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A prospective study of variability in systolic blood pressure and mortality in a rural Bangladeshi population cohort

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ABSTRACT

Objective. Limited studies suggest that blood pressure variability over time is a risk factor of long-term cardiovascular outcomes. However, most of these were in populations with pre-existing cardiovascular diseases (CVD) and studies in general population are lacking.

Methods. The study included 11,153 participants in a population-based, prospective cohort study in Araihazar, Bangladesh. Resting blood pressure was measured at baseline and every two years thereafter. Participants were followed up for an average of 6.5 years (2002–2009).

Results. Male gender, older age, baseline systolic blood pressure (SBP), and absence of betel leaf use were independently positively associated with greater SBP variability over time. There was a significant association between SBP variability and the risk of death from overall CVD, especially from major CVD events. The positive association with the risk of death from any cause and stroke in age- and sex-adjusted models was attenuated in fully-adjusted models. In addition, the hazard ratio (HR) of stroke mortality was greater for individuals with both high baseline and high SBP variability. Similar patterns of HRs were observed for all-cause and CVD mortalities.

Conclusion. In this rural Bangladeshi population, variability in SBP contributes to the risk of death from CVD and may further potentiate the increased mortality risk associated with high SBP.

Introduction

Cardiovascular diseases (CVD) are the primary cause of death globally, accounting for approximately 30% of all deaths with over 80% of all cases occurring in low- and middle-income countries (World Health Organization (WHO), 2011). High blood pressure (BP) is the most prominent risk factor associated with CVD (Kaplan and Victor, 2009) and is the leading cause of deaths globally with the most significant contribution by low- and middle-income countries (Lawes et al., 2008; WHO, 2009). CVD mortality is projected to increase by approximately 30% by the year 2030 in low- and middle-income countries, comparing to 2008, while no significant change is projected in high-income countries (WHO, 2008). Therefore, there is a need to investigate the risk factors associated with CVD mortality with a special attention to populations from developing countries.

Variability in BP has long been considered a risk factor for CVD mortality among hypertensive people (Parati et al., 1987; Pringle et al., 2003) and there is also evidence for a positive association with left ventricular mass index, an important intermediate risk factor for CVD, in the general population (Sega et al., 2002). In recent years, several publications reported that long-term BP variability, on the scale of months through years, may also have a clinical significance (Brunelli et al., 2008; Cuffe et al., 2006; Muntner et al., 2011; Rothwell et al., 2010). However, most of these studies (except for Muntner et al., 2011) have focused on susceptible populations but not on the general population.

In this study, using data from 11,153 apparently healthy individuals participating in an ongoing population-based cohort study in Araihazar, Bangladesh, we assessed the association of BP variability over time with the risk of death from any cause, overall CVD, major CVD events, stroke, and heart disease.

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Materials and methods

Study population

The study population consists of individuals participating in the ongoing population-based, prospective cohort study, Health Effects of Arsenic Longitudinal Study (HEALS), in Araihazar, Bangladesh established in 2000 to investigate the health effects of arsenic exposure from groundwater. Details of the study have been presented elsewhere (Ashan et al., 2006). A total of 11,746 apparently healthy individuals were recruited between October, 2000 and May, 2002 from a well-defined 25 km^2 area in Araihazar with a response rate of 97.5%. The key eligibility criteria were being married, being 18 years of age or older, and being a resident in the area for at least 5 years. Participants were followed up with in-home visits every two years, including a physical examination, blood pressure measurement, and structured interview. Diabetes at baseline was assessed using a questionnaire. The self-report status has been shown to be related to levels of HbA1c and urinary glucose level in our cohort (Chen et al., 2010). Both height and weight were measured three times at baseline and averaged. BMI was calculated as average weight in kilograms divided by average height in meters, squared (Pierce et al., 2010). The study procedures were approved by the Ethical Committee of the Bangladesh Medical Research Council and the Institutional Review Boards of Columbia University and The University of Chicago.

The present study included data from baseline, follow-up 1 (9/2002–5/2004), follow-up 2 (6/2004–8/2006), and follow-up 3 (1/2007/3/2009). Mean period between visits was 2.2 years. Blood pressure was measured at baseline, first, second and third follow-ups with the same methodology as in the baseline and the participation rate was 97.5, 96.9, 93.6, and 92.2% of the cohort participants at the baseline, respectively. We limited the analysis to individuals who had their BP recorded at baseline and who completed at least one additional BP measurement during follow-up and estimated variability as the standard deviation (SD) across the study visits. Health awareness and knowledge about the etiology of hypertension are very limited in rural Bangladesh, and only 2–3% individuals with high BP have any treatments in our cohort (Chen et al., 2006, 2007). We also excluded individuals with missing information regarding body mass index (BMI), betel leaf use, smoking status and education. The total number of individuals excluded was 593 (5% of total cohort). The distributions of other lifestyle and demographic variables among those excluded were very similar to the overall cohort (data not shown). The final study population included 11,153 subjects. Details of baseline characteristics of the entire cohort relative to the participants included in this analysis are presented in Appendix Table 1.

Blood pressure measurements

Briefly, blood pressure was measured by trained clinicians using an automatic sphygmomanometer (HEM 712-C; Omron Healthcare GmbH, Hamburg, Germany) (Chen et al., 2007, 2011; Pierce et al., 2010). This model has been validated to have 85% of readings falling within 5–10 mm Hg of the mercury standard. Measurements were taken with participants in a seated position after 5 min of rest, with the cuff around the upper right arm, in accordance with recommended guidelines. Measurements were done in the right arm at all visits. Two additional measurements were taken after for respondents found to have a SBP of ≥140 mm Hg and/or a DBP of ≥90 mm Hg at the first measurement, and the measurement with the lowest blood pressure was recorded. Blood pressure data from individuals who were taking medicines for hypertension at the time of measurement during follow-up were censored (<2%). The number of participants who had their BP measured more than once was 1407, 1125, 1506, and 1229 in follow-ups 1, 2, 3, and 4 respectively. Study participants were asked to show all medicines they were taking regularly, and the interviewers recorded generic names. A total of 818 participants were hypertensive at baseline and only 110 participants were taking antihypertensive medicines at the time of baseline interview.

Follow-up

The study outcome of interest was 1) all-cause mortality; 2) CVD mortality, defined as deaths due to disease of the circulatory system (ICD-10 I00–I99); 3) major CVD mortality (ICD-10 I20–I25 and I60–I69); 4) stroke mortality (I60–I69); and 5) heart disease mortality, which included deaths due to ischemic heart disease (I20–I25) and deaths due to other forms of heart disease (I30–I52). We *a priori* combine deaths due to ischemic heart disease and other forms of heart disease in a category for heart disease (Chen et al., 2011). Deaths were identified among cohort participants from baseline to March 18, 2009 (end of third follow-up). Details of the methods for the assessment of causes of deaths are described elsewhere (Argos et al., 2010; Chen et al., 2011; Pierce et al., 2010). Briefly, we adapted a validated verbal autopsy procedure, developed by the International Centre for Diarrhea Disease Research, Bangladesh (ICDDR, B) in collaboration with WHO. During the follow-up, upon receipt of a death reported by family or neighbors, a team of study physician and a trained social worker administered the verbal autopsy form to the next of kin. Medical records of the deceased were collected. Information on death certificates and biopsies was ascertained. Causes of deaths were coded by an outcome assessment committee blinded to participants' blood pressure records according to the WHO classification (WHO, 2007) and the International Classification of Diseases, 10th Revision (ICD-10). ICDDR, B has used this method to ascertain causes of deaths since 1971 (Baqui et al., 1998; Sohel et al., 2009) and documented an overall 95% specificity and up to 85% sensitivity for cardiovascular deaths (Howard and Rothwell, 2009). We observed 113, 120, and 174 deaths during the first, second, and the third follow-ups, respectively. The ascertainment for cause of death had a minimal loss, as previously described (Argos et al., 2010). We were unable to ascertain the relationship status of one informant. In three cases, we could not ascertain the causes of death.

Statistical analysis

For each subject, we estimated SD of SBP using all available longitudinal measurements of BP ascertained at baseline and during follow-up before death or end of the third biennial follow-up visit, whichever came earlier. We first conducted descriptive analyses to examine trends in baseline characteristics across tertiles of SD of SBP. In linear regression models, log-transformed SD of SBP was used as the dependent variable. We assessed the baseline characteristics first individually as the independent variables and then repeated the analysis including all the variables that were significantly related to the SD of SBP ($P < 0.05$) in the model.

We then used Cox proportional hazards models to estimate hazard ratios (HRs) for deaths due to any cause, CVD, major CVD, heart disease, and stroke per increase in SD of SBP. The assumption of proportional hazards was examined by testing the cross product terms between covariate variables and log function of survival time, and P values for all the terms were >0.10. We used SD of SBP (log transformed) as a continuous variable first in an unadjusted model. In separate models, we adjusted potential confounders including age, sex, baseline SBP, and betel leaf use; these were risk factors of all-cause and CVD mortalities that were also predictive of SD of SBP in our population, based on the results of the linear regression. Evidence from several epidemiologic studies has suggested that betel nut use, which is common in South Asians, is related to CVD (Guh et al., 2007; Heck et al., 2012; Lin et al., 2008). Analyses with additional adjustments for BMI and smoking status were conducted; however the effect estimates did not change appreciably and therefore the results are not shown. We also calculated HRs comparing each of the higher tertiles of SD of SBP with the lowest tertile as the referent group to describe the shape of the associations.

In addition, we estimated the joint effect of baseline SBP and the SD of longitudinal SBP. We estimated hazard ratios for all-cause, overall CVD, major CVD, heart disease, and stroke mortalities comparing joint status of baseline SBP and the SD of longitudinal SBP, with each variable dichotomized using the median in the population, using individuals with low baseline SBP and low SD of SBP as the reference group. Sensitivity analyses were conducted excluding individuals who were taking blood pressure medicine at baseline ($n = 105$). All analyses were conducted using R version 2.14.0.

Results

The average number of SBP measurements was 3.84 (range: 2–4). The characteristics of our study population were similar to those of the entire cohort (Appendix Table 1). The majority of study participants (88%) completed all four BP measurements, 8% exactly three and the remaining 2% completed only two. The mean SD of SBP did not differ by number of BP measurements available for analyses; the mean SD of SBP was 10.17, 10.62, and 10.27, for participants who completed 2, 3, and 4 BP measurements, respectively. Summary of SBP per visit according to sex and age group is presented in Appendix Table 2.