Is the relationship between supine blood pressure and postural changes in blood pressure artefactual? Results from the Kuopio Ischemic Heart Disease Risk Factor Study

Thomas W. Wilson, Richard D. Cohen*, Peter A. Lachenbruch†, Melien Wu‡, George A. Kaplan** and Jukka T. Salonen††

Objective: To investigate whether there is an association between initial supine blood pressure and postural changes in blood pressure (standing minus supine blood pressure).

Methods: Using data from the Kuopio (Finland) Ischemic Heart Disease Risk Factor Study (KIHD), we simulated the problem and found the suggested solution based on the work of Blomqvist. We then applied the Blomqvist correction to the KIHD data with real measurement errors.

Results: The observed regression slope was substantially reduced, indicating that there is no relationship between the initial blood pressure and the postural change in blood pressure.

Conclusion: Only the broad application of the method of Blomqvist to other data sets will determine the generalizability of the present finding that initial blood pressure is unrelated to the postural change in blood pressure.

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Introduction

In an excellent review article of orthostatic hypotension in elderly humans, Lipsitz [1] stressed the probable etiological role of blood pressure itself (i.e. hypertension) in orthostatic hypotension, a condition that is primarily defined by a significant fall in blood pressure when the subject initially stands. Biological and statistical evidence supports this contention.

MacLennan *et al.* [2], having noted a strong statistical association between supine blood pressure and postural change in blood pressure, provided a biologically plausible reason for the relationship. They speculated that elevated blood pressure might lead to mechanical defects in the artery wall and increased arterial rigidity, and thus underlie orthostatic hypotension. Other investigators, citing cases of orthostatic hypotension associated with autonomic dysfunction, emphasize evidence suggesting that abnormalities in baroreflex sensitivity may be partially corrected by blood pressure normalization [3]. A relationship has also been reported between blood pressure and 'collapse tendency on tilt table' [4] or 'fainting' [5], both of which are symptoms of orthostatic hypotension.

The strongest evidence for a relationship between initial blood pressure and the postural change in blood pressure is the frequently reported statistical association showing that higher supine (or sitting) blood pressures are

From the M.I. Bassett Research Institute, Columbia University, Cooperstown, New York, the *Human Population Laboratory, California Public Health Foundation, Berkeley, the †Department of Biostatistics, UCLA, School of Public Health, Los Angeles, California, USA, the ‡Chung-Yuan Christian University, Chungli, Republic of China, the **Human Population Laboratory, California Department of Human Services, Berkeley, California, USA, and the ††Department of Community Health and General Practice and Research, Institute of Public Health, University of Kuopio, Kuopio, Finland.

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Requests for reprints to: Dr T.W. Wilson, Assistant Professor of Clinical Public Health (Epidemiology), M.I. Bassett Research Institute, Columbia University, 1 Atwell Road, Cooperstown, NY 13326, USA.

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associated with a larger fall in postural blood pressure than lower initial supine blood pressures. This relationship has been observed in numerous biomedical research projects [6], including those in aerospace medicine [7,8], on tilt-tables [9], in clinical studies [2,10,11] and in large epidemiological studies [12–15]. However, because of the inherent mathematical relationship between an initial value and a change in score, the observed relationship between an initial blood pressure and a postural change in blood pressure is certainly exaggerated; indeed, it may be completely artefactual.

This mathematical phenomenon has been described as the 'law of initial value' [16]. Technically, it is a form of 'regression to the mean' [17] because, when measures are repeated, extreme values tend to be followed, on average, by less-extreme values. This can be viewed as resulting from random fluctuations about a 'true' value, due partly to measurement error. In 1962 Oldham [18] elegantly discussed this problem in relation to blood pressure research, and his correction method has been used occasionally in blood pressure studies [19–21]. Using the example of two independent (uncorrelated) variables, x_1 and x_2, he showed that the correlation between the initial value (x_1) and the change in score ($x_2 - x_1$) was $-1/2^{1/2}$ (i.e. approximately −0.707). To avoid drawing erroneous conclusions from this 'spurious' correlation, he suggested using the mean (or sum) of the initial and second value, instead of the initial value, and correlating it with the change in score. Oldham also noted that replacing the actual change score with a percentage change did not correct the error.

However, MacGregor *et al.* [22] argued that the biological significance of 'Oldham's correction' is difficult, if not impossible, to interpret. Hayes [23] also showed that 'Oldham's correction', used in the context of treatment comparisons, might yield biased results if (as often happens) the true treatment effect varies among individuals with the same initial value.

At least two other methods have been proposed to deal with the problem of relating postural changes in systolic blood pressure to initial value. In the first method [13] the investigators suggested stratifying on the initial value to correct the problem of 'regression to the mean'. We have recently shown [24] that misleading results occur when the initial value is divided into two strata (such as hypertensives and normotensives) or quartiles. In a second proposed method Rutan *et al.* [25] suggested replacing the actual initial value (supine systolic blood pressure) with a separate, although highly correlated, variable (sitting systolic blood pressure), stating that, because the errors in initial value and surrogate value were mutually independent, there would be no regression to the mean. However, the problem is not caused by correlated errors. In the models used by Oldham and by Blomqvist (described below) to describe the problem, measurement errors are assumed to be uncorrelated both with the true values and with each other.

In a very readable discussion, Hayes [23] recommended a correction based on Blomqvist's work. Blomqvist [26] showed that the regression of a change in score on an initial value leads to a biased estimate of the regression coefficient because of errors in the measurement of initial and subsequent values. These measurement errors can include both human or instrument errors and intrinsic biological variability. In other words, random within-person variation in the measurements produces a misleading relationship between the initial blood pressure and the postural change in blood pressure.

Two examples which illustrate the effect of Blomqvist's correction are presented here, using data from the Kuopio Ischemic Heart Disease Risk Factor Study (KIHD). In the first example, we simulate the effect of measurement error on the relationship between change and initial value, and show how Blomqvist's correction reduces the apparent relationship. In the second example data with real measurement errors are used.

An earlier version of this paper appeared in a dissertation [27].

Methods

The Kuopio Ischemic Heart Disease Risk Factor Study

Details concerning the KIHD study design have been published elsewhere [28]. Briefly, the KIHD participants consist of two randomly selected samples from the Kuopio region in eastern Finland. The first sample was of 54-year-old males. Of those sampled, 1399 were considered eligible (i.e. alive and residing in the sampling catchment area at the time of the examination), and 1166 elected to participate. All examinations were conducted between March 1984 and June 1986. The second sample was an age-stratified sample of males aged 42, 48, 54 or 60 years and from the same area. A total of 1836 were eligible for the study, of whom 1516 participated. They were examined between August 1986 and December 1989. The overall participation rate for both samples was 82.5% (2682 out of 3235). This sample is based on 2669 individuals for whom complete readings on supine and standing blood pressure and age had been taken.

Blood pressure readings

Blood pressure readings were taken by trained observers using a Hawskley random-zero sphygmomanometer on the right brachial artery. The blood pressure cuff size was determined by arm circumference. Supine blood pressure was taken after the subject had rested for 5, 10 and 15 min. Standing blood pressure was taken 1 min after the subject attained upright posture with the arm hanging to the side. Systolic blood pressure was recorded as Korotkoff phase I and diastolic blood pressure was taken as Korotkoff phase V. As is customary, the first blood pressure reading was discarded and supine blood pressure

(the initial value) was taken as the average of the readings after 10 and 15 min.

Antihypertensive medication

All participants were asked whether they were currently taking any antihypertensive or other cardiovascular medication.

Statistical methods

Blomqvist's correction

In brief, Blomqvist's correction requires the calculation of the ratio of the measurement error variance to the between-person variance in the observed initial value. Hayes [23] suggested that the estimate of measurement error variance should ideally come from multiple readings on the initial value on each subject (or from a subset of subjects) in a study. External sources for this information may also be used, albeit with caution. Blomqvist's method assumes that the relationship between true initial value and true change is linear, and that the errors of measurement are uncorrelated with each other or with the true initial value [26].

Blomqvist's correction is based on the following statistical model for the data. Let X_1 and X_2 be the true values for initial and follow-up systolic blood pressure, which are distributed in the population with variance σ^2. Let $D=X_2-X_1$ be the true difference. The observed values of initial (supine) and follow-up (standing) blood pressure are x_1 and x_2, respectively. $x_1=X_1+\varepsilon_1$; $x_2=X_2+\varepsilon_2$, where ε_1 and ε_2 are random errors of measurement with mean 0 and variance δ^2; ε_1 and ε_2 are assumed to be correlated neither with X_1 and X_2 nor with each other. Let $d=x_2-x_1$ be the observed difference between standing and supine blood pressures.

The ordinary least-squares estimate of the regression of d on x_1 is misleading. Let β and β^* be the regressions of d on x_1 and D on X_1, respectively. Blomqvist derived the relationship between β and β^* as:

$$\beta=(\sigma^2\beta^*-\delta^2)/(\sigma^2+\delta^2) \quad (1)$$

This equation shows that the observed regression coefficient (β) is a weighted average of the true regression coefficient (β^*) and −1 [23], and is therefore biased away from the true value.

To correct this bias, Blomqvist suggested the estimator:

$$\hat{\beta}^* = (\hat{\beta} + \lambda)/(1 - \lambda) \quad (2)$$

where $\lambda=\delta^2/(\sigma^2+\delta^2)$. We note that λ is the proportion of the variance of x_1 that is due to measurement error, because its denominator is the variance of x_1. When there is no measurement error, $\lambda=0$ and there is no bias in the regression coefficient. As the proportion of the variance due to measurement error increases, the bias in the regression coefficient increases. We note that Blomqvist derived an approximate (delta method) variance for β^*:

$$V(\beta^*) = (1 + \beta^*)^2\left(\frac{V(\beta)}{(1 + \beta)^2} + \frac{V(\lambda)}{(1 - \lambda)^2}\right) \quad (3)$$

Simulation

To demonstrate the effect of measurement error and illustrate Blomqvist's correction, we randomly selected 500 supine systolic blood pressure readings from the KIHD study and called them 'true' supine systolic blood pressure (X_1); that is, we considered them to be without measurement error. We defined 'true' standing systolic blood pressure (X_2) to be the same value as 'true' supine systolic blood pressure. Under these conditions the regression of X_2-X_1 on X_1 is 0. Independent, normally distributed, random numbers with a mean of 0 and an SD of 6 were generated and added to the 'true' values to produce 'observed' values (x_1 and x_2) with measurement error. We then regressed the observed postural change in systolic blood pressure (x_2-x_1) on the observed initial systolic blood pressure value (x_1) to obtain the observed slope (β). To apply Blomqvist's correction, the actual variance of the random numbers was used as the value for within-person variability (δ^2), and the variance of the 'true' supine systolic blood pressures was used for between-person variability (σ^2). The value of λ and the corrected slope were then calculated from Equation (2). All calculations for this simulation and the following demonstration were programmed using the SAS version 6.04 statistical package [29] and performed on an IBM-PC-compatible computer.

The Kuopio Ischemic Heart Disease Risk Factor Study data

To apply Blomqvist's correction to actual KIHD blood pressure data, we followed the steps outlined below. The supine systolic blood pressure values taken at 10 and 15 min were averaged to produce an 'initial' value. Postural change in blood pressure was calculated from the difference between the standing systolic blood pressure and the 'initial' value. We then regressed the observed postural change in systolic blood pressure on the observed initial value to obtain $\hat{\beta}$. To obtain estimates of σ^2 and δ^2, we performed a repeated-measures analysis of variance on the 10- and 15-min supine blood pressure measures [30]. The parameter λ was estimated as:

$$\hat{\lambda}=2W/(W+B) \quad (4)$$

where W and B are the within- and between-subject mean squares, respectively, from the analysis of variance. The variance of $\hat{\beta}^*$ was calculated from Equation (3). $\hat{V}(\hat{\beta})$ was the variance of $\hat{\beta}$ from the regression and $\hat{V}(\lambda)$ is given by:

$$\hat{V}(\hat{\lambda}) = 2\hat{\lambda}^2 \left[\frac{B}{B+W}\right]^2 \left[\frac{1}{N} + \frac{1}{N-1}\right] \quad (5)$$

where $\hat{\lambda}$, B and W are as defined above and N is the total number of subjects. Two-sided significance probabilities were obtained by treating $\hat{\beta}^*/[\hat{V}(\hat{\beta}^*)]^{1/2}$ as a standard normal variable.

A repeated-measures analysis of variance can also be used to estimate the necessary variance components in cases in which two or more measures of initial value are available. In these cases Equations (4) and (5) must be modified. The necessary information was given by Fleiss [30].

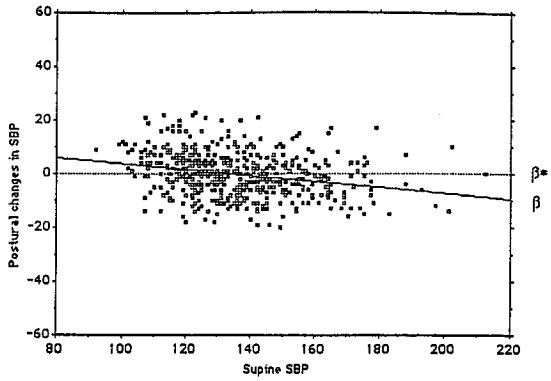

Fig. 1. The association between simulated postural change in systolic blood pressure (SBP, mmHg) and supine SBP (mmHg). Data are presented with simulated measurement error. The observed (artefactual) slope ($\hat{\beta}$=–0.109) and Blomqvist's corrected slope ($\hat{\beta}^*$=–0.0137) are shown

Results

Simulation results

The means±SD of both 'true' supine and 'true' standing systolic blood pressure values were 135.9±17.5 mmHg. Thus, the 'true' postural change in systolic blood pressure was zero for each 'subject' and there was no relationship between supine systolic blood pressure and change in systolic blood pressure upon standing. The correlation between the random errors added to simulate measurement error was 0.00. The means±SD of observed supine and standing systolic blood pressures were 136.0±18.8 and 135.6±18.6 mmHg, respectively. The difference in the mean±SD between observed supine and standing systolic blood pressures was –0.38±8.3 mmHg. This difference was caused entirely by the random errors that we added to each value. The correlation between the observed supine and standing systolic blood pressure readings was 0.90, and the correlation between the initial value and the difference was –0.25. Regression of the observed difference on the observed initial value yielded a slope of –0.109 (P=0.0001). This suggests a statistically significant relationship between the observed initial value and the change in score, a relationship that we know to be artefactual. The within-person variability (δ^2) was calculated to be 35.35 and the between-person variability (σ^2) was 307.7. The value of λ, or $\delta^2/(\sigma^2+\delta^2)$, was 0.10. The corrected slope, calculated from Blomqvist's formula, Equation (2), was –0.0137 (P=0.75), which is not statistically different from the true value of 0 (Fig. 1).

Results of analysis of the Kuopio ischemic Heart Disease Risk Factor Study

In the data from the KIHD study with real measurement errors, the mean±SD supine blood pressure was 135.3±17.9 mmHg, that of standing blood pressure was 133.4±19.3 mmHg and that of the postural change in systolic blood pressure was –1.9±11.4 mmHg. The correlation between supine and standing systolic blood pressures was 0.81, and the correlation between supine systolic blood pressure and postural change in systolic blood pressure was –0.20. The regression of postural change on the initial value produced a slope $\hat{\beta}$ of –0.12 (P=0.0001), indicating a strong negative relationship between supine systolic blood pressure and postural change in systolic blood pressure. The within-person variance ($\hat{\delta}^2$) was estimated to be 35.6 and the between-person variance ($\hat{\sigma}^2$) to be 303.2, with $\hat{\lambda}$=0.105. After Blomqvist's correction had been applied, the slope was reduced to –0.022 (P=0.12), indicating no statistically significant relationship between the initial value and change in score (Fig. 2).

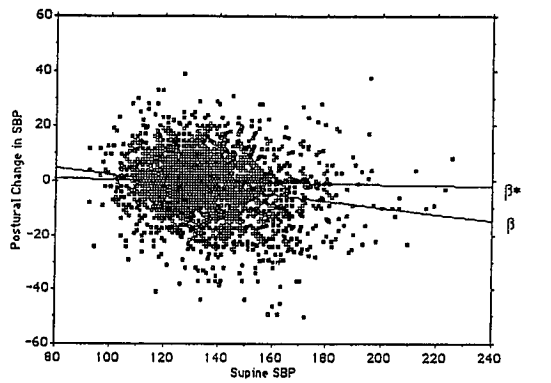

Fig. 2. The association between actual postural change in systolic blood pressure (SBP, mmHg) and supine SBP (mmHg). Data are presented with observed measurement error from the Kuopio Ischemic Heart Disease Risk Factor Study. The observed (artefactual) slope ($\hat{\beta}$=–0.1246) and Blomqvist's corrected slope ($\hat{\beta}^*$=–0.0218) are shown.

The results were replicated within each age group of the total sample (Table 1). In all strata the results were the same; what appears to be a strong relationship between initial systolic blood pressure and postural change in systolic blood pressure essentially disappears after employing Blomqvist's correction. The results were the same on a subsample (16% of the total sample) of those using antihypertensive medication.

Table 1. The regression of postural change in systolic blood pressure on the initial value with and without correction for acute measurement error.

Age (years)	n	Observed slope, $\hat{\beta}$	λ	Blomqvist's corrected slope, $\hat{\beta}^*$
42	336	−0.178 ($P<0.01$)	0.139	−0.044 ($P=0.31$)
48	356	−0.156 ($P<0.01$)	0.127	−0.032 ($P=0.38$)
54	1580	−0.115 ($P<0.01$)	0.095	−0.023 ($P=0.20$)
60	397	−0.076 ($P=0.02$)	0.121	−0.051 ($P=0.20$)
42–60	2670	−0.125 ($P<0.01$)	0.105	−0.022 ($P=0.12$)

Discussion

The simulation

The observed (i.e. uncorrected) value in the simulation seems to indicate that an individual with an initial systolic blood pressure of 160 mmHg would have a 4-mmHg greater postural drop in systolic blood pressure than an individual whose initial systolic blood pressure was 120 mmHg. However, this interpretation is wrong. We know that, in the 'true' data, postural change in systolic blood pressure is not associated with 'true' supine systolic blood pressure, because supine and standing blood pressure levels were set equal to one another. The apparent relationship is due solely to the presence of random errors of measurement, which have been added to the true values. Indeed, when we take the measurement errors into account, by employing Blomqvist's correction, we find no relationship between initial supine systolic blood pressure and standing blood pressure.

Analysis of the study data

The use of Blomqvist's correction in the observed blood pressure data from the KIHD study revealed that an apparently strong, statistically significant, association between supine systolic blood pressure and postural change in systolic blood pressure was a statistical artefact that disappeared when the correlation due to measurement error was taken into account. This is strong evidence that supine systolic blood pressure is not an important risk factor for postural changes in systolic blood pressure in this middle-aged male population. Other predictors such as stiffening of the arteries [25,31] or autonomic nervous system dysfunction [32] may be more closely associated with postural changes in blood pressure than is the initial supine blood pressure.

General issues

The use of the methods described here on other data sets will help to clarify the relationship between blood pressure and postural change in blood pressure. Although investigators cannot completely avoid intrinsic biological variability and human or instrument error, or both, in blood pressure measurement, steps can be taken to minimize these, leading to initial blood pressure values that are more stable. This can be done by standardizing the environment in which blood pressure readings are taken, in order to avoid the possible effects of 'cardiovascular reactivity' [33] (e.g. 'white-coat' hypertension). Biological variability can also be minimized by asking the subject to empty his or her bladder and to sit quietly in a quiet room for a few minutes before the measurement. Equally important is the use of well-trained observers and accurate equipment (including sphygmomanometers and properly sized blood pressure cuffs), as well as sophisticated quality control measures to test the reliability [34]. We would certainly recommend that future studies on postural changes in blood pressure include methods to enable the investigators to generate an estimate of within-person variability of the initial blood pressure (and to report that estimate) and to use Blomqvist's correction. This appears to have been done in at least one postural blood pressure study [35]; however, no estimates of the measurement error variance were provided by those authors. Estimates are easily carried out by incorporating multiple readings of the initial blood pressure of all subjects or a subset of them [36].

In conclusion, the biasing effects of within-person variability, as demonstrated in the present paper, are not specific to studies of postural change in blood pressure alone. Studies in the cardiovascular reactive field, in which a rise in blood pressure after a stimulus is often found, may be biased in the opposite direction. indeed, any investigation that relates change to initial value (e.g. change in serum cholesterol level to initial cholesterol level, weight gains to initial weight value, or tumor growth to initial tumor size and weight) will be similarly affected. Because within-person variability is always present, even precise measuring instruments are no guarantee that the bias can be avoided. However, this bias will be reduced when the within-person variability is small relative to the total variation.

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