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Original article

The optimal cut-off of blood pressure related to left ventricular diastolic dysfunction and remodeling in Asian diabetic patients

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ABSTRACT

Background: Although a recent randomized trial found no difference between intensive and standard blood pressure (BP) control in patients with diabetes mellitus (DM), the debate over the optimal BP target continues. Thus, the present study investigated the effect of BP on the subclinical left ventricular (LV) function and structural changes in diabetic patients.
Method: A total of 2649 patients with DM who received echocardiography were enrolled in this study. Study population was stratified by three groups according to BP and presence of hypertension (normal, <130/80 mmHg; prehypertension, ≥130/80 mmHg without hypertension; hypertension, ≥140/90 mmHg or history of hypertension). The odds ratios (ORs) of impaired LV diastolic function and LV remodeling were analyzed using multivariate logistic regression analysis. The adjusted mean values of echocardiographic parameters related to LV diastolic function and remodeling were also evaluated.
Result: When normal group was set as reference, the adjusted ORs [95% confidential interval (CI)] for impaired LV diastolic function was 2.45 (95% CI 1.84–3.24) in prehypertension, 3.51 (95% CI 2.57–4.80) in hypertension group. Adjusted ORs for LV remodeling only showed significant result in hypertension group [1.82 (95% CI 1.23–2.69)]. The adjusted mean value of LV diastolic function and structure also demonstrated LV deterioration in prehypertension and hypertension groups.
Conclusion: Our study showed the adverse influence of prehypertension and hypertension on subclinical LV deterioration. This finding suggested the potential clinical benefits of intensive BP control (<130/80 mmHg) in patients with DM.

Introduction

The optimal target of blood pressure (BP) in individuals with diabetes mellitus (DM) has been a subject of controversy. The Seventh Report of the Joint National Committee (JNC 7) and several other guidelines recommended a BP target lower than 130/80 mmHg in patients with DM, based on the increased risk of cardiovascular disease (CVD), stroke, renal failure, and other complications [1–3]. However, the revised BP target in individuals with DM is lower than 140/90 mmHg in JNC 8 and American Diabetes Association (ADA) 2016 guidelines [4,5]. Although previous epidemiological studies demonstrated mildly increased BP is associated with cardiovascular (CV) events and mortality [6], clinical trials and meta-analyses found there was no significant different between intensive BP targets (<130/80 mmHg) and standard BP target (<140/90 mmHg) [7–9].

The result of Action to Control Cardiovascular Risk in Diabetes (ACCORD) BP trial (ACCORD BP) questioned the clinical benefit of intensive BP control [9]. Additionally, recent meta-analysis showed evidence did not support intensive BP control in patients with DM [7]. However, most previous studies were conducted in the USA and Europe, and there is a possibility that other ethnic groups with DM had different optimal BP targets [10]. Furthermore, in a meta-analysis of randomized trials, it was suggested that systolic BP

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treatment goal of 130–135 mmHg was acceptable in individuals with DM and impaired glucose tolerance [11].

Left ventricular (LV) diastolic dysfunction and structural change is regarded as a preclinical form of heart failure that carries a substantial risk of subsequent heart failure and reduces survival even in asymptomatic condition [12,13]. Previous studies reported that subclinical LV dysfunction and structural changes are associated with increased risk of CVD and CV mortality [14–16]. However, the effect of elevated BP on subclinical LV changes in individuals with DM remains elusive. Furthermore, there is no epidemiology study to investigate the optimal cut-off of BP related to increased risk of LV functional and structural changes in Asians with DM. Thus, using data from a cohort with measurements of echocardiography and clinical parameters, we assessed LV diastolic dysfunction and geometry change according to BP level and the presence of hypertension in individuals with DM.

Methods

Study design and study population

A cross-sectional study was conducted to investigate LV diastolic dysfunction and structural changes in a Korean diabetic population. Study participants consisted of Korean men and women undergoing a medical health check-up program at the Health Promotion Center of Kangbuk Samsung Hospital, Sungkyunkwan University, Seoul, Korea. The purpose of the medical health check-up program is to promote the health of employees and to enhance early detection of existing diseases. All employees participated in either annual or biennial health check-ups, as required by Korea's Industrial Safety and Health Law. Most of the study population was employees of various companies or their family members from all around country. The costs of the medical examinations are largely paid by their employers.

Amongst patients in the original study, 55,214 men and women had received at least one echocardiogram including tissue Doppler echocardiography (TDI) between January 2013 and December 2014. We found 2941 participants had DM. 292 were excluded for various reasons including history of serious medical condition [e.g. cancer, history of myocardial infarction, chronic renal failure (glomerular filtration rate – GFR – $<$60 mL/min/1.73 m^2) or systolic LV dysfunction (ejection fraction – EF – $\leq$50%]. The total number of eligible participants was 2649. Ethics approvals for the study protocol and analysis of the data were obtained from the institutional review board of Kangbuk Samsung Hospital. The informed consent requirement was waived by the Institutional Review Board because the researchers only retrospectively accessed a de-identified database for analytical purposes.

Clinical and laboratory measurements

Study data included a medical history, a physical examination, information provided by a self-administered questionnaire, anthropometric measurements, and laboratory measurements. All study participants were asked to respond to a health-related behavior questionnaire, which included the topics of alcohol consumption, smoking, and exercise. The questions about alcohol intake included the frequency of alcohol consumption on a weekly basis and the typical amount that was consumed on a daily basis. We considered persons reporting that they smoked at the time of the questionnaire to be current smokers. The degree of physical activity was evaluated by the Korean-validated version of the International Physical Activity Questionnaire (IPAQ) [17]. The body mass index (BMI) was calculated by dividing weight (kilograms) by square of height ($meters^2$).

Diabetes mellitus was defined as fasting serum glucose level of at least 126 mg/dL, or serum HbA1c level of at least 6.5%, and participant have ever been diagnosed with diabetes, or the current use of blood glucose-lowering agents [5]. Although we did not ask the type of diabetes, previous studies have reported that the majority of Korean adult patients with diabetes had type 2 DM (T2DM) [18,19]. Therefore, most of our study population consisted of patients with T2DM. Hypertension was defined as either the current use of antihypertensive medication and participant have ever been diagnosed with hypertension or as having a measured blood pressure $\geq$140/90 mmHg at initial examinations. Trained nurses obtained sitting BP levels using automatic BP equipment (53000-E2, Welch Allyn, Skaneateles Falls, NY, USA) three times after a 5-minute rest. Final BP levels were obtained as average of second and third BP measurements. All participants were divided into one of three categories according to the presence of hypertension and BP; normal BP group (systolic BP $<$130 mmHg and diastolic BP $<$80 mmHg), prehypertension group (systolic BP $\geq$130 mmHg or diastolic BP $\geq$80 mmHg, and without hypertension), and hypertension group.

Blood samples were collected after more than 12 hours of fasting and were drawn from an antecubital vein. Insulin resistance was calculated by homeostasis model assessment-insulin resistance (HOMA-IR) and obtained using the following formula: HOMA-IR = fasting serum insulin (μU/mL) $\times$ fasting serum glucose (mg/dl)/405.

The fasting serum glucose was measured using the hexokinase method. Total cholesterol and triglyceride were measured using enzymatic colorimetric tests, low-density lipoprotein (LDL) cholesterol was measured using the homogeneous enzymatic colorimetric test, and high-density lipoprotein (HDL) cholesterol was measured using the selective inhibition method (Advia 1650 Autoanalyzer, Bayer Diagnostics; Leverkusen, Germany).

Fasting insulin concentration was measured by immunoradiometric assay (Biosource, Nivelles, Belgium), and hemoglobin A1c (Hba1c) was measured using an immunoturbidimetric assay with a Cobra Integra 800 automatic analyzer (Roche Diagnostics, Basel, Switzerland). Serum creatinine and uric acid levels were determined using the Jaffe reaction method (Advia 1650 kit, Bayer Corp., Pittsburgh, PA, USA) and the Uricase EMST method, respectively.

Echocardiographic measurements

Two-dimensional transthoracic echocardiography with a 4-MHz, sector-type transducer probe was performed on each individual (Vivid 7; GE, Milwaukee, WI, USA and E9; GE). Transthoracic echocardiography was performed by a trained registered sonographer following a standardized protocol. Images from standard parasternal long- and short-axis views were digitally stored and reviewed. In end diastole, the septum wall thickness (SWTd), posterior LV wall thickness (PWTd), and the diameter of the left ventricle (LVIDd) were routinely measured. The diameter of the left ventricle in systolic (LVIDs) also measured. LV mass was calculated with following formula: $\text{LV mass} = 0.8 \times \{1.04 \times [(\text{LVIDd} + \text{PWTd} + \text{SWTd})^3 - (\text{LVIDd})^3]\} + 0.6\text{ g}$ [20], and indexed for body surface area (BSA). LV end systolic volume (LVESV) and LV end diastolic volume (LVEDV) were calculated by the following formula: $\text{LVESV} = 7.0/(2.4 + \text{LVIDs}) \times \text{LVIDs}^3$ and $\text{LVEDV} = 7.0/(2.4 + \text{LVIDd}) \times \text{LVIDd}^3$. The ejection fraction (EF) is calculated from LVEDV and LVESV estimate, using the following formula: $\text{EF} = (\text{LVEDV} - \text{LVESV})/\text{LVEDV}$. The presence of LV remodeling is defined as relative wall thickness (RWT) $>$0.42 and increased LV mass index (LVMI) ($\geq$115 in male and $\geq$95 in female) [20].

Deceleration time (DT) was measured by pulsed wave (PW) Doppler in the apical four-chamber view. Peak velocities of the early (E) and late (A) phases of the mitral inflow were also