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Original Article

# Marked intrafamilial aggregation and heritability of aortic flow in a community with prevalent volume-dependent hypertension in Africa

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**Aims:** Although peak aortic flow ($Q$) is now recognized as a major determinant of hypertension in Africa, current therapy has no proven ability to target this change. The mechanisms of this effect, therefore, require elucidation. We compared the intrafamilial aggregation and heritability of $Q$ to that of the vascular determinants of pulse pressure (PP) and SBP in Africa.

**Methods:** The intrafamilial aggregation and heritability of $Q$ and aortic characteristic impedance ($Z_c$) or total arterial compliance (TAC) was determined in 669 participants of 194 families (69 father–mother, 385 parent–child, 157 sibling–sibling pairs) in a community in Africa with prevalent flow-dependent primary hypertension. Haemodynamics were determined from velocity and diameter measurements in the outflow tract (echocardiography) and central arterial pressures.

**Results:** No mother–father correlations were noted for either $Q$ or $Z_c$. However, with adjustments for confounders, parent–child ($P < 0.0001$) and sibling–sibling ($P < 0.0001$) correlations were noted for $Q$. Parent–child and/or sibling–sibling correlations were also noted for $Z_c$ or TAC but were weaker for $Z_c$ and mother–father correlations were noted for TAC. Moreover, $Q$ showed markedly stronger multivariate adjusted heritability estimates ($h^2 = 0.82 \pm 0.07$, $P < 0.0001$) than $Z_c$ ($h^2 = 0.44 \pm 0.10$, $P < 0.0001$)($P < 0.005$ for comparisons) and TAC ($h^2 = 0.47 \pm 0.08$, $P < 0.0001$)($P < 0.005$ for comparisons). Importantly, the heritability of $Q$ was also greater than that for PP ($h^2 = 0.12 \pm 0.09$, $P = 0.11$) ($P < 0.0001$ for comparisons), or SBP ($h^2 = 0.13 \pm 0.10$, $P = 0.08$) ($P < 0.0001$ for comparisons).

**Conclusion:** Of the haemodynamic determinants of SBP, peak aortic flow is the most strongly inherited in Africa. Peak aortic flow, therefore, represents an important target for identifying novel therapeutic approaches to controlling SBP in Africa.

**Keywords:** Africa, aortic flow, heritability, impedance to flow, primary hypertension

**Abbreviations:** AoD, aortic root diameter; h2, heritability; HbA1c, percentage glycated haemoglobin; MAP, mean arterial pressure; PP, pulse pressure; PPb, brachial pulse pressure; PPc, central aortic pulse pressure; $Q$, peak aortic flow; SBPb, brachial SBP; SBPc, central aortic SBP; SVR, systemic vascular resistance; TAC, total arterial compliance; $Z_c$, aortic characteristic impedance

## INTRODUCTION

Groups of African descent are well recognized as having a higher prevalence of hypertension than other ethnic groups, and are poorly responsive to several classes of antihypertensive agents [1–3]. This effect may in-part be mediated by the development of a low-renin form of hypertension determined largely by renal effects [2–5]. Although a dominant renal mechanism has been postulated to explain an increased blood pressure (BP) in this ethnic group [4,5], it is only more recently that in this group, a striking age-related increase in systemic blood flow [6,7], strongly associated with alterations in renal tubular function [8], has been identified as a major determinant of increases in BP. Importantly, the impact of increases in aortic blood flow ($Q$) on pulse pressure (PP) and hence SBP in this ethnic group is at least as strong as that of aortic stiffness-induced increases in characteristic impedance ($Z_c$) (resistance to flow in pulsatile system) [6], the major determinant of PP and hence SBP in alternative ethnic groups [9]. In this regard, variations in brachial PP are largely determined by the pressure generated by the

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product of aortic $Q$ and $Z_c$. Furthermore, the impact of systemic flow on BP is far greater than that of systemic vascular resistance (SVR) [6]. Thus, in contrast, to several populations around the world, in groups of African ancestry living in Africa, increases in systemic flow are as important as the vascular determinants of BP in the pathogenesis of hypertension [6,7]. Although renal mechanisms explain the marked increases in systemic flow but not alternative haemodynamic determinants of BP [8], current antihypertensive therapy, including diuretic therapy has no proven ability to produce sustained decreases in systemic blood flow. Thus, antihypertensive therapy is unlikely to target a dominant haemodynamic mechanism responsible for hypertension in Africa. The mechanism of this renal-related increase in systemic flow in Africa [6–9], therefore, requires identification.

Originating from hot equatorial countries [10], groups of African descent are thought to have evolved to develop hypertension frequently attributed to a genetically predetermined alteration in renal tubular $Na^+$ reabsorption that enhances fluid retention [11,12]. Although possibly improving the chances of survival in fluid losing states, together with an age-related loss of nephrons, this effect is now recognized as accounting for an enhanced systemic flow in primary hypertension in Africa [8]. Thus, genetic as opposed to environmental factors may play a critical role in mediating the dominant haemodynamic determinant of hypertension in Africa, that is renal-related increases in systemic flow [8]. Genetic studies may, therefore, be an important approach to unravelling the mechanisms of hypertension in Africa. In this regard, these studies may identify targets for the development of novel therapeutic approaches that modify renal-related increases in systemic flow in Africa [8]. If a genetic predisposition to increases in flow does occur in populations of African ancestry, this would be in distinct contrast to the lack of heritability of systemic flow noted in alternative populations [13]. However, the extent to which increases in systemic flow as compared with vascular mechanisms responsible for increases in BP are inherited in African populations is unknown. As the impact of increases in systemic flow in Africa is on hypertension associated with increases in SBP rather than on isolated increases in DBP [7], in the present study, we therefore, aimed to compare the intrafamilial aggregation and heritability of peak aortic flow ($Q$) to that of aortic characteristic impedance to flow ($Z_c$), and total arterial compliance (TAC), the dominant vascular factors that determine PP and hence SBP in Africa [6,7].

# METHODS

## Study group

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, M12-04-108 and M17-04-01). Participants gave informed, written consent. The present study design has previously been described [14–18]. Briefly, families of black African descent (Nguni and Sotho chiefdoms) with siblings older than 16 years of age were randomly recruited from the South West Township (SOWETO) of Johannesburg, South Africa. An age threshold of 16 years was employed to avoid the confounding effects of the rapid age-related increase in BP that occurs in younger individuals [19]. A total of 669 participants from 194 nuclear families with 14 families including three generations with complete familial pairing and with all haemodynamic measurements available were included in the present analysis.

## Clinical, demographic, anthropometric and laboratory information

A questionnaire was administered to obtain demographic and clinical data [16]. Height and weight were measured using standard approaches and participants were considered to be overweight if their BMI was at least 25 kg/m$^2$ and obese if their BMI was at least 30 kg/m$^2$. Laboratory blood tests of renal function, liver function, blood glucose, lipid profiles, haematological parameters and percentage glycated haemoglobin (HbA1c) were performed. Serum creatinine concentrations were measured using the Advia Chemistry systems (Siemens) with calibration traceable to isotope dilution mass spectrometry (IDMS). The four-variable CKD-EPI equation was employed to estimate GFR (eGFR). Participant's blood groups (ABO and Rhesus) were evaluated to confirm Mendelian segregation. Mendelian inconsistencies were identified if blood groups of family members were incompatible with relationships between family members representing first, second, or third generations. Diabetes mellitus was defined as the use of insulin or oral glucose-lowering agents or an HbA1c value greater than 6.5%. High-quality office brachial BP measurements were obtained in the seated position and after 5 min of rest, by a trained nurse-technician using a standard mercury sphygmomanometer [16,18] according to guidelines. The mean of five measurements obtained at least 30 s apart was taken as office BP. Hypertension was defined as a mean office BP at least 140 mmHg systolic or at least 90 mmHg diastolic or the use of antihypertensive medication.

## Haemodynamic assessments

Haemodynamic parameters were determined from noninvasive central arterial pressure measurements derived from peripheral pulse wave analysis and the assessment of aortic velocity and diameter in the outflow tract [6–8]. After participants had rested for 15 min in the supine position, arterial waveforms at the radial (dominant arm) pulse were recorded by applanation tonometry during an 8 s period using a high-fidelity SPC-301 micromanometer (Millar Instrument, Inc., Houston, Texas, USA) interfaced with a computer employing SphygmoCor, version 9.0 software (AtCor Medical Pty. Ltd., West Ryde, New South Wales, Australia). The pulse wave was calibrated by manual measurement (auscultation) of brachial SBP and DBP taken immediately before the recordings. The peripheral pressure waveform was converted into a central aortic waveform using a validated generalized transfer function incorporated in SphygmoCor software. Recordings where the systolic or



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diastolic variability of consecutive waveforms exceeded 5% or the amplitude of the pulse wave signal was less than 80 mV, were discarded.

Immediately after central arterial pressure waveforms were obtained, aortic velocity and diameter measurements were acquired by an experienced observer (A.J.W.) in participants in the left lateral decubitus position using an Acuson SC2000 Diagnostic ultrasound system (Siemens Medical Solutions, USA, Inc., Malvern, Pennsylvania, USA). Velocity waveforms were obtained in the five-chamber view (Figure S1, http://links.lww.com/HJH/B811). High-quality velocity assessments were identified as those with a smooth velocity waveform with a dense leading (outer) edge and a clear maximum velocity. Aortic diameter measurements were obtained just proximal to the aortic leaflets in the long-axis parasternal view (Figure S1, http://links.lww.com/HJH/B811). The largest diameter recorded in early systole was used to construct the aortic flow waveform. Aortic flow waveforms were generated from aortic velocity and diameter measurements. Taking care to avoid any overshoot of the image, the leading (outer) edge or the most dense, or brightest portion of the spectral image of the velocity waveform was outlined using graphics software and using aortic diameter measurements employed to construct a flow waveform where flow ($Q$) = velocity × aortic root cross-sectional area calculated from diameter assessments (Figure S1, http://links.lww.com/HJH/B811). Stroke volume (SV) was calculated from the product of the velocity–time integral and aortic root cross-sectional area.

In line with the recommendation that either time or frequency domains may be employed for the assessment of characteristic impedance ($Z_c$) [20], $Z_c$ was determined in the time domain using approaches previously described by groups from both Framingham and Ghent [9,21] and validated against invasive pressure measurements [22]. The volume flow waveform was paired with central arterial pressure waveforms by aligning the foot ($t_0$) of the respective signal averaged waveforms (Figure S1, http://links.lww.com/HJH/B811). The point at which flow achieves 95% of its peak ($t_{Q95}$) was identified (Figure S1, http://links.lww.com/HJH/B811). The corresponding pressure change between $t_0$ and $t_{Q95}$ was determined. Characteristic impedance was calculated as the ratio of change in pressure to change in flow in the window $t_0$ to $t_{95}$ (Figure S1, http://links.lww.com/HJH/B811). As the accuracy of this approach is determined by the similarity of ejection durations in sequential pressure and then flow assessments, we first determined the differences in ejection duration observed during pressure (foot of the wave to the dicrotic notch) versus flow (duration of velocity) measurements. In this regard, Bland–Altman analysis showed a 2.8 ms difference over an average 320.4 ms period, representing a 0.73% difference in ejection duration. TAC was calculated as stroke volume/aortic PP.

## Data analysis

Database management and statistical analyses were performed with SAS software, version 9.4 (The SAS Institute, Cary, North Carolina, USA). Continuous variables are expressed as mean (±SD). Dichotomous variables are expressed as percentages. To evaluate differences in demographic, clinical and anthropometric measurements between parents and offspring, means and proportions were compared using Student's unpaired $t$ tests and the $\chi^2$-statistic, respectively. For intrafamilial aggregation analysis, intrafamilial correlations were determined from the PROC GENMOD procedure of the SAS package to determine concordance between family members. Unadjusted and multivariate adjusted correlation coefficients were determined in 69 father–mother pairs, 385 pa-rent-child pairs and 157 sibling–sibling pairs. Heritability ($h^2$) of haemodynamic values was estimated using Statistical Analysis for Genetic Epidemiology (S.A.G.E) software (version 6.4.2) (Department of Epidemiology and Statistics, Case Western Reserve, University of Cleveland, Ohio, USA) using the Marker-Trait Associations in Pedigree Data (ASSOC) program. The ASSOC program estimates by maximum likelihood, assuming a generalization of multivariate normality, familial variance components and hence heritability, assuming correlation structures [23] and regression models [24] previously described. The ASSOC program uses a linear regression model, in which the residual variance is partitioned into the sum of an additive polygenic component and a participant-specific random component. Heritability is the polygenic component divided by the total variance. For the heritability estimates, adjustments were made for potential confounders. To ensure that antihypertensive therapy did not influence the results of the study, sensitivity analysis was performed in only those participants not receiving BP-lowering therapy. For both intrafamilial aggregation and heritability, analysis, adjustments were for mean arterial pressure (MAP), age, age$^2$, sex, heart rate, BMI, regular smoking, regular alcohol intake, DM, total/HDL cholesterol, eGFR and treatment for hypertension. In addition, to identify the heritability and intrafamilial aggregation of $Z_c$ beyond aortic root diameter, further adjustments were for aortic root diameter. In this regard, beyond aortic root diameter, proximal aortic $Z_c$ is determined by stiffness.

# RESULTS

## Characteristics of participants

Table 1 summarizes the characteristics of the parents and their offspring. The number of offspring (second and third generations) per family ($n$ = 194) amounted to one in 89 families, two in 80 families, three in 19 families and more than three in six families. No cases of Mendelian inconsistency were noted. More women than men participated in the study. Importantly, a high proportion of participants were hypertensive, a significant proportion had uncontrolled hypertension, and only 25% of participants were receiving antihypertensive medication. None of the participants were receiving lipid-lowering therapy. Through age-related effects, PP, SBP and the determinants thereof were higher in parents than in offspring. The differences noted between parents and offspring were similar when excluding those 18 participants who were both offspring of first generation participants and parents of third generation participants.



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**TABLE 1. Characteristics of parents and offspring of the study sample**

| Characteristic | Parents ($n = 331$) | Offspring ($n = 356$) |
|---|---|---|
| Sex (% females) | 67.7 | 67.9 |
| Age (years) | 58.8 ± 14.3 | 33.2 ± 11.6* |
| BMI (kg/m$^2$) | 31.7 ± 7.4 | 27.3 ± 7.2* |
| % Regular smoking | 12.2 | 15.9 |
| % Regular alcohol intake | 18.6 | 20.3 |
| % With DM or HbA1c >6.5% | 19.8 | 5.1* |
| % With hypertension | 68.1 | 23.5* |
| % Treated for hypertension | 42.6 | 7.6* |
| Total/HDL cholesterol | 3.85 ± 1.22 | 3.20 ± 0.91 |
| Estimated GFR (ml/min per 1.73 m$^2$) | 84.0 ± 20.5 | 107.6 ± 16.8 |
| Haemodynamics | | |
| Brachial SBP/DBP (mmHg) | 139 ± 24/86 ± 13 | 119 ± 18*/79 ± 11* |
| Mean arterial pressure (MAP) (mmHg) | 105 ± 16 | 94 ± 13* |
| Brachial pulse pressure (PPb) (mmHg) | 52 ± 17 | 40 ± 13* |
| Central aortic SBP (SBPc) (mmHg) | 130 ± 24 | 110 ± 18* |
| Central aortic PP (PPc) (mmHg) | 44 ± 16 | 31 ± 12* |
| Aortic velocity (cm/s) | 118.3 ± 37.1 | 110.0 ± 31.1 |
| Aortic velocity-time integral (cm) | 19.4 ± 7.3 | 17.6 ± 6.2 |
| Aortic root diameter (cm) | 2.66 ± 0.46 | 2.45 ± 0.40* |
| Peak aortic flow ($Q$) (ml/s) | 393 ± 197 | 318 ± 141* |
| Stroke volume (ml/beat) | 97.3 ± 30.8 | 78.9 ± 32.9 |
| Characteristic impedance ($Z_c$) (dynes s/cm$^5$) | 89 ± 45 | 79 ± 33* |
| Total arterial compliance (TAC) (mls/mmHg) | 2.28 ± 1.08 | 2.56 ± 1.16* |
| Heart rate (beats/min) | 68 ± 13 | 66 ± 12 |

As 18 of the offspring are also parents of third-generation offspring, they are included in both parent and offspring columns. Data are shown as mean ± SD or proportions.
*$P$ less than 0.001 versus offspring.

## Intrafamilial aggregation

In unadjusted models, or age and sex-adjusted models SBP and PP showed weak correlations between parents and children, and between fathers and mothers (Fig. 1). Either no correlation or a weak correlation was noted between siblings (Fig. 1). In unadjusted models or age-adjusted and sex-adjusted models, relationships between SBP or PP between parents were in some instances stronger than between parents and children or between siblings (Fig. 1). With adjustments for age, age$^2$, sex and additional confounders with or without MAP included as an adjustor, no significant correlations were noted for PP or SBP between family members (Fig. 1).

In contrast to the weak or inconsistent correlations noted between family members for PP or SBP, in unadjusted models, or with adjustments for age, age$^2$ and sex, or age, age$^2$, sex and additional confounders, $Q$ showed strong correlations between parents and children, and between siblings and no correlations between fathers and mothers (Fig. 2). Similarly, the velocity–time integral and peak aortic velocity showed strong correlations between parents and children ($P < 0.0001$), and between siblings ($P < 0.0005$) and no correlations between fathers and mothers ($P = 0.12$ and $P = 0.46$, respectively). Although SV showed correlations between fathers and mothers ($P < 0.001$), the strong correlations between parents and children ($P < 0.0001$) and between siblings ($P < 0.0005$) were significantly greater ($P = 0.013$ and $P = 0.003$, respectively, for comparisons with correlations between fathers and mothers) than the correlations for fathers and mothers. In unadjusted or adjusted models including models with MAP; $Z_c$ and TAC showed more modest correlations between parents and children but no correlations were noted between fathers and mothers for $Z_c$ (Fig. 2). Additionally, in unadjusted or adjusted models TAC but not $Z_c$ showed correlations between siblings (Fig. 2). In line with the role of proximal aortic stiffness as a genetic determinant of $Z_c$, further adjustments for aortic root diameter failed to modify the intrafamilial correlations for $Z_c$ (Fig. 2).

## Heritability estimates

Consistent with the weak intrafamilial correlations noted for PP and SBP, with adjustments for age, age$^2$ and sex, or age, age$^2$, sex, MAP and additional confounders, with the exception of SBP in untreated participants, SBP and PP showed no significant heritability (Table 2 and Fig. 3). In contrast, in keeping with the strong intrafamilial correlations, with adjustments for age, age$^2$ and sex, or age, age$^2$, sex and additional confounders, $Q$ showed strong heritability (Table 3, Fig. 3). Similarly, with adjustments for age, age$^2$, sex and additional confounders, the velocity–time integral ($h^2 \pm \text{SEM} = 0.71 \pm 0.08$, $P < 0.0001$), peak aortic velocity ($h^2 \pm \text{SEM} = 0.62 \pm 0.08$, $P < 0.0001$) and SV ($h^2 \pm \text{SEM} = 0.69 \pm 0.08$, $P < 0.0001$) showed strong heritability. Also consistent with the significant intrafamilial correlations, with adjustments for age, age$^2$ and sex, or age, age$^2$, sex, MAP and additional confounders, or age, age$^2$, sex, MAP and aortic root diameter (for $Z_c$), $Z_c$ and TAC showed heritability (Table 3 and Fig. 3). Importantly, however, the heritability estimates of $Q$ were significantly greater than those for $Z_c$ or TAC and markedly greater than those for PP or SBP (Fig. 3), In addition, the heritability estimates of $Z_c$ and TAC were stronger than the heritability estimates for PP or SBP (Fig. 3).

# DISCUSSION

The main findings of the present study are as follows: In a large ($n = 669$) community sample in Africa, recently demonstrated to show a striking contribution of age-dependent, renal-related increases in systemic blood flow to PP and SBP in hypertension [6–8], we compared the intrafamilial aggregation and heritability of systemic flow to that of the vascular determinants of PP and hence SBP. In this regard, in-line with conventional physiological principles, and the 'Windkessel' model of the systemic circulation, PP in the brachial pulse is determined by the product of flow ($Q$) and the resistance to flow in a pulsatile system ($Z_c$) with an additional contribution from arterial compliance. We show that after adjustments for confounders, peak aortic flow ($Q$) showed marked intrafamilial aggregation and heritability, and these were substantially greater than the intrafamilial aggregation and heritability of the vascular determinants of PP and SBP, including $Z_c$ or TAC. Importantly, the haemodynamic determinants of PP and SBP ($Q$, $Z_c$ and TAC) considered separately, showed a far stronger degree of heritability than the pressures generated by their combined effects (PP or SBP per se).



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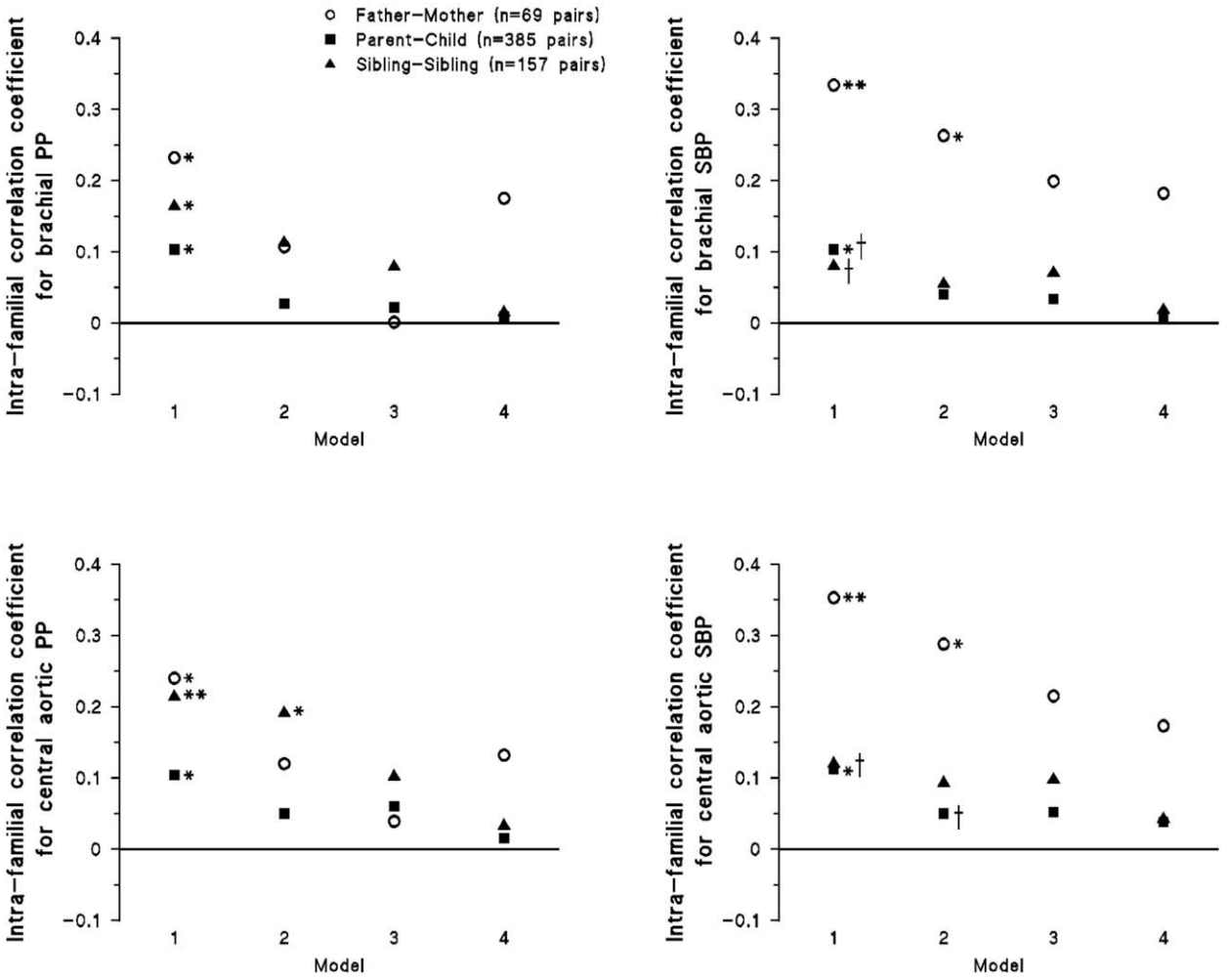



**FIGURE 1** Unadjusted (model 1) and multivariate adjusted (models 2–4) intrafamilial correlations (*r* values) of brachial and central aortic pulse pressure and SBP in a group of African ancestry. Adjustments are for age, age$^2$ and sex (model 2); age, age$^2$, sex and other confounders including BMI, heart rate, regular smoking, regular alcohol intake, treatment for hypertension, diabetes mellitus, total/HDL cholesterol concentrations and eGFR (model 3); or age, age$^2$, sex other confounders and MAP (model 4). $^*P$ less than 0.05, $^{**}P < 0.005$ for correlations. $^+P$ less than 0.05 for comparisons with father and mother correlations. HDL, high-density lipoprotein; MAP, mean arterial pressure.

Although a contribution of increases in systemic blood flow to hypertension has been demonstrated in several populations [25–28], relative to alternative haemodynamic factors (e.g. aortic stiffness), the effect of systemic flow on BP in many studies may not be as important. In contrast, the recent evidence for a marked contribution of age-related increases in systemic flow to hypertension in groups of African ancestry living in Africa [6,7] suggests a distinct pathophysiological mechanism driving hypertension in this ethnic group. Indeed, a strong interaction between age-related decreases in nephron number (as indexed by decreases in GFR) and increases in renal tubular $Na^+$ reabsorption clearly explain age-related increases in stroke volume and hence peak aortic *Q* [8]. Although all antihypertensives mediate their beneficial effects, in-part through renal mechanisms, there is no proven evidence that current therapy (including diuretics) are able to target increases in systemic blood flow associated with hypertension [8]. Thus, identifying the mechanisms responsible for the increases in blood flow in this group is essential. Consistent with increases in systemic blood flow resulting from an evolutionary adaptation in groups originating from hot, arid, equatorial countries [11], the present study demonstrates that in direct contrast to the lack of heritability of systemic flow in a European population [13], systemic flow shows a strong degree of inheritance in Africa. Importantly, in this same community, the heritability was significantly stronger than several vascular factors that influence PP and SBP (proximal aortic characteristic impedance or total arterial compliance). In contrast, PP and SBP showed no significant or only modest heritability. The present study, therefore, suggests that genetic factors play an important role in determining peak aortic *Q*, and that when assessing the genetic variants that determine SBP in groups of African descent, the individual haemodynamic components, particularly peak aortic *Q*, are likely to be more revealing than BP *per se*. In this regard, genome-wide association studies for BP traits alone (hypertension) have largely produced disappointing results to date. The present results suggest that part of the inability to show consistent genetic determinants of BP, is that although BP overall has a limited degree of heritability, the individual haemodynamic



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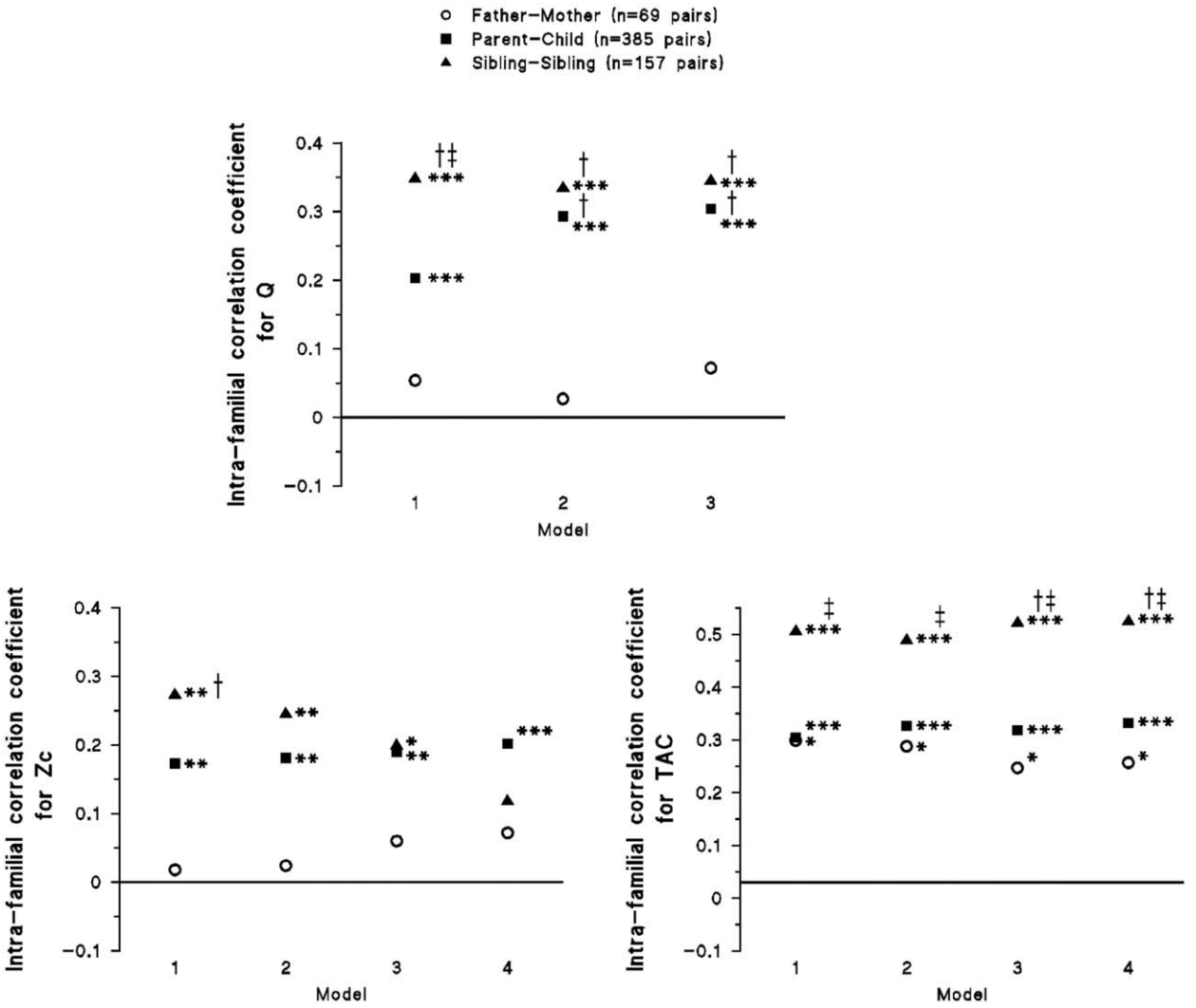



**FIGURE 2** Unadjusted (models 1) and multivariate adjusted (models 2–4) intrafamilial correlations (*r* values) of the haemodynamic variables [peak aortic flow ($Q$), $Z_c$ and TAC] that determine pulse pressure and SBP in a group of African ancestry. Adjustments are for age, age$^2$ and sex (model 2); age, age$^2$, sex and other confounders including BMI, heart rate, regular smoking, regular alcohol intake, treatment for hypertension, diabetes mellitus, total/HDL cholesterol concentrations and eGFR (model 3); or age, age$^2$, sex, other confounders and MAP when assessing TAC (model 4); or age, age$^2$, sex, other confounders, MAP and aortic root diameter when assessing $Z_c$ (model 4). $^*P$ less than 0.05, $^{**}P$ less than 0.001, $^{***}P$ less than 0.0001 for correlations. $^{\dagger}P$ less than 0.05 for comparisons with father and mother correlations. $^{\ddagger}P$ less than 0.05 for comparisons with parent and child correlations. eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; MAP, mean arterial pressure; TAC, total arterial compliance.

determinants are strongly inherited. These data, therefore, offer a novel approach to unravelling the genetic targets for hypertension in groups of African ancestry, which in-turn, could lead to better therapeutic approaches to managing low-renin hypertension.

The intrafamilial aggregation and heritability of forward travelling pressure waves in the community reported on in the present study, have previously been described [18]. In that study [18], we report modest heritability estimates ($h^2$) of 0.16–0.22. Importantly, forward wave pressures are strongly determined by the peak pressures generated by the product of aortic flow ($Q$) and characteristic impedance to flow ($Z_c$). However, the present study provides clear evidence that even if forward travelling pressure waves show modest degrees of heritability that the individual haemodynamic components show a high degree of inheritance ($h^2$ of $Q = 0.82$ and $Z_c = 0.44$), The present data, therefore, support a strong contribution of genetic factors to the determinants of PP, and hence SBP in this population. However, the present study highlights a need to consider the genetic determinants of the individual haemodynamic determinants of PP and SBP ($Q$, $Z_c$ and TAC), rather than the pressure effects produced.

Several factors explain increases in $Q$ and $Z_c$. In this regard, age-related increases in systemic flow in the present population are strongly associated with decreases in fractional $Na^+$ reabsorption ($FeNa^+$) and glomerular filtration rate [8]. In previous studies, we have reported on significant heritability estimates for $FeNa^+$ and that these effects are mostly marked in African populations in the proximal rather than the distal tubule [12]. As current diuretic agents decrease distal tubular $Na^+$ reabsorption, this may explain why current diuretics are unable to reduce blood volume and hence systemic flow in volume-dependent forms of



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**TABLE 2. Multivariate adjusted heritability estimates ($h^2$) of pulse pressure and systolic blood pressure in a group of African ancestry**

| Haemodynamic variable | Adjustments | All participants | | Not receiving antihypertensive therapy | |
|---|---|---|---|---|---|
| | | $h^2 \pm$ SEM (n = 669) | *P* value | $h^2 \pm$ SEM (n = 495) | *P* value |
| Brachial PP | None | 0.023 ± 0.075 | =0.38 | 0.041 ± 0.083 | =0.31 |
| | Age, age$^2$, sex | 0.053 ± 0.101 | =0.30 | 0.057 ± 0.114 | =0.31 |
| | Age, age$^2$, sex +a | 0.044 ± 0.101 | =0.32 | 0.046 ± 0.113 | =0.34 |
| | Age, age$^2$, sex +a +MAP | 0.064 ± 0.098 | =0.26 | 0.141 ± 0.127 | =0.13 |
| Aortic PP | None | 0.030 ± 0.074 | =0.35 | 0.047 ± 0.082 | =0.29 |
| | Age, age$^2$, sex | 0.093 ± 0.099 | =0.18 | 0.102 ± 0.114 | =0.19 |
| | Age, age$^2$, sex +a | 0.103 ± 0.100 | =0.15 | 0.086 ± 0.108 | =0.21 |
| | Age, age$^2$, sex +a +MAP | 0.103 ± 0.095 | =0.14 | 0.196 ± 0.122 | =0.05 |
| Brachial SBP | None | 0.004 ± 0.072 | =0.48 | 0.026 ± 0.095 | =0.39 |
| | Age, age$^2$, sex | 0.119 ± 0.107 | =0.13 | 0.131 ± 0.138 | =0.17 |
| | Age, age$^2$, sex +a | 0.112 ± 0.107 | =0.15 | 0.132 ± 0.133 | =0.16 |
| | Age, age$^2$, sex +a +MAP | 0.061 ± 0.101 | =0.27 | 0.134 ± 0.131 | =0.15 |
| Aortic SBP | None | 0.012 ± 0.074 | =0.44 | 0.039 ± 0.095 | =0.34 |
| | Age, age$^2$, sex | 0.157 ± 0.106 | =0.07 | 0.183 ± 0.139 | =0.10 |
| | Age, age$^2$, sex +a | 0.168 ± 0.107 | =0.06 | 0.182 ± 0.136 | =0.09 |
| | Age, age$^2$, sex +a +MAP | 0.116 ± 0.097 | =0.11 | **0.194 ± 0.100** | **<0.05** |

Significant values are highlighted in bold. MAP, mean arterial pressure; PP, pulse pressure. a, other confounders including BMI, heart rate, regular smoking, regular alcohol intake, treatment for hypertension (in all), diabetes mellitus, total/HDL cholesterol concentrations and eGFR.

hypertension. With respect to proximal aortic $Z_c$, this is a function of aortic stiffness and diameter and in the present population the contribution of $Z_c$ to increases in BP is beyond aortic root diameter [6,7]. Thus, as with populations of largely European origins [9], in Africa, age-related increases in aortic stiffness explain $Z_c$ effects on BP [6,7]. In this regard, several studies have determined the heritability of aortic stiffness as assessed from carotid–femoral pulse wave velocity, in populations of European ancestry [13,29–31], consistently reporting significant heritability. Similarly, in the present study, we show significant intrafamilial aggregation and heritability of $Z_c$, effects that are independent of aortic root diameter. This is, therefore, likely to be attributed to the impact of genetic determinants of proximal aortic stiffness on $Z_c$. Consequently, in the search for the candidate genes responsible for PP and hence SBP in groups of African descent and hence the development of novel antihypertensive approaches better able to control low-renin hypertension, genetic studies should evaluate both the renal mechanisms responsible for *Q*, and the mechanisms responsible for increases in aortic stiffness and hence $Z_c$ and TAC.

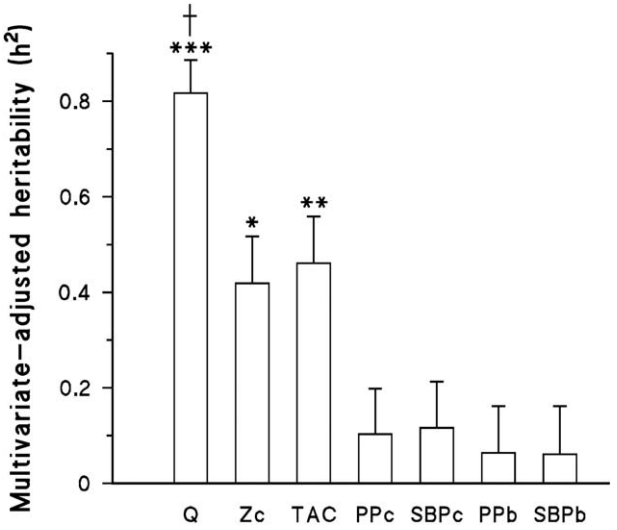



**FIGURE 3** Comparison of fully adjusted heritability estimates ($h^2 \pm$SEM) shown in Tables 3 and 4 for SBP, pulse pressure or the haemodynamic determinants thereof in a group of African ancestry. Adjustments are for age, age$^2$, sex, BMI, heart rate, regular smoking, regular alcohol intake, treatment for hypertension, diabetes mellitus, total/HDL cholesterol concentrations, eGFR and MAP. Significance of heritability estimates are given in Tables 3 and 4. $^*P$ less than 0.05, $^{**}P$ less than 0.005, $^{***}P$ less than 0.0001 for comparisons with SBP and PP and $^+P$ less than 0.005 for comparisons with $Z_c$ or TAC. eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; MAP, mean arterial pressure.

The markedly greater peak aortic flow in older (parents) as compared with younger (offspring) participants in the present study is in apparent contrast to age-related decreases in myocardial systolic function that have frequently been described in other populations. However, in the present population, the increases in systemic flow are attributed to an age-related, volume-dependent increase in left ventricular preload (Frank–Starling effect) [6]. The presence of an age-related volume-dependent increase in systemic flow is supported by strong relations of systemic flow with age-related increases in left ventricular end diastolic volume, an age-related reduction in circulating renin concentrations and both age-related and nonage-related alterations in several indices of renal tubular function [6,8]. In contrast, no relationships between systemic flow and ejection fraction are noted in this population [6].

There are several limitations to the present study that warrant consideration. In this regard, more women than men volunteered for the present study and hence the present findings may relate more to women than to men. However, the contribution of *Q* to age-related increases in BP and the correlates of *Q* in the present population are similar in women and men [6]. Thus, it is likely that the genetic factors that determine *Q* have similar effects in both sexes. Second, whether the presence of antihypertensive treatment resulted in the loss of some of the genetic



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**TABLE 3. Multivariate adjusted heritability estimates ($h^2$) of the haemodynamic variables (peak aortic flow [$Q$], $Z_c$ and total arterial compliance) that determine pulse pressure and SBP in a group of African ancestry**

| | | All participants | | Not receiving antihypertensive therapy | |
|---|---|---|---|---|---|
| Haemodynamic variable | Adjustments | $h^2 \pm$ SEM | $P$ value | $h^2 \pm$ SEM | $P$ value |
| Peak aortic $Q$ | None | $0.617 \pm 0.096$ | <0.0001 | $0.460 \pm 0.134$ | <0.0005 |
| | Age, age$^2$, sex | $0.828 \pm 0.046$ | <0.0001 | $0.595 \pm 0.115$ | <0.0001 |
| | Age, age$^2$, sex +a | $0.817 \pm 0.069$ | <0.0001 | $0.627 \pm 0.117$ | <0.0001 |
| Aortic $Z_c$ | None | $0.389 \pm 0.090$ | <0.0001 | $0.314 \pm 0.119$ | <0.005 |
| | Age, age$^2$, sex | $0.407 \pm 0.090$ | <0.0001 | $0.352 \pm 0.117$ | <0.005 |
| | Age, age$^2$, sex +a | $0.413 \pm 0.088$ | <0.0001 | $0.354 \pm 0.099$ | <0.0005 |
| | Age, age$^2$, sex +a +MAP +AoD | $0.419 \pm 0.098$ | <0.0001 | $0.373 \pm 0.108$ | <0.0005 |
| Total arterial compliance | None | $0.412 \pm 0.098$ | <0.0001 | $0.340 \pm 0.114$ | <0.005 |
| | Age, age$^2$, sex | $0.452 \pm 0.095$ | <0.0001 | $0.409 \pm 0.113$ | <0.0005 |
| | Age, age$^2$, sex +a | $0.437 \pm 0.097$ | <0.0001 | $0.403 \pm 0.113$ | <0.0005 |
| | Age, age$^2$, sex +a +MAP | $0.461 \pm 0.098$ | <0.0001 | $0.428 \pm 0.104$ | <0.0001 |

AoD, aortic root diameter; MAP, mean arterial pressure; TAC, total arterial compliance; $Z_c$, characteristic impedance. a, other confounders including BMI, heart rate, regular smoking, regular alcohol intake, treatment for hypertension (in all), diabetes mellitus, total/HDL cholesterol concentrations and eGFR.

information, and thus, an underestimation of the heritability of $Z_c$ and TAC, is uncertain. However, similar heritability estimates were noted on sensitivity analysis in untreated participants, a significant number of whom were hypertensive patients. Third, in-keeping with previous studies performed in the Framingham cohort [9], we determined aortic flow, $Z_c$ and TAC from velocity and diameter measurements in the outflow tract using echocardiography and central arterial pressure assessments. In this regard, the use of MRI is the accepted referent measure of systemic flow. However, the use of MRI prevents the ability to calculate $Z_c$ from central arterial pressures and requires the use of indirect techniques, which use the water hammer equation [28]. Moreover, we have demonstrated remarkably similar age-related increases in systemic flow in the present population using the biplane Simpson approach (applied to left ventricular dimension measurements) as compared with measures obtained using outflow tract velocity and diameter measurements [6]. Fourth, we determined $Z_c$ in the time rather than the frequency domain. However, contemporary recommendations indicate that $Z_c$ can be determined in either domain [20]. Last, the stigma attached to HIV infection in South Africa prevented routine testing for this condition. However, the impact of HIV on $Q$ is most likely to be through renal effects, and in the present study, we adjusted for eGFR.

In conclusion, in the present study, we show that in distinct contrast to alternative populations, a striking intrafamilial aggregation and heritability of systemic flow (peak aortic $Q$) is noted in a community of African ancestry living in Africa, effects that were significantly greater than the vascular determinants of PP and SBP ($Z_c$ and TAC). Importantly, the individual haemodynamic determinants of PP and SBP, including $Q$, $Z$c and TAC, considered separately, showed a markedly higher inheritance than the BP values that they determine (PP or SBP). These data suggest that genetic factors are indeed strong determinants of BP in Africa, and that the dominant genes are likely to be those that influence volume-dependent increases in systemic flow. As current antihypertensive therapy produces no sustained reductions in systemic flow, identifying the genetic determinants of systemic flow in groups of African ancestry may uncover novel therapeutic targets for drug development that may produce better BP control in low renin hypertension.

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### Conflicts of interest

There are no conflicts of interest.

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