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Aortic characteristic impedance-induced increases in forward wave but not central arterial pulse pressure beyond brachial blood pressure in coronary artery disease

Vernice R. Peterson[a,*], Danelle Els[a,*], Eitzaz Sadiq[b], Ravi Naran[a], Taalib Monareng[b], Talib Abdool-Carrim[b], Ismail Cassimjee[b], Girish Modi[b], Gavin R. Norton[a], Ferande Peters[a], and Angela J. Woodiwiss[a,*]

Background: Whether coronary artery disease (CAD) associates with proximal aortic stiffness-induced increases in central arterial forward wave pressures (Pf), but not peak central arterial pulse pressure (PPc) beyond peripheral PP, is uncertain. Therefore, we aimed to investigate the relationship between CAD and aortic characteristic impedance (Zc) and Pf beyond brachial PP and PPc.

Methods: From central pressure (SphygmoCor), and aortic velocity and diameter measurements (echocardiography), we compared Zc ($n = 71$) and central arterial pressure wave morphology ($n = 189$) in patients with CAD, to 210 age- and sex-matched controls, and patients with stroke or critical limb ischemia (CLI) ($n = 287$).

Results: With adjustments for confounders, including mean arterial pressure and aortic root diameter, Zc was increased in patients with CAD compared to controls and patients with stroke or CLI ($P < 0.0001$). The early systolic pressures generated by the product of peak aortic flow (Q) and Zc (P_{QxZc}), and Pf were also increased in patients with CAD compared to controls and patients with alternative arterial diseases ($P < 0.0005$). Enhanced P_{QxZc} at peak PPc, rather than increases in re-reflected wave pressures, accounted for increases in Pf. After further adjustments for brachial PP or SBP, the higher Pf values in patients with CAD were retained ($P < 0.01$ to $P < 0.0005$). In contrast, although peak PPc was higher in patients with CAD or alternative arterial diseases compared to controls ($P < 0.05$ to $P < 0.0005$), these differences were abolished by further adjustments for brachial BP.

Conclusion: Increases in stiffness-associated proximal aortic Zc in patients with CAD translate into increases in Pf, but not peak PPc, beyond brachial BP. Hence, the pulsatile load responsible for CAD is beyond brachial BP and poorly indexed by PPc.

Graphical abstract: http://links.lww.com/HJH/C771

Keywords: aortic impedance, Aortic stiffness, coronary artery disease, critical limb ischaemia, stroke

Abbreviations: AUC, area under the curve; BMI, body mass index; BP, blood pressure; CAD, coronary artery disease; CLI, critical limb ischemia; HDL, high-density lipoprotein; LDL, low-density lipoprotein; LV, left ventricular; LVOT, left ventricular outflow tract; Pb, backward travelling pressure waves; Pf, forward wave pressures; PP, pulse pressure; PPc, peak central arterial pulse pressure; P_{QxZc}, pressures generated by product of peak aortic flow and aortic characteristic impedance; Q, peak aortic flow; ROC, receiver operator characteristic; SBP, systolic blood pressure; Zc, aortic characteristic impedance

INTRODUCTION

The role of central arterial as opposed to brachial blood pressure (BP) as a cause of cardiovascular disease remains controversial. Several factors determine differences between central aortic and peripheral BP. Through a graded increase in impedance to flow, pulse pressure (PP) is amplified from the central to the peripheral pulse [1]. Moreover, peak central arterial PP (PPc) in the aorta, but not peripheral PP in the brachial artery, is determined by the sum of forward pressure (Pf) waves and backward (Pb) travelling pressure waves derived from reflections off distal arterial sites [1]. Increases in large artery stiffness, which increase central more than peripheral arterial impedance, decrease amplification of the arterial pulse from the aorta to the brachial pulse [1]. Thus, brachial BP is thought to be limited as a surrogate of aortic stiffness-induced

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[a]Cardiovascular Pathophysiology and Genomics Research Unit, Schools of Physiology and [b]Clinical Medicine, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa

Correspondence to Angela J. Woodiwiss, Cardiovascular Pathophysiology and Genomics Research Unit, School of Physiology, University of the Witwatersrand Medical School, 7 York Road, Parktown, 2193, Johannesburg, South Africa.
Tel: +27 11 717 2363; e-mail: angela.woodiwiss@wits.ac.za

*V.R.P., D.E. and A.J.W. contributed equally to this work.

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increases in aortic impedance to flow and hence BP. Nonetheless, despite a clear ability of indexes of aortic stiffness to predict cardiovascular risk beyond brachial BP [2,3,4], peak PPc has demonstrated a limited [5], or no [4,6] ability to predict risk independent of brachial BP. However, while peak PPc may not predict risk beyond brachial BP, the role of Pf as a risk predictor beyond both brachial PP and peak PPc, is uncertain.

Arterial beds distal to the aorta that are affected by plaque rupture or stenoses, and which are responsible for myocardial infarction, stroke and peripheral arterial disease, have an arterial pulse wave that differs from that noted in the central aorta. Indeed, while central arterial wave reflections that determine PPc are the sum of waves derived from a variety of arterial sites often close to the aorta [7,8], wave reflections that contribute to distal arterial PP are derived from local vascular beds. Thus, while the contribution of reflected waves to cardiac afterload is indeed Pb measured in the central aorta [9], the contribution of reflected waves to load in arterial beds affected by plaque rupture or stenosis may not be the same as Pb identified in the proximal aorta. As peak PPc is determined by summation of Pf and Pb, peak PPc may therefore also be an inappropriate reflection of pulsatile load in arterial beds affected by plaque rupture or stenoses. However, the pressure wave in arterial branches of the aorta affected by plaque rupture or stenosis is derived from the pulse generated in the proximal aorta and transmitted into distal arterial sites, in other words Pf [1]. Thus, while peak PPc may not be a determinant of arterial events beyond brachial BP, Pf could predict cardiovascular risk beyond brachial BP. In this regard, when aortic stiffness is increased, while PPc is not related to cardiovascular risk factors beyond brachial BP, Pf is associated with risk factors independent of brachial BP [10]. Furthermore, while PPc is not associated with either stroke or critical lower limb ischemia (CLI) beyond brachial BP, through effects of an enhanced aortic stiffness on characteristic impedance, Pf is markedly increased in stroke and CLI independent of brachial BP, particularly over a younger adult age [11,12]. Furthermore, in the Framingham Heart Study, while PPc was not an independent predictor of largely arterial events beyond brachial BP [4], through effects of an enhanced aortic stiffness on characteristic impedance [13], Pf was an independent predictor of events beyond brachial BP [14]. Nevertheless, whether the ability of Pf, but not PPc, to predict the risk of arterial events beyond brachial BP is attributed to an impact of coronary artery disease (CAD), is unknown. Consequently, in the present study we assessed whether a relationship exists between angiographically proven CAD and aortic characteristic impedance and Pf beyond both brachial PP and PPc. We compared proximal aortic function between patients with CAD and both age- and sex-matched controls and patients with stroke or CLI.

METHODS

Study groups

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 numbers: M21-01-34; M02-04-72 renewed as M07-04-69, M12-04-108, M17-04-01 and M22-03-93; M16-04-11 renewed as M2111155; M14-04-29 renewed as M19-06-88). Participants gave informed written consent. The datasets analyzed during the current study are not publicly available, but are available from the corresponding author on reasonable request. The study design [11,12] and the methodology [9,11,12,15,16] have previously been described. Consecutive patients undergoing coronary angiography with angiographically proven coronary artery disease (CAD) (>60% stenosis of at least one coronary artery) ($n = 189$) were recruited from Life Flora Hospital, Johannesburg, South Africa. Aortic function was assessed in 71 CAD patients with high-quality velocity assessments in the left ventricular (LV) outflow tract (LVOT) using paired pressure and flow wave analysis as well as using wave separation analysis assuming a physiological flow wave. The remaining patients with CAD had aortic function assessed using wave separation analysis assuming a physiological flow wave. For comparative purposes age- and sex-matched patients with either stroke ($n = 109$) or CLI ($n = 178$) were recruited from the Charlotte Maxeke-Johannesburg Academic Hospital, Johannesburg, South Africa, as previously described [11,12]. Inclusion was based on a diagnosis of angiographically proven CAD or stroke or CLI and in order to avoid a selection bias, there were no exclusion criteria other than an inability to consent or to obtain consent from a family member in the case of a dysphasia. The presence of CLI was defined as the occurrence of ischemic leg pain at rest for more than two weeks, or the existence of ulcers or gangrene attributable to occlusive arterial disease. Patients with a new stroke, defined as a focal neurological deficit of vascular origin were evaluated. Patients with meningitis based on cerebrospinal fluid examination, or the presence of intracranial malignancy or intracranial mass lesions on imaging, and those with a vasculitis were excluded. Data obtained in patients with vascular pathology were compared with data acquired in 210 age- and sex-matched randomly recruited participants living in the South-Western Townships (Soweto) of Johannesburg, South Africa, using the population census figures of 2001.

Clinical, demographic, and anthropometric measurements

A questionnaire was administered to obtain demographic and clinical information including each participant's medical history, the use of medication and tobacco and alcohol use [9,11,12,15,16]. Clinical information, including brain imaging and angiographic data, was also extracted from the hospital records and confirmed by the attending physician. Clinical data included the presence of risk factors (hypertension, and diabetes mellitus and the therapy thereof). Height and weight were measured using standard approaches and obesity was defined as a body mass index (BMI) $\geq 30\,kg/m^2$. Blood tests were performed including a fasting glucose and lipid profile. Participants were considered to have diabetes mellitus if they had a fasting plasma glucose concentration $\geq 7\,mmol/l$, or glucose-lowering agents had been prescribed. Brachial BP was measured according to guidelines and taken as the mean of five

measurements. Participants with a BP ≥140/90 mm Hg or those receiving antihypertensive medication were considered to have hypertension.

Central arterial hemodynamics

Central arterial hemodynamics were determined noninvasively from central arterial pressure recordings obtained using pulse wave analysis in all participants and, in addition, aortic velocity and diameter assessments obtained in the outflow tract in 71 patients with CAD, all patients with alternative arterial diseases and all controls, as previously described [9,11,12,15,16]. After participants had rested for 15 min in the supine position, arterial waveforms at the radial (dominant arm) pulse were recorded by applanation tonometry using a high-fidelity SPC-301 micromanometer (Millar Instrument, Inc., Houston, Texas) interfaced with a computer employing SphygmoCor, version 9.0 software (AtCor by CARDIEX Limited, Sydney, New South Wales, Australia). A central arterial pulse was derived from the radial pulse using a validated generalized transfer function in SphygmoCor software. Immediately after central arterial pressure waveforms were obtained, aortic velocity and diameter measurements were obtained with the participant in the supine position using an ACUSON SC2000 Diagnostic ultrasound system (Siemens Medical Solutions, USA, Inc.). Velocity waveforms were obtained in the 5-chamber view. 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. The largest diameter recorded in systole was used to construct an aortic flow waveform where flow (Q) is velocity x aortic cross-sectional area.

Central arterial function

Characteristic impedance (Zc) was determined in the time domain [13,17] using approaches previously described [9,11,15,16] and validated against invasive pressure measurements [18]. In this regard, Zc was calculated as change in pressure/change in flow up until 95% of peak aortic flow. Using Zc values and flow and pressure waveforms, wave separation analysis was performed, and Pf determined from (aortic PP + QxZc)/2 and Pb from (aortic PP − QxZc)/2. The contribution to Pf of pressures determined by an interaction between Q and Zc was identified from the pressures generated by the product of peak aortic Q and Zc (P_{QxZc}) [19]. Re-reflected wave pressures were determined from the difference between Pf and P_{QxZc} assessed at peak PPc [19]. All patients with CAD, all patients with alternative arterial diseases and all controls, also had wave separation analysis performed assuming a physiological flow wave, as previously described [20].

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). Dichotomous variables are expressed as proportions or percentages. Multiple logistic regression analysis was performed to determine the independent relations between central arterial function and arterial disease. Multivariate adjusted analysis of variance was employed to determine differences in arterial function between cases and controls. Adjustments were for age and sex, those factors associated with arterial disease, for distending pressure effects on pulsatile hemodynamic parameters (mean arterial pressure), heart rate and for brachial PP or SBP where indicated. Factors associated with arterial disease that were included in the models were BMI, hypertension, diabetes mellitus, smoking and HDL cholesterol concentrations. The predictive accuracy of central arterial function in the detection of CAD was determined from the area under (AUC) the receiver operator characteristic (ROC) curve. As no differences in arterial function were noted at any age in patients with stroke versus CLI [11], analysis was performed in these groups together.

RESULTS

Participant characteristics

The CAD patients were primarily in the middle to older age range, 93% were greater than 45 years of age. The participant characteristics with adjustments for age and sex are given in Table S1, Supplemental Digital Content, http://links.lww.com/HJH/C770. Irrespective of the type of vascular pathology, patients with vascular disease (CAD and stroke/CLI) had a greater prevalence of conventional risk factors. HDL cholesterol concentrations were lower in patients with vascular disease compared to age- and sex-matched controls (Table S1, Supplemental Digital Content, http://links.lww.com/HJH/C770). Although LDL cholesterol concentrations were also lower in patients with arterial disease compared to age- and sex-matched controls (Table S1, Supplemental Digital Content, http://links.lww.com/HJH/C770), 47.6% of patients with CAD and 86.6% of patients with stroke/CLI were receiving lipid-lowering therapy at the time of obtaining fasting blood samples. BMI was higher in patients with CAD as compared to both controls and patients with stroke/CLI. No differences in demographic or clinical features were noted in CAD patients with or without high-quality velocity assessments in the LVOT.

Arterial function in coronary artery disease

Differences in brachial BP and multivariate-adjusted aortic function were noted between cases and controls (Fig. 1, Figure S1, Supplemental Digital Content, http://links.lww.com/HJH/C770, Table 1, Table S2, Supplemental Digital Content, http://links.lww.com/HJH/C770). Data for arterial function are shown both before and after adjustments for brachial PP and SBP. Both brachial PP and SBP were higher in patients with vascular disease compared to controls (Table 1, Table S2, Supplemental Digital Content, http://links.lww.com/HJH/C770). However, brachial PP and SBP were higher in patients with CAD compared to patients with stroke or CLI (Table 1, Table S2, Supplemental Digital Content, http://links.lww.com/HJH/C770). Pf, Zc, maxP_{QxZc} and P_{QxZc} at PPc, but not Pb, were greater in patients with vascular disease compared to controls (Fig. 1, Figure S1, Supplemental Digital Content, http://links.lww.com/HJH/C770, Table 1, Figure S1, Supplemental Digital Content, http://links.lww.com/HJH/C770). However, in

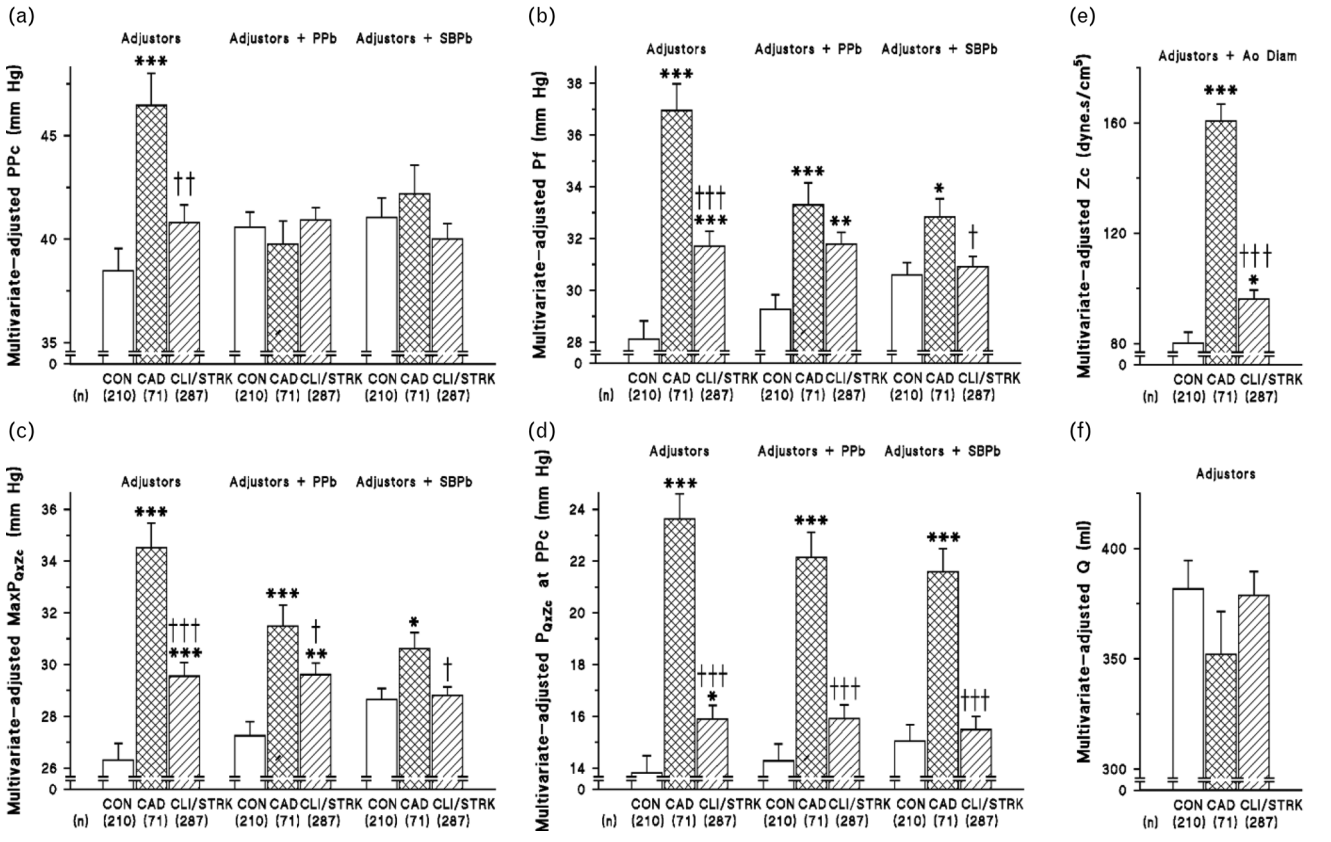

FIGURE 1 Impact of adjustments for brachial pulse pressure (PPb) or systolic BP (SBPb) on multivariate adjusted central arterial functional changes in those with angiographic coronary artery disease (CAD) or alternative arterial diseases (critical limb ischemia and stroke [CLI/STRK]) as compared to age and sex-matched controls (CON). Adjustments are for age, sex, BMI, heart rate, hypertension, mean arterial pressure, diabetes mellitus, smoking, HDL cholesterol concentrations and brachial PP or SBP as indicated. PPc, central arterial PP; Zc, proximal aortic characteristic impedance; Pf, forward wave pressures; maxP_{QxZc}, contribution of pressures generated by the product of aortic flow (Q) and Zc; P_{QxZc} at PPc, contribution of pressures generated by the product of aortic flow (Q) and Zc at the peak of PPc. $n = 71$ for CAD with high-quality aortic velocity assessments in the LV outflow tract (LVOT). $^{*}P < 0.05$, $^{**}P < 0.005$, $^{***}P < 0.0005$ versus age and sex-matched controls; $^{+}P < 0.05$, $^{++}P < 0.005$, $^{+++}P < 0.0005$ versus CAD.

TABLE 1. Multivariate adjusted brachial and central arterial pulsatile pressures

	Adjustments	Controls ($n = 210$)	CAD ($n = 71$)*	Stroke + CLI ($n = 287$)
Brachial pulse pressure (PPb) (mmHg)	†	47.4 ± 16.8	61.0 ± 13.7‡‡‡	51.5 ± 16.1‡,ǁǁ
Brachial SBP (mmHg)	†	128 ± 11	139 ± 9‡‡‡	133 ± 11‡‡‡,ǁǁ
P_{QxZc} at peak PPc (mmHg)	†	26.3 ± 9.4	34.5 ± 8.0‡‡‡	29.6 ± 9.0‡‡,ǁ
P_{QxZc} at peak PPc (mmHg)	† + PPb	27.3 ± 8.0	31.5 ± 6.9‡‡‡	29.6 ± 7.6‡‡,ǁ
P_{QxZc} at peak PPc (mmHg)	† + SBPb	28.6 ± 6.1	30.6 ± 5.2‡	28.8 ± 5.8ǁ
Backward wave pressure (Pb) (mmHg)	†	13.2 ± 6.4	13.9 ± 5.4	13.8 ± 6.1
Backward wave pressure (Pb) (mmHg)	† + PPb	13.8 ± 5.4	11.9 ± 4.7‡‡	13.8 ± 5.1ǁ
Backward wave pressure (Pb) (mmHg)	† + SBPb	14.1 ± 5.8	12.4 ± 5.0‡	13.5 ± 5.4
Backward wave pressure (Pb) (mmHg)#	†	13.7 ± 6.7	14.4 ± 5.8	14.4 ± 6.6
Backward wave pressure (Pb) (mmHg)#	† + PPb	14.3 ± 5.2	12.7 ± 5.0‡	14.8 ± 5.1ǁ
Backward wave pressure (Pb) (mmHg)#	† + SBPb	14.2 ± 4.6	13.4 ± 4.6	14.4 ± 4.6
Re-reflected wave pressure (mmHg)	†	12.0 ± 6.4	11.4 ± 5.5	12.5 ± 6.1
Re-reflected wave pressure (mmHg)	† + PPb	12.5 ± 5.8	9.6 ± 5.1‡‡‡	12.5 ± 5.4ǁǁ
Re-reflected wave pressure (mmHg)	† + SBPb	12.7 ± 6.2	10.2 ± 5.3‡‡	12.3 ± 5.8ǁ

Data are mean ± SD. P_{QxZc} at peak PPc, pressure generated by the product of aortic flow (Q) and characteristic impedance to flow (Zc) at the peak of PPc. Alternative central arterial pulsatile pressures are given in Fig. 1.
*Indicates CAD with high-quality aortic velocity assessments in the LV outflow tract (LVOT).
†Adjustments are for age, sex, BMI, heart rate, hypertension, mean arterial pressure, diabetes mellitus, smoking and HDL cholesterol concentrations. Pb#, backward wave pressures determined from wave separation analysis with a physiological flow wave.
‡$P < 0.05$.
‡‡$P < 0.005$.
‡‡‡$P < 0.001$ versus controls.
ǁ$P < 0.05$.
ǁǁ$P < 0.005$.
ǁǁǁ$P < 0.0001$ versus CAD.

patients with CAD, Zc, Pf, maxP_{QxZc} and P_{QxZc} at PPc were greater than in patients with stroke/CLI (Fig. 1, Figure S1, Supplemental Digital Content, http://links.lww.com/HJH/C770). The higher Pf in patients with CAD persisted after adjustments for either brachial PP or SBP. Whereas after adjustments for brachial SBP, Pf in in patients with stroke/CLI was not greater than in controls (Fig. 1, Figure S1, Supplemental Digital Content, http://links.lww.com/HJH/C770). Although, PPc was greater in patients with vascular disease compared to controls, adjustments for either brachial PP or SBP eliminated these differences (Fig. 1, Figure S1, Supplemental Digital Content, http://links.lww.com/HJH/C770).

Risk of coronary artery disease with arterial function

Figure 2 and Figure S2, Supplemental Digital Content, http://links.lww.com/HJH/C770 show the risk factor-independent relations (odds ratios) between arterial function and CAD. Central pulse pressure (PPc), Pf, maxP_{QxZc}, Zc and P_{QxZc} at PPc were independently associated with CAD (Fig. 2a, Figure S2A, Supplemental Digital Content, http://links.lww.com/HJH/C770). Moreover, the risk of CAD associated with Pf, maxP_{QxZc}, Zc and P_{QxZc} at PPc persisted with adjustments for either brachial PP or SBP (Fig. 2b and c, Figure S2B and S2C, Supplemental Digital Content, http://links.lww.com/HJH/C770). However, the risk of CAD associated with PPc was eliminated after adjusting for either brachial PP or SBP (Fig. 2B and C, Figure S2B and S2C, Supplemental Digital Content, http://links.lww.com/HJH/C770).

Aortic function versus conventional risk factors and coronary artery disease

In stepwise regression with brachial PP included in the models, Pf, Zc, maxP_{QxZc} and P_{QxZc} at peak PPc were independently associated with CAD (Table 2, Table S3, Supplemental Digital Content, http://links.lww.com/HJH/C770). However, peak PPc failed to show independent positive relations beyond brachial PP and conventional risk factors (Table 2, Table S3, Supplemental Digital Content, http://links.lww.com/HJH/C770). While brachial PP was associated with CAD in the absence of aortic function variables (Table 2, Table S3, Supplemental Digital Content, http://links.lww.com/HJH/C770), brachial PP was not associated with CAD in the presence of either Pf, maxP_{QxZc} or P_{QxZc} at peak PPc (Table 2, Table S3, Supplemental Digital Content, http://links.lww.com/HJH/C770). With Zc in the model, brachial PP was associated with CAD. However, Zc showed a stronger relationship with CAD than brachial PP ($P < 0.005$ for comparison of standardized β-coefficients). Notably, each of the aortic function variables demonstrated stronger associations with CAD than traditional risk factors (diabetes mellitus, HDL cholesterol, smoking), and were similar to (Pf and maxP_{QxZc}) or greater than (Zc and P_{QxZc} at peak PPc) hypertension in associations with CAD (Table 2).

Performance of aortic function

Brachial PP but not brachial SBP showed significant performance (AUC) for the detection of CAD (Fig. 3a and b). Central PP (PPc), Pf, Zc, P_{QxZc}, P_{QxZc} at peak PPc and Pb all showed a significant performance for the detection of CAD (Fig. 3c–f). The AUC for the detection of CAD for Zc and P_{QxZc} at peak PPc was significantly greater than that for both brachial PP and SBP (Fig. 3e and f). The AUC for CAD detection for Pf (Figure 3C and D) and P_{QxZc} (Fig. 3e and f) was significantly greater than that for brachial SBP and similar to that for brachial PP. However, Pb showed a significantly lower AUC for CAD detection compared to brachial PP and SBP (Fig. 3c and d). PPc showed a significantly lower AUC for CAD detection compared to brachial PP, and a similar performance to brachial SBP (Fig. 3a and b).

DISCUSSION

In the present study, we assessed the extent to which, through increases in proximal aortic stiffness, increases in Pf are independently associated with CAD beyond brachial BP, while peak aortic PPc is not. We show that in patients with angiographically proven CAD compared to controls, a markedly enhanced proximal aortic Zc is noted independent of aortic root diameter and additional confounders, thus supporting the view that increases in proximal aortic stiffness are striking. These increases in Zc in CAD are even greater than that noted in patients with alternative arterial diseases (stroke or CLI). The increases in Zc in CAD translate into an enhanced forward travelling pressure wave (Pf) (via increases in the pressure generated by the product of Q and Zc [P_{QxZc}]) independent of brachial BP. In contrast, because backward wave pressures were not increased in CAD, no differences in PPc were noted beyond brachial BP.

While measures of aortic stiffness have provided a clear ability to predict cardiovascular events beyond brachial BP [2,3], central aortic BP, which is strongly determined by aortic stiffness, does not [4–6]. Several hypotheses have therefore been developed to explain the impact of aortic stiffness beyond either central arterial or peripheral BP. However, little attention has been given to the fact that even when peak central arterial BP fails to associate with risk factors, end organ measures, and stroke or CLI, or to predict events beyond brachial BP, that aortic stiffness-induced increases in forward travelling pressure waves both associate with risk factors [10], stroke and CLI or end organ measures [11,12] and predict events [14] beyond brachial BP. What has not been given due consideration is that because Pb in the proximal aorta are quite distinct from those seen in arterial beds where plaque rupture or occlusion occurs [7,8], and that Pb contributes significantly to age-related increases in PPc [21], that PPc is a poor surrogate of the arterial pulse that contributes to arterial events. In contrast, the arterial wave generated in arterial beds that contributes to arterial events is derived from Pf generated in the central aorta. Consequently, Pf may be the central arterial pressure measurement that predicts arterial events beyond brachial PP. Although relationships between Zc-induced increases in Pf, but not peak PPc beyond brachial BP have previously been demonstrated with stroke and CLI [11,12], no previous studies have been performed with CAD. The present study therefore provides the first

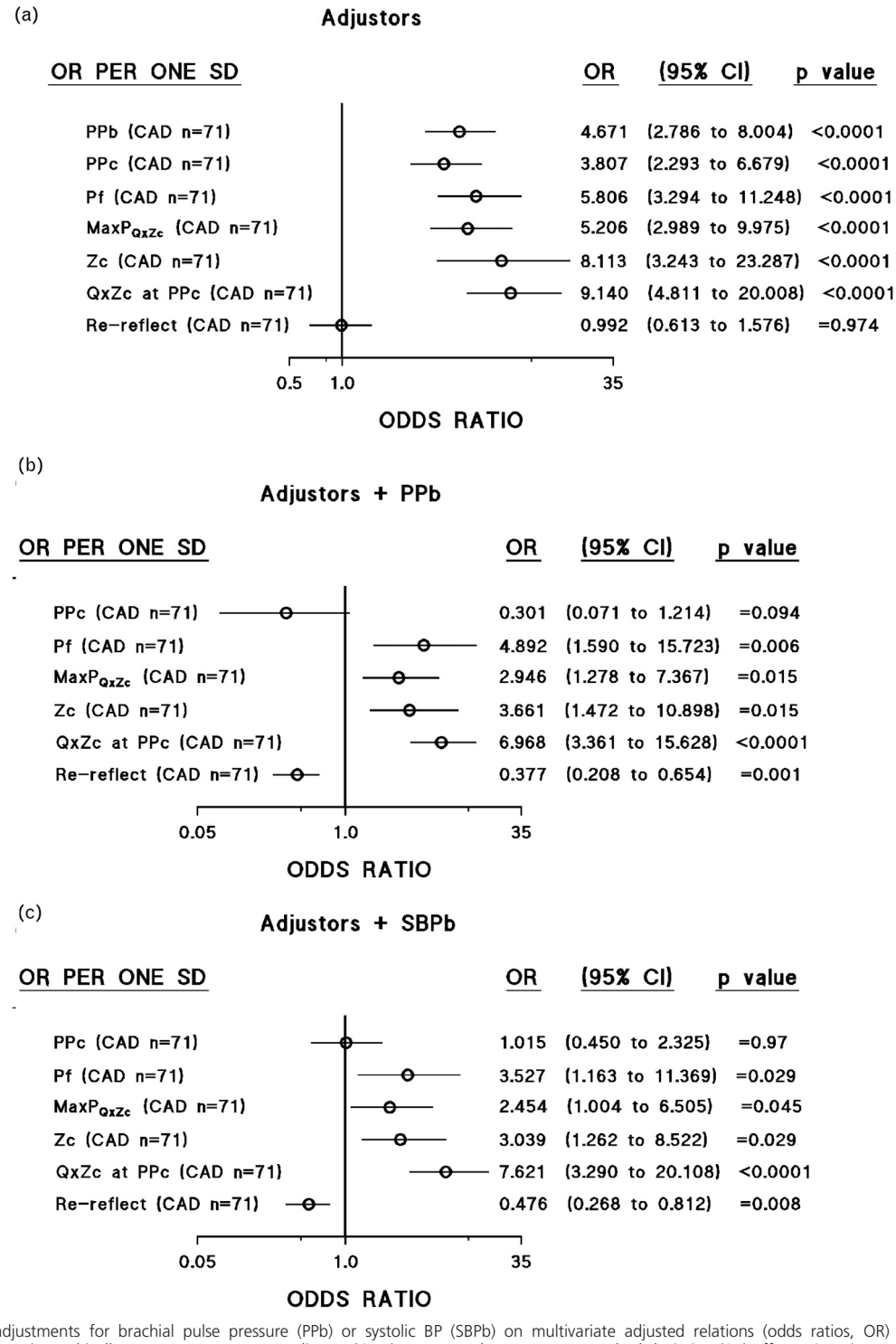

FIGURE 2 Impact of adjustments for brachial pulse pressure (PPb) or systolic BP (SBPb) on multivariate adjusted relations (odds ratios, OR) between central arterial functional changes and angiographically proven coronary artery disease (CAD). Data are shown as one standard deviation (SD) effects. See Figure 1 for abbreviations. Adjustments are for age, sex, BMI, heart rate, hypertension, mean arterial pressure, diabetes mellitus, smoking, HDL cholesterol concentrations and brachial PP or SBP as indicated. $N = 71$ for CAD with high-quality aortic velocity assessments in the LV outflow tract (LVOT).

evidence that Zc-dependent increases in Pf, but not peak PPc are associated with CAD, compared to controls, beyond brachial BP (PP or SBP). Importantly, these increases in Pf beyond brachial BP were far more striking in patients with CAD than in patients with stroke or CLI.

The general mechanisms of arterial stiffening include: elastin fragmentation, collagen deposition, advanced glycosylation end-product mediated collagen and elastin cross-linking, vascular smooth muscle stiffening or enhanced tone, calcification, endothelial dysfunction and inflammation [22]. Furthermore, aging and increased burden of traditional cardiovascular risk factors, including dyslipidaemia, hypertension and diabetes, are associated with increased arterial stiffness [23]. These same factors are

TABLE 2. Relative contribution (standardized slopes [β-coefficients]) of central arterial functional changes versus conventional risk factors in associations with coronary artery disease, in CAD patients with high-quality aortic velocity assessments in the LV outflow tract (LVOT) (cases: $n = 71$: controls: $n = 210$)

CAD versus models with→	β-coeff. ± SEM PPb	β-coeff. ± SEM PPc	β-coeff. ± SEM Pf	β-coeff. ± SEM Zc	β-coeff. ± SEM P_{QxZc}	β-coeff. ± SEM P_{QxZc} at peak PPc
Brachial PP	0.368 ± 0.059***	0.746 ± 0.172***	0.129 ± 0.105	0.170 ± 0.057**	0.157 ± 0.093	0.043 ± 0.068
PPc	–	-0.432 ± 0.185*	–	–	–	–
Pf	–	–	0.277 ± 0.101**	–	–	–
Zc	–	–	–	0.421 ± 0.049***,†,‡	–	–
maxP_{QxZc}	–	–	–	–	0.255 ± 0.087**	–
P_{QxZc} at peak PPc	–	–	–	–	–	0.472 ± 0.061***,‡
Hypertension	0.254 ± 0.058***	0.249 ± 0.057***	0.263 ± 0.057***	0.257 ± 0.051***	0.260 ± 0.057***	0.254 ± 0.052***
Diabetes mellitus	0.061 ± 0.053	0.053 ± 0.052	0.048 ± 0.052	0.060 ± 0.047	0.041 ± 0.052	0.018 ± 0.048
Smoking	0.078 ± 0.053	0.102 ± 0.053	0.073 ± 0.052	0.070 ± 0.047	0.077 ± 0.052	0.065 ± 0.048
HDL cholesterol	-0.075 ± 0.052	-0.074 ± 0.052	-0.077 ± 0.052	-0.078 ± 0.047	-0.075 ± 0.052	-0.073 ± 0.047

β-coeff., standardized β-coefficient. See Figure 1 for abbreviations. Also included in the regression models are age, sex, BMI, heart rate and mean arterial pressure. For other abbreviations see Table 1.
*$P < 0.05$.
**$P < 0.005$.
***$P < 0.0001$ for relationship.
†$P < 0.005$ versus relationship with brachial PP.
‡$P < 0.005$ versus relationship with hypertension.

believed to play a role in CAD. Certainly, given the etiology of CAD, dyslipidaemia, endothelial dysfunction, inflammation and calcification play a role in increasing arterial stiffness in CAD. In turn, arterial stiffness causes early arrival of wave reflections in systole instead of diastole, thereby increasing systolic afterload and reducing diastolic coronary perfusion pressure, hence worsening CAD [24].

The clinical implications of the present study, although speculative, are worthy of consideration. There have been several suggestions that peak aortic central SBP or PP should be employed to either replace brachial BP measurements or enhance risk prediction beyond brachial BP. However, contemporary evidence does not support this approach [4–6]. Nevertheless, whether forward wave pressures enhance risk prediction for at least arterial events beyond brachial BP is uncertain. In this regard, while several studies suggest that this may be the case [10,11,12,14], alternative studies [25–27], suggest otherwise. However, those studies indicating a lack of ability of forward wave pressures to predict events, either reported on a small number of events [25,27], or where heart failure [26] was a dominant event. In this regard, through effects on afterload to the LV, wave reflection is a well described determinant of LV dysfunction [9] and heart failure [26]. The present study further supports the notion that forward wave pressures are enhanced beyond brachial BP in patients at risk of arterial disease, including stroke, peripheral arterial disease [11,12] and as indicated by the present study, CAD, compared to controls. Further studies are therefore required to assess the potential role of forward wave pressures as predictors of arterial events (not heart failure) beyond brachial BP.

In the present study, the role of Zc-induced increases in Pf beyond brachial BP was assessed in patients over the middle and older age range, rather than at a younger adult age range. This was because in South Africa, CAD seldom occurs over a younger adult age range. In contrast, in previous work where stroke and CLI were studied [11,12], in-part reported for comparator purposes in the present study, these studies [11,12] included patients who experienced events over a young adult age range (20–40 years). Although, as demonstrated in the present study, Pf failed to associate with stroke and CLI beyond brachial SBP over a largely older adult age range, as previously reported, Zc-induced increases in Pf were strongly associated with stroke and CLI beyond brachial BP over a younger adult age range [11,12]. Thus, the impact of stiffness-associated increases in Pf on arterial disease should not be seen as a change that affects only the elderly, but also those over a young to middle age range.

There are several limitations to the present study. Firstly, as the study design was a case-control analysis, the results may be subject to population stratification. However, data for a relatively large control sample were obtained from age- and sex-matched controls derived from a randomly selected community sample and data from relatively large case samples were obtained from sequentially admitted patients with similar demographic features. Secondly, as the patients were recruited from two hospitals, variations in patient populations, treatment protocols, and data collection methods, may introduce heterogeneity, which can affect the generalizability of the findings. Therefore, caution should be exercised when generalizing the outcomes due to the risk of bias.

In conclusion, in the present study, we show markedly enhanced proximal aortic Zc in patients with CAD, compared to controls, which is independent of confounders and greater than that noted in patients with alternative arterial diseases. The increased proximal aortic Zc in patients with CAD, compared to controls, translates into an enhanced Pf via an enhanced pressure generated by the product of Q and Zc [P_{QxZc}]). Aortic PP was not greater in patients with CAD independent of brachial BP, as Pb was not increased. However, the enhanced Pf and pressure generated by the product of Q and Zc (P_{QxZc}) in patients with CAD, compared to controls, were independent of brachial BP. Hence, the pulsatile load that causes CAD extends beyond brachial BP and is not measured well by PPc. The results provide new insight into the significance of arterial function in the etiology of CAD.

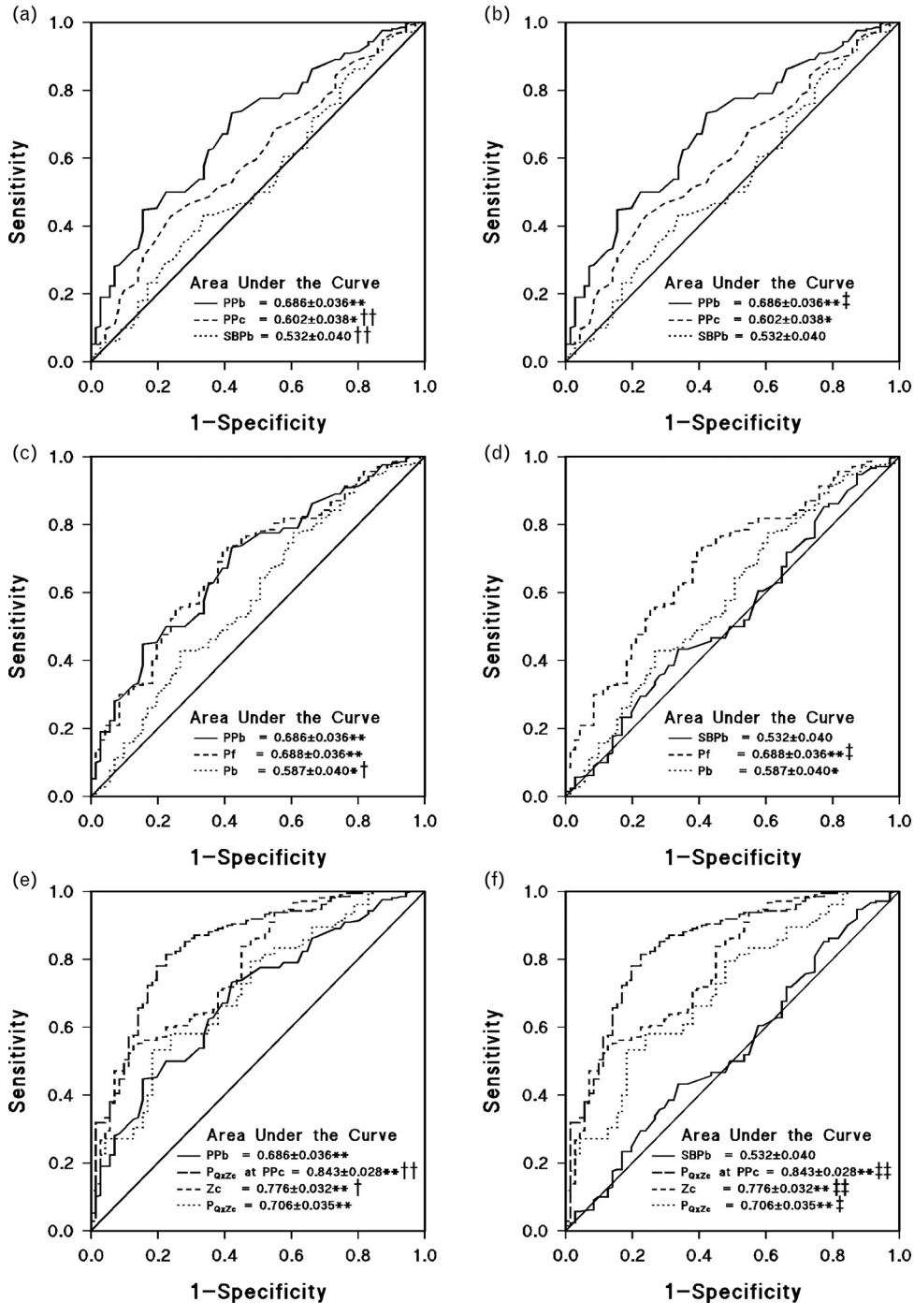

FIGURE 3 Receiver operator characteristic curves of arterial functional changes versus brachial pulse pressure (PPb) or systolic BP (SBPb) for the detection of angiographically proven coronary artery disease (CAD). See Figure 1 for abbreviations. $^{*}P<0.05$, $^{**}P<0.0001$ for the significance of AUC; $^{+}P<0.01$, $^{++}P<0.0001$ for comparison with AUC for brachial PP (left panels); $^{\ddagger}P<0.01$, $^{\ddagger\ddagger}P<0.0001$ for comparison with AUC for brachial SBP (right panels). All data are for CAD patients with high quality aortic velocity assessments in the LV outflow tract (LVOT) (n = 71).

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Conflicts of interest

There are no conflicts of interest.

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