables that affect responsiveness as, mode of exercise, intensity, frequency, duration, genetic endowment, age, epigenetics, and baseline phenotype must be considered<sup>6,40</sup>.

Yet, few researchers acknowledge the issue in their published studies, and attempts to quantify individual response are usually deficient<sup>41</sup>. Furthermore, the cut-off adopted in this study and previous research<sup>11,12,29,39</sup> is another point of criticism and from the perspective of practical application a better criterion for the discrimination of responders and non-responders by the use of SRD is suggested, however this approach make the classification of subjects as responders more conservative<sup>40</sup>. In summary, in order to avoid misleading interpretation of results and obtain useful practical information, the complementary statistics presented herein as responsiveness classification, regression to the mean, standard error of measurement, and minimal difference are particularly suitable when hemodynamic parameters are analyzed.

## Conclusions

When one-way repeated measure ANOVA was conducted to determine whether there was a statistically significant difference in SBP levels over the course of 10-week RT, results showed a non-significant reduction of  $-2.24$  mmHg, while classifying subjects by responsiveness provides a different perspective of the results. Furthermore, initial SBP was the more powerful predictor of post-exercise SBP response, as analyzed by the regression to the mean effect. Finally, the reductions of  $-2.24$  mmHg were not statistically significant nor clinically meaningful, but fell within the measurement error of the SBP measurements. This approach demonstrates the importance of incorporating SRD to determine what should be clinically important from what is known as the error of measurement.

## References

1. Dos Santos ES, Asano RY, Filho IG, Lopes NL, Panelli P, Nascimento Dda C, et al. Acute and chronic cardiovascular response to 16 weeks of combined eccentric or traditional resistance and aerobic training in elderly hypertensive women: a randomized controlled trial. *J Strength Cond Res* 2014;28(11):3073-3084. Doi: 10.1519/JSC.0000000000000537
2. Nascimento Dda C, Tibana RA, Benik FM, Fontana KE, Ribeiro Neto F, Santana FS, et al. Sustained effect of resistance training on blood pressure and hand grip strength following a detraining period in elderly hypertensive women: a pilot study. *Clin Interv Aging* 2014;9:219-225. Doi: 10.2147/CIA.S56058. eCollection 2014.
3. Moraes MR, Bacurau RF, Casarini DE, Jara ZP, Ronchi FA, Almeida SS, et al. Chronic conventional resistance exercise reduces blood pressure in stage 1 hypertensive men. *J Strength Cond Res* 2012;26(4):1122-1129. Doi: 10.1519/JSC.0b013e31822dfc5e.
4. Sharman JE, La Gerche A, Coombes JS. Exercise and cardiovascular risk in patients with hypertension. *Am J Hypertens* 2015;28(2):147-158. Doi: 10.1093/ajh/hpu191.

5. Warren RE, Marshall T, Padfield PL, Chrubasik S. Variability of office, 24-hour ambulatory, and self-monitored blood pressure measurements. *Br J Gen Pract* 2010;60 (578):675-680. Doi: 10.3399/bjgp10X515403.
6. Mann TN, Lamberts RP, Lambert MI. High responders and low responders: factors associated with individual variation in response to standardized training. *Sports Med* 2014;44(8):1113-1124. Doi: 10.1007/s40279-014-0197-3.
7. Schwartz S, Carpenter KM. The right answer for the wrong question: consequences of type III error for public health research. *Am J Public Health* 1999;89 (8):1175-1180. PMID: 10432902.
8. Kimball AW. Errors of the third kind in statistical consulting. *J Am Stat Assoc* 1957;52(278):133-142. Doi: 10.2307/2280840.
9. Bouchard C, Blair SN, Church TS, Earnest CP, Hagberg JM, Hakkinen K, et al. Adverse metabolic response to regular exercise: is it a rare or common occurrence? *PloS One* 2012;7(5):e37887. Doi: 10.1371/journal.pone.0037887.
10. Garcia P, Nascimento DD, Tibana RA, Barboza MM, Willardson JM, Prestes J. Comparison between the multiple-set plus 2 weeks of tri-set and traditional multiple-set method on strength and body composition in trained women: a pilot study. *Clin Physiol Funct Imaging* 2016;36(1):47-52. doi: 10.1111/cpf.12192
11. Prestes J, Nascimento DC, Tibana RA, Teixeira TG, Vieira DC, Tajra V, et al. Understanding the individual responsiveness to resistance training periodization. *Age* 2015;37(3):9793. Doi: 10.1007/s11357-015-9793-x.
12. Tajra V, Tibana RA, Vieira DC, de Farias DL, Teixeira TG, Funghetto SS, et al. Identification of high responders for interleukin-6 and creatine kinase following acute eccentric resistance exercise in elderly obese women. *J Sci Med Sport* 2014;17(6):662-666. Doi: 10.1016/j.jsams.2013.09.012.
13. Moker EA, Bateman LA, Kraus WE, Pescatello LS. The relationship between the blood pressure responses to exercise following training and detraining periods. *PLoS One* 2014;9(9):e105755. Doi: 10.1371/journal.pone.0105755.
14. Adamopoulos S, Davos CH. Determining exercise training responders through inflammatory status in heart failure. *Eur J Prev Cardiol* 2017;24(10):1015-1016. Doi: 10.1177/2047487317703823.
15. Pocock SJ, Bakris G, Bhatt DL, Brar S, Fahy M, Gersh BJ. Regression to the mean in SYMPLICITY HTN-3: Implications for design and reporting of future trials. *J Am Coll Cardiol* 2016;68(18):2016-2025. Doi 10.1016/j.jacc.2016.07.775.
16. Barnett AG, van der Pols JC, Dobson AJ. Regression to the mean: what it is and how to deal with it. *Int J Epidemiol* 2005;34(1):215-220. Doi: 10.1093/ije/dyh299.
17. Weir JP. Quantifying test-retest reliability using the intraclass correlation coefficient and the SEM. *J Strength Cond Res* 2005;19(1):231-240.
18. Dvir Z. Difference, significant difference and clinically meaningful difference: The meaning of change in rehabilitation. *J Exerc Rehabil* 2015;11(2):67-73. Doi: 10.12965/jer.150199
19. American College of Sports Medicine. American College of Sports Medicine position stand. Progression models in resistance training for healthy adults. *Med Sci Sports Exerc* 2009;41(3):687-708. Doi: 10.1249/MSS.0b013e3181915670.
20. National Institute of Health [Internet]. Understanding adult obesity — National Institute of Diabetes and Digestive and Kidney Diseases 2001. [Accessed March 16, 2018]. Available from: <https://www.niddk.nih.gov/health-information/communication-programs/win>.
21. Lima-Costa MF, Peixoto SV, Firmo JO. Validity of self-reported hypertension and its determinants (the Bambui study). *Rev Saude Publica*. 2004;38(5):637-642. Doi: 10.1590/S0034-89102004000500004.
22. Alonso A, Beunza JJ, Delgado-Rodriguez M, Martinez-Gonzalez MA. Validation of self reported diagnosis of hypertension in a cohort of university graduates in Spain. *BMC Public Health* 2005;5:94. Doi: 10.1186/1471-2458-5-94.
23. Gomides RS, Costa LA, Souza DR, Queiroz AC, Fernandes JR, Ortega KC, et al. Atenolol blunts blood pressure increase during dynamic resistance exercise in hypertensives. *Br J Clin Pharmacol* 2010;70(5):664-673. Doi: 10.1111/j.1365-2125.2010.03742.x.
24. Prestes J, Shiguemoto G, Botero JP, Frollini A, Dias R, Leite R, et al. Effects of resistance training on resistin, leptin, cytokines, and muscle force in elderly post-menopausal women. *J Sports Sci* 2009;27(14):1607-1615. Doi: 10.1080/02640410903352923.
25. Gentil P, Bottaro M. Influence of supervision ratio on muscle adaptations to resistance training in nontrained subjects. *J Strength Cond Res* 2010;24(3):639-643. Doi: 10.1519/JSC.0b013e3181ad3373.
26. Cuckson AC, Reinders A, Shabeeh H, Shennan AH. Validation of the Microlife BP 3BTO-A oscillometric blood pressure monitoring device according to a modified British Hypertension Society protocol. *Blood Press Monit* 2002;7(6):319-324.
27. Jones DW, Hall JE. Seventh report of the joint national committee on prevention, detection, evaluation, and treatment of high blood pressure and evidence from new hypertension trials. *Hypertension* 2004;43(1):1-3. Doi: 10.1161/01.HYP.0000110061.06674.ca

28. Whelton PK, Carey RM, Aronow WS, Casey DE, Collins KJ, Himmelfarb CD, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: executive summary: A report of the American College of Cardiology/American Heart Association Task Force on clinical practice guidelines. *Hypertension* 2018;71(6):1269-1324. Doi: 10.1161/HYP.0000000000000066.
29. Machado M, Willardson JM. Short recovery augments magnitude of muscle damage in high responders. *Med Sci Sports Exerc* 2010;42(7):1370-1374. Doi: 10.1249/MSS.0b013e3181ca7e16.
30. Laerd Statistics [Internet]. One-way repeated measures ANOVA using SPSS Statistics. Statistical tutorials and software guides. 2015. [Accessed March 16, 2018]. Available from: <https://statistics.laerd.com/spss-tutorials/one-way-anova-repeated-measures-using-spss-statistics.php>
31. Laerd Statistics [Internet]. One-way ANCOVA using SPSS Statistics. [Accessed March 16, 2018]. Available from: Statistical tutorials and software guides. <https://statistics.laerd.com/spss-tutorials/ancova-using-spss-statistics.php>
32. Gueorguieva R, Krystal JH. Move over ANOVA: progress in analyzing repeated-measures data and its reflection in papers published in the Archives of General Psychiatry. *Arch Gen Psychiatry* 2004;61(3):310-317. Doi: 10.1001/archpsyc.61.3.310.
33. Landau S, Everitt B. A handbook of statistical analyses using SPSS. Boca Raton: Chapman & Hall/CRC; 2004.
34. Ma Y, Mazumdar M, Memsoudis SG. Beyond Repeated measures ANOVA: advanced statistical methods for the analysis of longitudinal data in anesthesia research. *Reg Anesth Pain Med* 2012;37(1):99-105. Doi: 10.1097/AAP.0b013e31823ebc74.
35. Hardy ST, Loehr LR, Butler KR, Chakladar S, Chang PP, Folsom AR, et al. Reducing the Blood Pressure-Related Burden of Cardiovascular Disease: Impact of Achievable Improvements in Blood Pressure Prevention and Control. *J Am Heart Assoc* 2015;4(10):e002276. Doi: 10.1161/JAHA.115.002276.
36. Lawes CM, Bennett DA, Feigin VL, Rodgers A. Blood pressure and stroke: an overview of published reviews. *Stroke* 2004;35(4):1024. Doi: 10.1161/01.STR.0000126208.14181.DD.
37. Loenneke JP, Fahs CA, Abe T, Rossow LM, Ozaki H, Pujol TJ, et al. Hypertension risk: exercise is medicine\* for most but not all. *Clin Physiol Funct Imaging* 2014;34(1):77-81. Doi: 10.1111/cpf.12059.
38. Fethney J. Statistical and clinical significance, and how to use confidence intervals to help interpret both. *Aust Crit Care* 2010;23(2):93-97. Doi: 10.1016/j.aucc.2010.03.001.
39. Prestes J, Nascimento DDC, Neto IVS, Tibana RA, Shiguemoto GE, Perez SEA, et al. The Effects of Muscle Strength Responsiveness to Periodized Resistance Training on Resistin, Leptin, and Cytokine in Elderly Postmenopausal Women. *J Strength Cond Res* 2018;32(1):113-120. Doi: 10.1519/JSC.0000000000001718.
40. Hecksteden A, Kraushaar J, Scharhag-Rosenberger F, Theisen D, Senn S, Meyer T. Individual response to exercise training - a statistical perspective. *J Appl Physiol* 2015;118(12):1450-1459. Doi: 10.1152/jappphysiol.00714.2014.
41. Hopkins WG. Individual responses made easy. *J Appl Physiol* 2015;118 (12):1444-1446. Doi: 10.1152/jappphysiol.00098.2015.

**Acknowledgments:** The first author wants to dedicate this paper to his family (Rita de Cassia and Nicolas Cunha). The author Dahan da Cunha Nascimento also acknowledge the financial support from Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES).

**ORCID** dos autores:

Dahan da Cunha Nascimento: 0000-0002-6580-9404

Cristiane Rocha Silva: 0000-0003-3558-8804

Denis Cesar Leite Vieira: 0000-0002-0761-1846

Brad Jon Schoenfeld: 0000-0003-4979-5783

Jonato Prestes: 0000-0003-0399-8817

Received on Mar, 17, 2018.

Reviewed on Sep, 22, 2018.

Accepted on Oct, 20, 2018.

---

**Author address:** Dahan da Cunha Nascimento. Programa de Pós-Graduação em Educação Física, Universidade Católica de Brasília - Q.S. 07, Lote 01, EPTC – Bloco G. Código Postal: 71966-700 – Distrito Federal, Brasília, Brazil. Telephone: 61 3356 9350 - Fax: + 21/55/61 3356 9350. E-mail: dahanc@hotmail.com