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Research Article

Intrafamilial aggregation and heritability of tissue Doppler indexes of left ventricular diastolic function in a group of African descent

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Abstract

Although several indexes of left ventricular (LV) diastolic function show heritability, the genetic influence on the tissue Doppler index, E/e′ (early transmitral velocity/velocity of myocardial tissue lengthening), an index of LV filling pressures in those of black African descent is currently unknown. Furthermore, whether any genetic influences on E/e′ are through an impact of LV remodeling or aortic function is unknown. Intrafamilial aggregation and heritability (SAGE software) of E/e′ (echocardiography) were assessed in 129 nuclear families (29 spouse pairs, 216 parent–child pairs, and 113 sibling–sibling pairs) from an urban developing community of black Africans, independent of LV mass index (LVMI), LV relative wall thickness (RWT), central aortic systolic pressure (SBPc), and backward wave pressures (Pb) (applanation tonometry, SphygmoCor software). Independent of confounders including LVMI and RWT, E/e′ was correlated in parent–child ($r = 0.23$; $P < .001$) and sibling–sibling ($r = 0.29$; $P < .005$), but not in spouse ($r = 0.13$; $P = .51$) pairs. The relationships between parent–child ($r = 0.22$; $P < .001$) and sibling–sibling ($r = 0.29$; $P < .005$) pairs persisted with adjustments for SBPc. The relationships between parent–child ($r = 0.22$; $P < .001$) and sibling–sibling ($r = 0.26$; $P < .01$) pairs also persisted with adjustments for Pb. Independent of confounders including LVMI and RWT, E/e′ showed significant heritability ($h^2 \pm$ standard error of the mean [SEM] $= 0.51 \pm 0.11$; $P < .0001$) which similarly persisted with adjustments for SBPc ($h^2 \pm \text{SEM} = 0.50 \pm 0.11$; $P < .0001$) and Pb ($h^2 \pm \text{SEM} = 0.49 \pm 0.11$; $P < .0001$). In conclusion, in a group of African ancestry, independent of LV remodeling and aortic function, E/e′ shows significant intrafamilial aggregation and robust heritability. Hence, genetic factors may play an important role in determining moderate-to-severe LV diastolic dysfunction independent of cardiac remodeling or aortic function in groups of black African ancestry. J Am Soc Hypertens 2016;10(6):517–526.

Keywords: Aortic function; inheritance; transmitral velocity; tissue Doppler indexes.

Conflict of interest: None.

Vernice R. Peterson, Gavin R. Norton, and Angela J. Woodiwiss contributed equally to this work.

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Introduction

The prevalence of heart failure with a preserved ejection fraction (EF) may soon exceed that of a reduced EF.[1] The outcomes of heart failure with a preserved EF are as poor as in heart failure with a reduced EF,[2–4] yet there is presently no treatment with proven benefit for heart failure with a preserved EF.[1,5,6] Understanding the pathophysiological mechanisms responsible for heart failure with a preserved EF may reveal potential therapeutic targets. Cardiac diastolic dysfunction (DD) is central to the pathophysiology and outcomes of heart failure with a preserved EF.[7–11] However, the factors that determine cardiac diastolic function have not been completely elucidated.

Several studies have demonstrated heritability or intrafamilial aggregation of various aspects of left ventricular (LV) diastolic function identified from transmitral blood flow velocity measurements.[12–18] However, contemporary evaluation of LV DD also includes E/velocity of myocardial tissue lengthening at the mitral annulus (Ea or e′) (E/e′), an index of filling pressures used to identify moderate-to-severe DD and which is independently associated with the development of heart failure with a preserved EF.[19,20] The genetic influence on E/e′ across ethnic groups is nevertheless unclear. Although a Korean study showed significant heritability for E/e′,[17] a study conducted in Europeans failed to do so,[16] but subsequent analysis in an expanded data set showed significant heritability.[18] Whether E/e′ is inherited in groups of African ancestry and the extent to which this occurs is unknown. Moreover, whether significant heritability of E/e′ occurs independent of LV remodeling, which is also inherited and a well-recognized determinant of DD, or of aortic function, which is similarly inherited and a strong determinant of DD,[21–24] is unknown. Hence, in the present study, we aimed to assess whether intrafamilial aggregation and heritability of E/e′ occurs independent of LV remodeling and aortic function in a community of African ancestry.

Methods

Study Participants

The present study was conducted according to the principles outlined in the Helsinki declaration. The Committee for Research on Human Subjects of the University of the Witwatersrand approved the protocol (approval number: M02-04-72 and renewed as M07-04-69 and M12-04-108). Participants gave informed, written consent. The present study design has previously been described.[25–29] Briefly, families of black African descent (Nguni and Sotho chiefdoms) with siblings older than 16 years were randomly recruited (based on population census figures from 2001) from the South West Township (SOWETO) of Johannesburg, South Africa. Eight hundred twenty-nine participants (91% consent rate) consented to an echocardiographic procedure and had no evidence of significant valve abnormalities assessed using two-dimensional and color Doppler imaging. None of the participants had previously had a myocardial infarction (only three had a history of ischemic heart disease), and there were no cases of atrial fibrillation. High-quality echocardiograms with complete familial pairing could be obtained in 694 participants, and in a substudy, 442 participants from 129 nuclear families with 12 families including three generations with complete familial pairing had myocardial tissue Doppler imaging (TDI) (see Figure 1 for derivation of the study sample).

Clinical, Demographic, Anthropometric, and Laboratory Assessments

A standardized questionnaire was administered to obtain demographic and clinical data.[25–29] Regular alcohol consumption was defined as at least five glasses of beer per week or 1 bottle of wine per week or ½ bottle of spirits per week. Height and weight were measured using standard approaches, and participants were identified as being overweight if their body mass index (BMI) was $\geq$25 kg/m^2 and obese if their BMI was $\geq$30 kg/m^2. Standard laboratory blood tests of renal function, liver function, blood glucose, hematological parameters, and percentage glycated hemoglobin (HbA_{1C}) were performed. Diabetes mellitus or abnormal blood glucose control was defined as the use of insulin or oral hypoglycemic agents or an HbA_{1C} value greater than 6.1%. Menopause was confirmed with measurements of follicle-stimulating hormone concentrations. Participants' blood groups (ABO and Rhesus) were evaluated to confirm Mendelian segregation. Mendelian inconsistencies were identified if blood groups of family

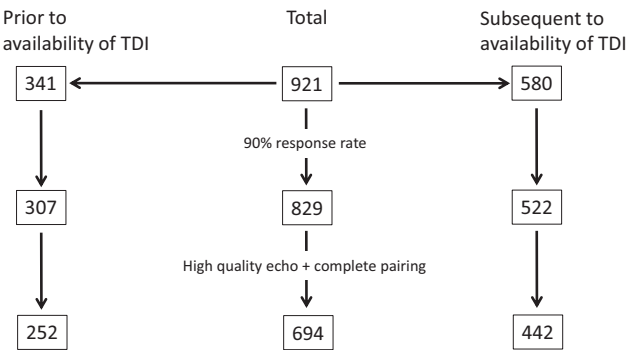

Figure 1. Flow chart summarizing the derivation of the study sample. Complete pairing refers to sample with at least either two parents and one sibling or one parent and two siblings. Three hundred forty-one participants were approached to participate in the study before the availability of tissue Doppler imaging (TDI), and 580 participants were approached to participate in the study after the availability of TDI. Echo, echocardiography.