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INFOGRAPHIC

Marked increases in systemic blood flow in resistant or refractory hypertensives of African ancestry in Africa

Nico Malan*, Gavin R. Norton*, Carlos D. Libhaber, Vernice Peterson, Hamza Bello, Mohlabani Masiu, Daniel Da Silva Fernandes, Nonhlanhla H. Mthembu, Keneilwe N. Mmopi, Grace Tade, Ferande Peters, Patrick H.C. Dessein, Pinas Sareli, and Angela J. Woodiwiss*

Aims: A distinct volume-dependent increase in systemic blood flow has recently been demonstrated to contribute to hypertension in groups of African ancestry. We determined whether systemic blood flow contributes to resistant or refractory hypertension (RHTN).

Methods: We compared the multivariate adjusted haemodynamic correlates of blood pressure in RHTN ($n=100$) on diuretic and other therapy, to those in age and sex-matched normotensives (NT, $n=128$), untreated hypertensives (Untreat-HTN, $n=124$), and treated-controlled hypertensives (Control-HTN, $n=74$) of African ancestry in South Africa. Haemodynamics were determined from velocity and diameter measurements in the left ventricular outflow tract, and central arterial pressures.

Results: All hypertensives had higher stroke volume (SV), cardiac output (CO) and peak aortic flow (Q) compared to NT ($P<0.05$ to <0.0001). However, RHTN had higher SV, CO and Q than Untreat-HTN and Control-HTN ($P<0.0001$). Proximal aortic characteristic impedance (Zc) in RHTN was similar to Untreat-HTN, but greater than NT ($P<0.005$), and Control-HTN ($P<0.05$). In RHTN, systemic vascular resistance was lower compared NT, Untreat-HTN and Control-HTN ($P<0.005$ to <0.0001), and total arterial compliance was higher compared to Untreat-HTN and Control-HTN ($P<0.02$ to <0.0001). The pressure generated by the product of Q and Zc (P_{QxZc}) and hence aortic pulse pressure were higher in RHTN compared to NT, Untreat-HTN and Control-HTN ($P<0.0001$), effects attributed primarily to increases in SV and Q.

Conclusions: Despite the use of diuretic therapy, increases in systemic blood flow are the main determinant of RHTN in groups of African ancestry in South Africa. Novel approaches to targeting volume-dependent increases in blood flow in this population are therefore required.

Graphical abstract: http://links.lww.com/HJH/C786

Keywords: aortic flow, primary hypertension, renal function, stroke volume

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; APOGH, African Programme on Genes in Hypertension; AUC, area under the receiver operating characteristic curves; BMI, body mass index; BP, blood pressure; CCB, dihydropyridine type calcium-channel blocker; CO, cardiac output; COBSA, cardiac output per body surface area; Control-HTN, treated-controlled hypertensives; DM, diabetes mellitus; EDV, left ventricular end diastolic volume; EDVBSA, left ventricular end diastolic volume per body surface area; EF, ejection fraction; HbA1c, percentage glycated haemoglobin; HCTZ, hydrochlorothiazide; HR, heart rate; IDI, integrated discrimination improvement; MAP, mean arterial pressure; NRI, net reclassification improvement; NT, normotensives; PQxZc, pressure generated by the product of Q and Zc; Q, peak aortic flow; RAP, right atrial pressure; RHTN, resistant or refractory hypertension; ROC, receiver operating characteristic; RWT, relative wall thickness; SD, standard deviation; SV, stroke volume; SVBSA, stroke volume per body surface area; SVR, systemic vascular resistance; SVRBSA, systemic vascular resistance expressed per body surface area; TAC, total arterial compliance; TACBSA, total arterial compliance expressed per body surface area; Untreat-HTN, untreated hypertensives; Vmax, maximum aortic velocity; Zc, aortic characteristic impedance

INTRODUCTION

Through both a lack of detection and poor blood pressure (BP) control in those on antihypertensive therapy, approximately 10 million deaths per year globally are accounted for by hypertension [1]. Groups of African descent are well recognized as developing arterial

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hypertension that is poorly responsive to several classes of antihypertensives often requiring combinations of agents to manage BP [2–5], and indeed are noted to have a high prevalence of resistant hypertension [6]. The limited responses to renin-angiotensin system blockers in Africans, is thought to be mediated in-part through a volume-dependent, low-renin form of hypertension [3,4,7,8]. Although a renal mechanism resulting in fluid retention is thought to explain an increased BP in this ethnic group [7,8], it is only more recently that a striking age-related, volume-dependent increase in systemic blood flow has been identified as a major haemodynamic correlate of increases in both systolic and diastolic BP in this ethnic group [9,10]. Importantly, the impact of increases in systemic blood flow on hypertension in this ethnic group is at least as strong as that of aortic stiffness-induced increases in characteristic impedance (Zc) [9], the major determinant of systolic BP in populations of European descent [11]. Furthermore, in groups of African descent, the impact of systemic blood flow on hypertension is far greater than that of systemic vascular resistance (SVR) [9], which is the major haemodynamic target of most antihypertensive agents. The strong contribution of systemic blood flow to hypertension in groups of African ancestry living in Africa, suggests that volume-dependent increases in systemic blood flow may be an important target for managing hypertension in this population group. However, whether currently available therapy reduces systemic blood flow is unknown.

Low dose thiazide or thiazide-like diuretic agents are currently recommended for managing volume-dependent hypertension. However, several lines of evidence suggest that thiazide diuretics have a limited impact on systemic blood flow. Indeed, 98% of hypertensives receiving antihypertensives at a community level in Africa are receiving low dose hydrochlorothiazide (HCTZ), and these individuals have the same striking increases in systemic blood flow as untreated hypertensives [10]. This is indeed in keeping with the fact that HCTZ has never been demonstrated to produce sustained reductions in plasma volume and hence systemic blood flow [12]. Furthermore, despite the greater impact of systemic blood flow as opposed to SVR on hypertension in groups of African ancestry in Africa [9], when employed as monotherapy, HCTZ produces a less marked effect on BP than vasodilator calcium channel blockers that target SVR [2]. Thus, it is possible that increases in systemic blood flow contribute to uncontrolled BP levels in groups of African ancestry, despite the use of therapy designed to target volume-dependent hypertension. To determine whether systemic blood flow is an important cause of uncontrolled BP levels in groups of African ancestry living in Africa, we therefore assessed the haemodynamic correlates of BP in resistant or refractory hypertensives (RHTN) on thiazide diuretic and other therapy in this ethnic group.

METHODS

Study groups

The present studies were 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 protocols (approval numbers: M02-04-72, M07-04-69, M12-04-108, M17-04-01, M17-02-71 and M22-03-93). Participants gave informed, written consent. 100 resistant or refractory hypertensives (RHTN) (defined as described below) of black African ancestry, were recruited from the Hypertension Clinic at the Charlotte Maxeke Johannesburg Academic Hospital. For comparative purposes age and sex-matched normotensives ($n = 128$), untreated hypertensives ($n = 124$), and treated and controlled hypertensives ($n = 74$) (defined as described below) of black African ancestry were selected from a community-based study (African Programme on Genes in Hypertension, APOGH) previously described [13–15]. In APOGH, families of black African descent from the South West Township (SOWETO) of Johannesburg, South Africa, with at least one or two offspring older than 16 years of age, and one or both parents available for examination, were randomly recruited (from the population census figures of 2001). Normotensives, untreated hypertensives, and treated and controlled hypertensives were selected from a substudy of APOGH consisting of 824 participants who had high quality velocity measurements in the outflow tract (a smooth velocity waveform with a dense leading [outer] edge and a clear maximum velocity).

Clinical and demographic information

A questionnaire was administered to obtain demographic and clinical data [15]. Height and weight were measured using standard approaches and participants were considered to be overweight if their body mass index (BMI) was $\geq 25\,kg/m^2$ and obese if their BMI was $\geq 30\,kg/m^2$. Basal metabolic rate (calories/day) was calculated using the Mifflin-St Jeor equation: Basal metabolic rate = 10 × weight + 6.25 × height – 5 × age + 5 (for males); Basal metabolic rate = 10 × weight + 6.25 × height – 5 × age – 161 (for females). Laboratory blood tests of percentage glycated haemoglobin (HbA1c) were performed. Diabetes mellitus (DM) was defined as the use of insulin or oral glucose lowering agents or an HbA1c value >6.5%. High quality office brachial blood pressure (BP) measurements were obtained in the seated position and after 5 min of rest, by a trained nurse-technician using a standard mercury sphygmomanometer [15] according to guidelines. The mean of five measurements obtained 30–60 s apart was taken as brachial office BP in order to define hypertension. Normotension (NT) was defined as mean office BP <140 mm Hg systolic and <90 mm Hg diastolic BP and no use of antihypertensive medication. Resistant or refractory hypertension (RHTN) was defined as uncontrolled brachial BP (≥140/90 mmHg) despite receiving 3 or more different classes of antihypertensive agents, one of which was a thiazide diuretic agent (HCTZ) [16], and included those with brachial BP controlled on four or more medications, and those with uncontrolled brachial BP despite using five or more different classes of antihypertensive agents (refractory hypertension) [16]. Untreated hypertension (Untreat-HTN) was defined as a mean office BP ≥140 mmHg systolic or ≥90 mmHg diastolic BP and no use of antihypertensive medication. Treated and controlled hypertension (Control-HTN) was defined as mean office BP <140 mmHg systolic and <90 mmHg diastolic BP and 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 [9,10]. 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) 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 systolic and diastolic BP taken in the supine position 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 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 (AJW) using an Acuson SC2000 Diagnostic ultrasound system (Siemens Medical Solutions, USA, Inc.). Velocity waveforms were obtained in the 5-chamber view. Aortic diameter measurements were obtained just proximal to the aortic leaflets in the long axis parasternal view. 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 as described [17]. 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 [17] where flow (Q) = velocity × aortic root cross-sectional area calculated from diameter assessments. Intra-observer variability studies conducted on 35 participants on whom repeat echocardiographic measurements were performed within a 2-week period of the initial measurements showed Pearson's correlation coefficients for aortic diameter and aortic velocity of 0.94 and 0.98, low variances (mean difference ± SD of 0.02 ± 0.12 cm and 0.10 ± 6.82 cm/s, and mean % difference ± SD of 0.68 ± 4.76% and 0.65 ± 5.45%), and no significant differences between repeat measurements (paired *t*-test) ($P = 0.38$ and $P = 0.93$). Inter-observer variability studies conducted on 42 participants showed Pearson's correlation coefficients for aortic diameter and aortic velocity of 0.82 and 0.97, low variances (mean difference ± SD of 0.07 ± 0.25 cm and 3.40 ± 7.76 cm/sec, and mean % difference ± SD of 2.36 ± 9.93% and 3.10 ± 7.53%), and no significant differences between measurements (unpaired t-test) ($P = 0.21$ and $P = 0.66$ respectively).

Stroke volume (SV) was assessed from the product of the aortic velocity-time integral and aortic cross-sectional area estimated from aortic root diameter. Cardiac output (CO) was determined from SV × heart rate (HR). Heart rate was determined from the length (period, PD) of an averaged peripheral waveform captured over a 10 s period, using the formula: HR=1000/PDx60. Characteristic impedance (Zc) was determined in the time domain using approaches previously described [11,18] and validated against invasive pressure measurements [19]. The volume flow waveform was paired with central arterial pressure waveforms as described [17] and Zc was calculated as the ratio of change in pressure to change in flow. To identify the pressures generated by increases in flow, the peak pressure generated from the product of flow (Q) and Zc (P_{QxZc}) was determined [17]. Systemic vascular resistance (SVR) was calculated from mean arterial pressure (MAP, average arterial pressure for the peripheral wave form as described [17]) and cardiac output (SVR = [MAP − RAP]/CO), assuming right atrial pressure (RAP) = 0 mmHg. Total arterial compliance (TAC) was calculated as SV/aortic pulse pressure. Left ventricular end diastolic volume (EDV) was determined from echocardiography using the biplane Simpson approach.

Data analysis

For database management and statistical analysis, SAS software, version 9.4 (SAS Institute Inc., Cary, NC) was employed. Continuous variables are expressed as mean (±SD) or median and interquartile range. Dichotomous variables are expressed as percentages. Multivariate analysis of covariance was performed to compare variables (continuous data) across the groups. Multivariate adjusted logistic regression analysis was performed to determine the relative contribution of haemodynamic factors to RHTN. Odds ratios per 1SD increment in each haemodynamic variable were determined and compared using z statistics. To evaluate whether haemodynamic components were associated with an RHTN diagnosis beyond conventional risk factors, we compared the area under the receiver operating characteristic curves (AUC), and determined the integrated discrimination improvement, and net reclassification improvement [20,21]. The covariates (adjustors) included in the multivariate regression analyses were age, sex, regular alcohol intake, regular tobacco intake, BMI, diabetes mellitus, and heart rate. In all analyses, a 2-sided *P* value of <0.05 was considered statistically significant.

RESULTS

Characteristics of hypertensives vs. normotensives

The characteristics of the normotensives (NT) and the three hypertensive groups are given in Table S1, Supplemental Digital Content, http://links.lww.com/HJH/C785. The RHTN and Control-HTN had a higher BMI than the NT, and the Control-HTN had a higher prevalence of diabetes mellitus than the other three groups. Heart rate was higher in the Control-HTN compared to the RHTN and Untreat-HTN. 52% of RHTN were being treated with three antihypertensive agents, and 48% of RHTN were being treated with 4 or more antihypertensive agents. All of the RHTN were receiving the thiazide diuretic, HCTZ, and 28% of RHTN were receiving spironolactone (25–50 mg/day). In

RHTN, the most commonly employed agents, other than HCTZ, were maximum doses of calcium channel blocker (amlodipine), angiotensin-converting enzyme inhibitor (enalapril), and 50 mg of β-adrenoreceptor blocker (atenolol). 25% of RHTN were receiving hydralazine, and/or α_1-adrenergic receptor blockers. In comparison, 96% of Control-HTN were receiving the thiazide diuretic, HCTZ, and only 41.9% of Control-HTN were receiving antihypertensive agents in addition to HCTZ. The only factor identified that could have contributed to resistance or refractoriness to hypertension was the use of nonsteroidal antiinflammatories in 12% of participants.

Blood pressures in resistant or refractory hypertension

Without (Table S2, Supplemental Digital Content, http://links.lww.com/HJH/C785) or with (Table S3, Supplemental Digital Content, http://links.lww.com/HJH/C785) adjustments for age, sex and standard risk factors for hypertension, Untreat-HTN and RHTN had increased brachial and central arterial BP as compared to NT and Control-HTN. Importantly, 53.0% of RHTN had an uncontrolled BP despite being treated with 3 or more antihypertensive agents. Although, brachial and central arterial systolic and diastolic BP were lower in RHTN compared to Untreat-HTN, brachial and central arterial pulse pressure (PP), and the pressure generated by the product of Q and Zc (P_{QxZc}) were higher in RHTN compared to Untreat-HTN. Furthermore, the higher PP and P_{QxZc} in the RHTN compared to Untreat-HTN remained after adjustments for MAP (Table S3, Supplemental Digital Content, http://links.lww.com/HJH/C785).

Systemic blood flow in resistant or refractory hypertension

Without (Table S4, Supplemental Digital Content, http://links.lww.com/HJH/C785) or with (Fig. 1) adjustments for age, sex, and standard risk factors for hypertension, RHTN had markedly higher SV, CO and peak aortic Q as compared to all other groups. Although, basal metabolic rate was higher in RHTN compared to NT (Table S1, Supplemental Digital Content, http://links.lww.com/HJH/C785), this was attributed to the higher BMI in RHTN compared to NT. Indeed, after adjustments for age, sex, and BMI, basal metabolic rate did no differ between the groups (NT: 1441.8 ± 109.1; RHTN: 1449.8 ± 108.9; Untreat-HTN: 1441.4 ± 108.8; Control-HTN: 1444.8 ± 109.5, $P > 0.46$). Moreover, the markedly higher SV, CO and peak aortic Q in RHTN compared to the other groups, remained after further adjustments for basal metabolic rate (Table S5, Supplemental Digital Content, http://links.lww.com/HJH/C785). Although Untreat-HTN and Control-HTN also showed greater SV, CO and peak aortic Q values compared to NT, the values were lower than those observed in RHTN (Fig. 1, Table S4, Supplemental Digital Content, http://links.lww.com/HJH/C785). The higher SV and CO in the hypertensives were noted irrespective of whether expressed per body surface area or not (Fig. 1, Table S4, Supplemental Digital Content, http://links.lww.com/HJH/C785). The higher Q in the hypertensives was paralleled by a greater aortic root velocity (Fig. 1, Table S4, Supplemental Digital Content, http://links.lww.com/HJH/C785) and diameter (Fig. 2, Table S4, Supplemental Digital Content, http://links.lww.com/HJH/C785). The greater SV, CO and peak aortic Q in RHTN were also accompanied by greater EDV and EF (Fig. 1, Table S4, Supplemental Digital Content, http://links.lww.com/HJH/C785). However, relative all thickness was not lower in RHTN compared to NT (NT: 0.36 ± 0.06; RHTN: 0.37 ± 0.08; Untreat-HTN: 0.39 ± 0.06 [$P < 0.05$ vs. NT and Control-HTN]; Control-HTN: 0.37 ± 0.07).

Vascular mechanisms in resistant or refractory hypertension

Without (Table S4, Supplemental Digital Content, http://links.lww.com/HJH/C785) or with (Fig. 2) adjustments for age, sex and standard risk factors for hypertension, RHTN had lower SVR compared to NT, Untreat-HTN and Control-HTN. In Untreat-HTN, after adjustments, SVR was higher than in NT and Control-HTN (Fig. 2). In Control-HTN, SVR was lower than in NT (Fig. 2, Table S4, Supplemental Digital Content, http://links.lww.com/HJH/C785). TAC was greater in RHTN compared to Untreat-HTN and Control-HTN, but did not differ from NT. Zc was higher in RHTN and Untreat-HTN compared to NT and Control-HTN (Fig. 2, Table S4, Supplemental Digital Content, http://links.lww.com/HJH/C785). However, no differences in Zc were noted between RHTN and Untreat-HTN (Fig. 2, Table S4, Supplemental Digital Content, http://links.lww.com/HJH/C785). The greater Zc in both RHTN and Untreat-HTN were paralleled by increases in aortic root diameter (Fig. 2, Table S4, Supplemental Digital Content, http://links.lww.com/HJH/C785), and hence are likely accounted for by increases in proximal aortic stiffness.

Relative contribution of haemodynamic factors to resistant or refractory hypertension

In multivariate regression models with various haemodynamic factors included in the models (in addition to age, sex, BMI, regular smoking, regular drinking, diabetes mellitus and heart rate), as compared to NT, Untreat-HTN or Control-HTN, peak aortic Q or SV contributed more (greater Wald ^{2}) to RHTN than did Zc or TAC (Table 1). A decrease, rather than increase, in SVR was predictive of RHTN (Table 1). Similarly, an increase, rather than a decrease, in TAC was predictive of RHTN (Table 1). The predictive performance (Uno's *C* statistic) of peak aortic Q and SV for RHTN was greater than that for Zc and TAC (Fig. 3, Table 2). Moreover, the addition of peak aortic Q or SV to the base model consisting of established risk factors for hypertension, resulted in significant improvements in Uno's C statistic (Table 2); whereas Uno's C was unchanged by the addition of Zc or TAC. Importantly, the addition of peak aortic Q or SV to the base model resulted in improvements in average sensitivity without sacrificing average specificity (an increase in the integrated discrimination improvement [IDI], Table 2). Furthermore, both peak aortic Q and SV showed predictive value for RHTN beyond conventional risk factors for HTN, as indicated by the increases in the net reclassification improvement (NRI) (Table 2).

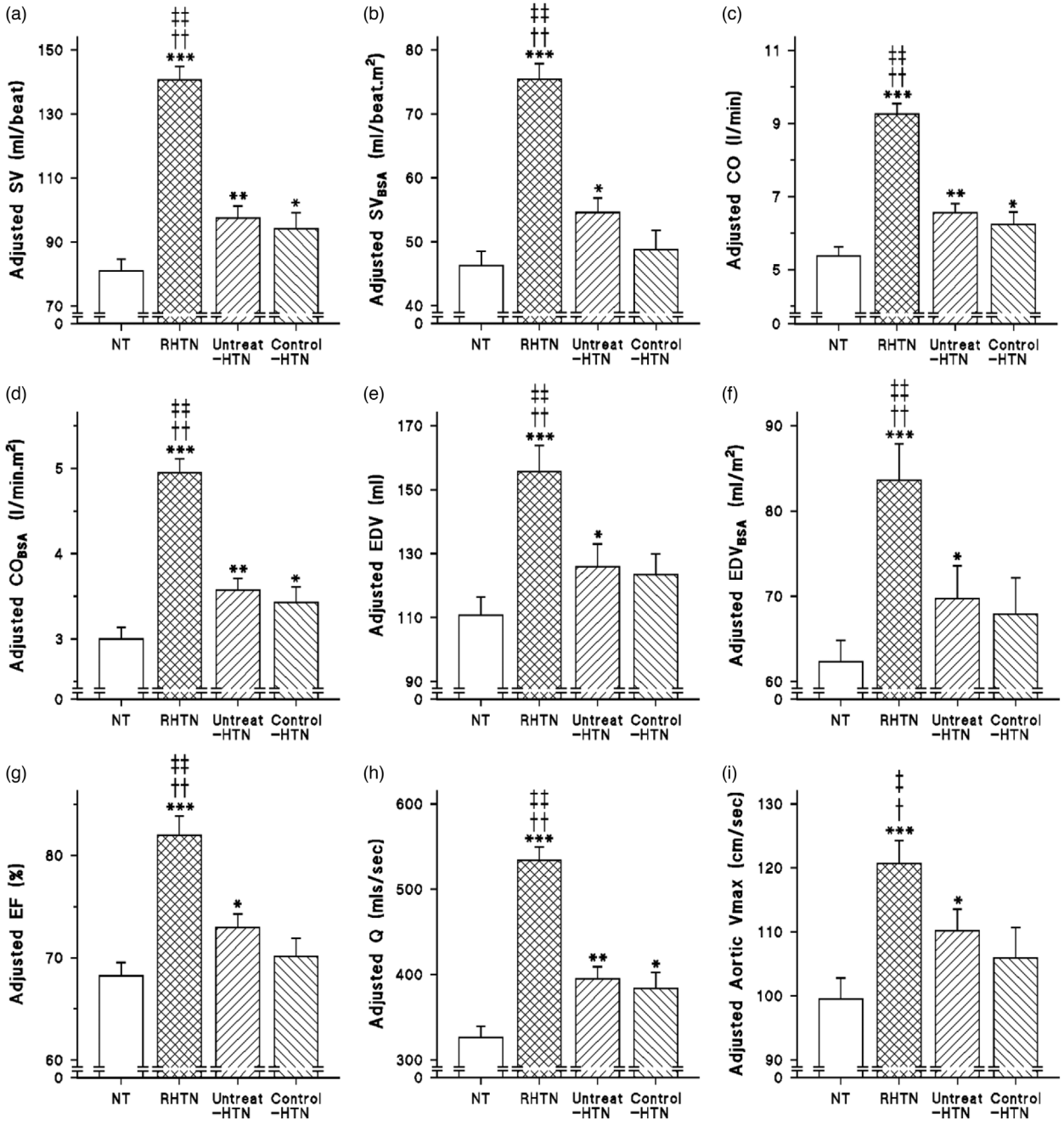


FIGURE 1 Multivariate adjusted systemic blood flow in resistant or refractory hypertensives (RHTN) vs. normotensives (NT), untreated hypertensives (Untreat-HTN), or controlled hypertensives (Control-HTN) of African ancestry. Data shown are multivariate adjusted mean ± SEM for stroke volume (SV) (panels a and b), cardiac output (CO) (panels c and d), end diastolic volume (EDV) (panels e and f), ejection fraction (EF) (panel g), peak aortic blood flow (Q) (panel h), and maximum aortic velocity (V_{max}) (panel I). See Table 1 for sample sizes. SV_{BSA}, SV per body surface area; CO_{BSA}, CO per body surface area; EDV_{BSA}, EDV per body surface area. Adjustments are for age, sex, BMI, regular smoking, regular alcohol, diabetes mellitus and heart rate. $^{*}P<0.05$, $^{**}P<0.005$, $^{***}P<0.0001$ vs. NT; $^{\dagger}P<0.05$, $^{\dagger\dagger}P<0.0001$ vs. Untreat-HTN; $^{\ddagger}P<0.05$, $^{\ddagger\ddagger}P<0.0001$ vs. Control-HTN.

DISCUSSION

The main findings in the present study are as follows: We show that resistance or refractoriness to antihypertensive therapy is strongly associated with increases in systemic blood flow in a community of African ancestry. As compared to age- and sex-matched normotensives, as well as untreated hypertensives and treated and controlled hypertensives, resistant or refractory hypertensives showed marked increases in SV, CO and peak aortic Q. In contrast, in resistant or refractory hypertensives, Zc was similar to untreated hypertensives, but greater than normotensives or treated and controlled hypertensives. Moreover, in resistant or refractory hypertensives, SVR was markedly lower than in normotensives, untreated hypertensives or treated and controlled hypertensives. In addition, in resistant or refractory hypertensives, TAC was higher than in untreated hypertensives or treated and controlled hypertensives. Increases in peak aortic Q translated into striking increases in the central arterial pressures generated by the product of

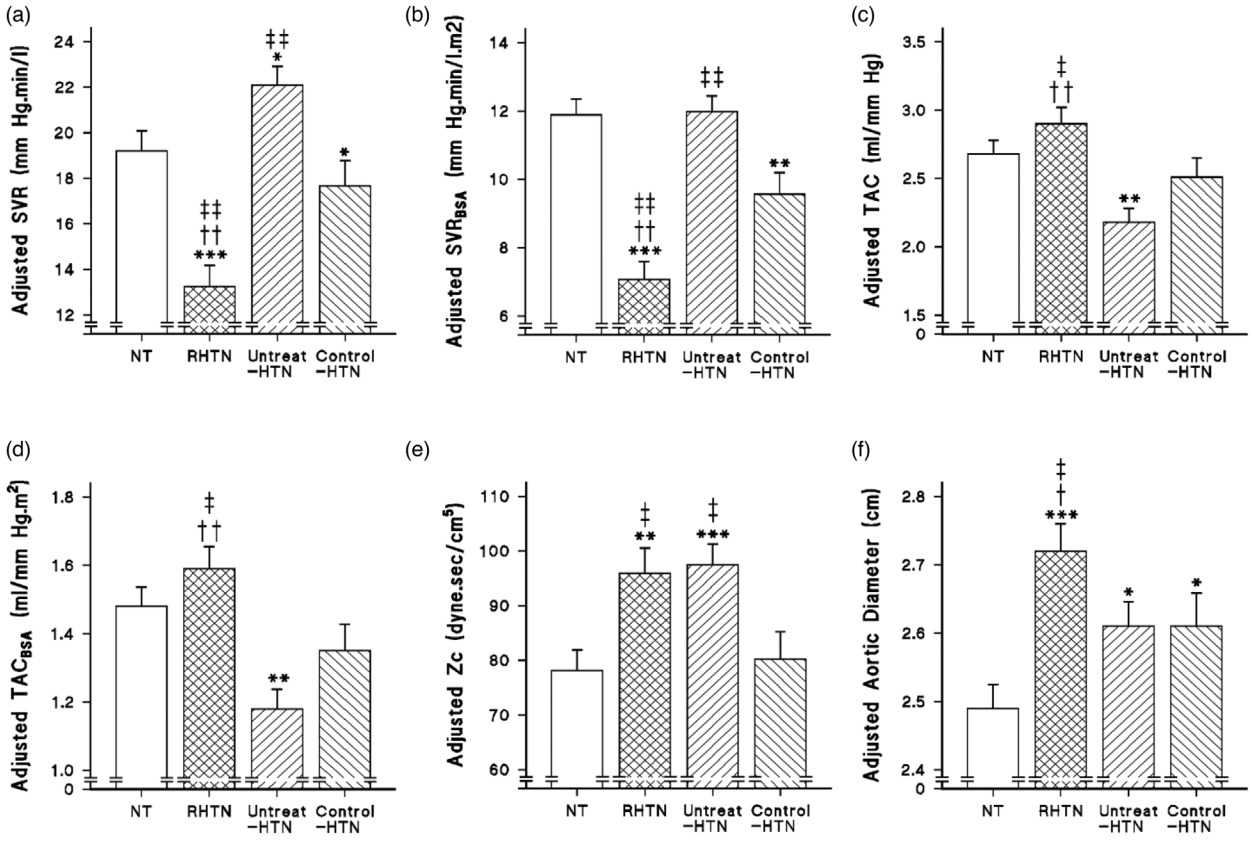


FIGURE 2 Multivariate adjusted vascular correlates of blood pressure in resistant or refractory hypertensives (RHTN) vs. normotensives (NT), untreated hypertensives (Untreat-HTN), or controlled hypertensives (Control-HTN) of African ancestry. Data shown are multivariate adjusted mean ± SEM for systemic vascular resistance (SVR) (panels a and b), total arterial compliance (TAC) (panels c and d), aortic characteristic impedance (Zc) (panel e), and aortic root diameter (aortic diameter) (panel f). See Table 1 for sample sizes. SVR_{BSA}, SVR expressed per body surface area; TAC, total arterial compliance; TAC_{BSA}, TAC expressed per body surface area. Adjustments are for age, sex, BMI, regular smoking, regular alcohol, diabetes mellitus and heart rate. $^{*}P<0.05$, $^{**}P<0.005$, $^{***}P<0.0001$ vs. NT; $^{\dagger}P<0.05$, $^{\dagger\dagger}P<0.0001$ vs. Untreat-HTN; $^{\ddagger}P<0.05$, $^{\ddagger\ddagger}P<0.005$ vs. Control-HTN.

Q and Zc (P_{QxZc}) and hence in high central aortic pulse pressure and uncontrolled SBP values. Indeed, 53% of resistant or refractory hypertensives had uncontrolled BP. Importantly, all resistant or refractory hypertensives were receiving low dose HCTZ and 28% were receiving spironolactone therapy.

Until recently, there has been little evidence to suggest a marked contribution of increases in systemic blood flow to

TABLE 1. Relative contribution of one standard deviation (SD) increase in haemodynamic factors to resistant or refractory hypertension

	One SD	Wald ^{2}	Odds ratio (95% CI)	*P* value
RHTN vs. NT				
SV	52.59	46.60	5.61 (3.55 to 9.60)	<0.0001
Q	190.9	44.10	5.16 (3.29 to 8.72)	<0.0001
SVR	9.93	29.69	0.26 (0.15 to 0.41)	<0.0001
1/TAC	0.23	4.83	0.72 (0.52 to 0.96)	0.028
Zc	43.33	0.41	1.10 (0.83 to 1.46)	0.52
RHTN vs. Untreat-HTN				
SV	52.34	33.36	2.81 (2.01 to 4.07)	<0.0001
Q	185.0	28.74	2.56 (1.84 to 3.68)	<0.0001
SVR	10.26	34.24	0.22 (0.13 to 0.35)	<0.0001
1/TAC	0.27	18.16	0.43 (0.29 to 0.62)	<0.0001
Zc	49.35	2.60	0.78 (0.57 to 1.04)	0.107
RHTN vs. Control-HTN				
SV	52.50	24.93	3.79 (2.33 to 6.68)	<0.0001
Q	216.9	17.34	2.54 (1.67 to 4.04)	<0.0001
SVR	6.44	14.59	0.48 (0.32 to 0.69)	0.0001
1/TAC	0.26	5.89	0.62 (0.41 to 0.89)	0.015
Zc	40.19	0.77	1.18 (0.83 to 1.77)	0.379

Models include the haemodynamic factor listed as well as age, sex, BMI, regular smoking, regular alcohol, diabetes mellitus and heart rate. Control-HTN, treated and controlled hypertensives; NT, normotensives; RHTN, resistant or refractory hypertensives; Untreat-HTN, untreated hypertensives.

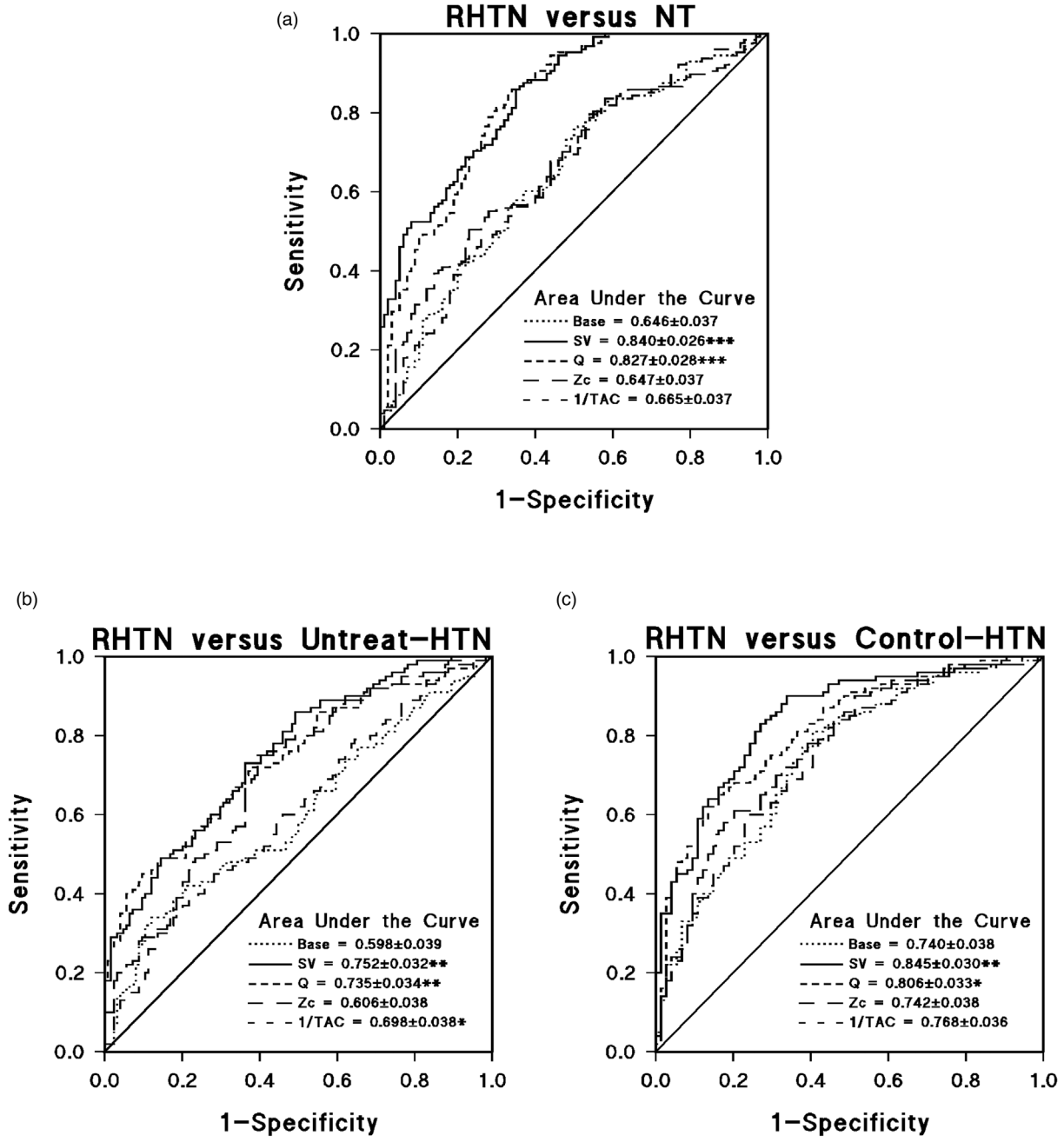


FIGURE 3 Predictive performance of haemodynamic correlates of blood pressure for resistant or refractory hypertension (RHTN) vs. normotension (NT) (panel a), untreated hypertension (Untreat-HTN) (panel b), or controlled hypertension (Control-HTN) (panel c), in participants of African ancestry. Data shown are the receiver operating characteristic (ROC) curves for the base model (base), consisting of conventional risk factors for hypertension, and the impact on the ROC curve of the addition of haemodynamic correlates of blood pressure to the base model (Base). Base model includes age, sex, BMI, regular smoking, regular alcohol, diabetes mellitus and heart rate. SV, stroke volume; Q, peak aortic flow; Zc, aortic characteristic impedance; TAC, total arterial compliance. $*P<0.05$, $**P<0.001$, $***P<0.0001$ vs. base model.

primary hypertension. In this regard, only some studies have demonstrated a modest contribution of systemic blood flow to isolated systolic hypertension particularly over a young adult age range [22–25]. However, more recent studies conducted in an African population have demonstrated a striking age-related increase in systemic blood flow as a major correlate of hypertension [9,10]. As the impact of systemic blood flow on hypertension in these studies was noted in treated hypertensives, all of whom were receiving low dose HCTZ [10], these data raise the question of whether, even on diuretic therapy, refractoriness or resistance to hypertension in this ethnic group is in-part determined by an inability to control increases in systemic blood flow. The present study provides clear evidence that resistance or refractoriness to antihypertensive agents in this ethnic group, is indeed strongly associated with high systemic blood flow despite treatment with low-dose diuretic therapy. In contrast, none of the vascular determinants of BP (increased SVR or Zc, or decreased TAC) were independently associated with resistant or

TABLE 2. Impact of adding haemodynamic correlates to the base model, consisting of standard risk factors for hypertension, on predictive performance for resistant or refractory hypertension

	AUC and difference			Integrated discrimination improvement		Net reclassification improvement	
Haemodynamic correlate	Base	Added	Δ (SE)	IDI (95% CI)	*P*	NRI (95% CI)	*P*
RHTN vs. NT							
SV	0.646	0.840	0.194 (0.037)**	0.303 (0.238 to 0.367)	<0.0001	0.679 (0.433 to 0.925)	<0.0001
Q	0.646	0.827	0.181 (0.037)**	0.287 (0.224 to 0.350)	<0.0001	0.864 (0.628 to 1.101)	<0.0001
1/TAC	0.646	0.665	0.022 (0.020)	0.020 (0.001 to 0.038)	0.037	0.201 (−0.057 to 0.458)	0.133
Zc	0.646	0.647	0.001 (0.007)	0.002 (−0.004 to 0.007)	0.535	0.003 (−0.253 to 0.259)	0.981
RHTN vs. Untreat-HTN							
SV	0.598	0.752	0.154 (0.041)**	0.171 (0.119 to 0.222)	<0.0001	0.591 (0.339 to 0.843)	<0.0001
Q	0.598	0.735	0.137 (0.042)**	0.146 (0.098 to 0.195)	<0.0001	0.592 (0.342 to 0.841)	<0.0001
1/TAC	0.598	0.698	0.100 (0.038)*	0.095 (0.057 to 0.133)	<0.0001	0.421 (0.166 to 0.675)	0.002
Zc	0.598	0.606	0.008 (0.022)	0.011 (−0.003 to 0.025)	0.123	0.236 (−0.021 to 0.492)	0.473
RHTN vs. Control-HTN							
SV	0.740	0.845	0.105 (0.030)**	0.172 (0.117 to 0.227)	<0.0001	0.604 (0.318 to 0.890)	<0.0001
Q	0.740	0.806	0.067 (0.028)*	0.102 (0.058 to 0.147)	<0.0001	0.634 (0.358 to 0.909)	<0.0001
1/TAC	0.740	0.768	0.028 (0.021)	0.036 (0.007 to 0.064)	0.016	0.159 (−0.137 to 0.455)	0.300
Zc	0.740	0.742	0.002 (0.009)	0.004 (−0.005 to 0.012)	0.411	0.049 (−0.247 to 0.345)	0.321

The base model included, sex, age, BMI, regular smoking, regular alcohol, diabetes mellitus and heart rate. IDI and NRI estimates are given with 95% CI.
AUC, area under the receiver operating characteristic (ROC) curve; Control-HTN, treated and controlled hypertensives; IDI indicates integrated discrimination improvement; NRI, net reclassification improvement; NT, normotensives; Q, peak aortic blood flow; RHTN, resistant or refractory hypertensives; SV, stroke volume; TAC, total arterial compliance; Untreat-HTN, untreated hypertensives; Zc, aortic characteristic impedance.
*$P < 0.01$.
**$P < 0.0005$ for significant change in AUC.

refractory hypertension. The present study therefore identifies a haemodynamic factor that accounts for resistant or refractory hypertension, a well recognized high-risk group [26], in groups in Africa.

The high systemic flow in resistant or refractory hypertension was accompanied by a greater filling volume. It is possible that reduced renal function and increased aldosterone-to-renin ratios may contribute to the high end diastolic volumes noted. In this regard, we have previously reported that age-related increases in stroke volume, and hence blood pressure, are associated with increases in end diastolic volume and aldosterone-to-renin ratios [9], and decreases in renal function (glomerular filtration rate and fractional sodium excretion) [27]. The high filling volumes in resistant or refractory hypertension were not accompanied by eccentric left ventricular hypertrophy. Indeed, both concentric and eccentric left ventricular hypertrophy are associated with similar increases in end diastolic volume and stroke volume [28].

Whether the high systemic blood flow in resistant or refractory hypertension noted in the present study is because systemic blood flow contributes to more severe forms of hypertension which require more extensive therapy to achieve BP control, or because of a lack of response to therapy, is not clear. This question requires an evaluation of the haemodynamic determinants of BP off therapy and then again after therapeutic intervention, in those with resistant or refractory hypertension, an approach which is not ethically feasible. However, all patients were receiving diuretic therapy, and hence, if diuretic therapy is indeed able to achieve reductions in systemic blood flow, the impact is clearly inadequate. Whether alternative diuretic approaches, including the use of spironolactone can achieve better effects requires further evaluation. In this regard, only 28% of resistant or refractory hypertensives in the current study were receiving spironolactone as part of their antihypertensive therapy.

In the present study, resistant or refractory hypertensives had markedly lower SVR values than normotensives, untreated hypertensives and treated-controlled hypertensives. In addition, resistant or refractory hypertensives had TAC values that were similar to normotensives and higher than untreated hypertensives and treated-controlled hypertensives. This is likely to be accounted for by the aggressive use of several classes of additional antihypertensive agents all of which decrease BP through arterial or arteriolar effects. Indeed, in the present study hydralazine, and/or α_1-adrenergic receptor blockers were employed in a quarter of the patients with resistant or refractory hypertension. Thus, to achieve even close to BP control in many patients, supraphysiological (pharmacological) levels of vasodilation were required. By decreasing SVR and increasing TAC, these agents are likely to have decreased resistance to flow and contributed toward even higher systemic blood flows. Hence, part of the striking increases in systemic flow noted in resistant or refractory hypertensives may be attributed to a high output state mediated by the necessary pharmacological interventions to achieve BP control. Indeed, the high systemic flow was accompanied by a high ejection fraction associated with low SVR, high TAC and high filling volume. Nevertheless, the fact that even close to BP control could only be achieved in 47% of these patients with supraphysiological vasodilation, points to the fact that systemic blood flow must have been uncontrolled even before pharmacological interventions were initiated.

A dominant factor accounting for the inability to control BP in resistant or refractory hypertension may be attributed to nonadherence to therapy [26,29,30]. Although we did not employ urinary samples to identify the presence of antihypertensives or their metabolites, the chances that

nonadherence to therapy explains resistant or refractory hypertension in a significant proportion of the study sample is low. In this regard, it is difficult to envisage a situation where nonadherence to therapy results in marked decreases in SVR in hypertensives not taking therapy. Indeed, the present study suggests that in populations where hypertension is so strongly volume dependent, that a reduction in SVR below normal levels may be a useful index indicating that resistant or refractory hypertensives are in fact taking therapy.

There are several limitations to the current study that warrant consideration. As the present investigation is cross-sectional in design, no conclusions can be drawn as to whether the relationships noted are indeed cause and effect. Longitudinal studies are therefore required to determine whether increases in systemic blood flow predict the development of resistance or refractoriness to therapy in hypertension. However, as increases in systemic blood flow begin from an early adult age and progress across the full adult lifespan [9], these studies will require follow-up across the full adult lifespan in this population. Second, we did not assess dietary salt intake, and hence whether an excess Na^+ intake contributed to resistance or refractoriness to hypertension is unknown. However, we have previously noted that in this population Na^+ intake is not particularly high, and that habitual Na^+ intake is not associated with systemic blood flow [31]. Third, we did not perform ambulatory BP monitoring to confirm the inability of 3 or more antihypertensive agents to control BP. However, it is unlikely that the marked increases in systemic blood flow noted in resistant or refractory hypertensives would reflect an in-office, but not an out-of-office effect. Last, we did not assess systemic blood flow using referent (gold-standard) magnetic resonance imaging. However, the age-dependent increases in systemic blood flow noted in a population of African ancestry, have previously been replicated using both outflow tract and LV internal diameter measurements and demonstrate consistent findings [9,10].

In conclusion, the present study shows a striking increase in systemic blood flow associated with resistant or refractory hypertension in a group of African ancestry living in sub-Saharan Africa. These effects were noted despite the consistent use of low-dose thiazide diuretic therapy. These data therefore suggest that resistance or refractoriness to antihypertensive therapy in groups of African ancestry living in sub-Saharan Africa may in-part be attributed to a limited ability to target a fundamental cause of hypertension (increased systemic blood flow) with commonly employed diuretics in this ethnic group.

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Conflicts of interest

There are no conflicts of interest.

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