Hypertension

ORIGINAL ARTICLE

Increased Backward Wave Pressures Rather than Flow Explain Age-Dependent Heart Rate Effects on Central, But not Peripheral Arterial Pressure

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ABSTRACT: Through both backward (Pb) and forward (Pf) wave effects, a lower heart rate (HR) associates with increased central (PPc), beyond brachial pulse pressure (PP). However, the relative contribution to Pf of aortic flow (Q) versus re-reflection of Pb, has not been determined. Using central pressure, aortic velocity and diameter measurements in the outflow tract (echocardiography), we constructed central pressure waveforms that account for the relative contribution of Q versus re-reflection to Pf. We thus evaluated the mechanisms of HR-PPc relations in a community sample (n=824) and the impact of age thereon. Inverse HR-PPc ($P<0.0001$), but not HR-brachial PP ($P=0.064$) relations were noted. The slope of HR-PPc relation was increased in older adults ($P<0.005$). HR was inversely associated with ventricular filling time, ejection duration, stroke volume, and peak Pf ($P<0.001$ to $P<0.0001$). However, an increased Q and hence pressures generated by the product of aortic characteristic impedance and Q did not account for Pf effects. Age-dependent HR-PPc and Pf relations were both accounted for by enhanced Pb ($P<0.0001$) with an increased Pf mediated by increments in wave re-reflection ($P<0.0001$). The lack of impact of ejection duration on PPc was explained by an increased time to peak Pb ($P<0.0001$). In conclusion, increases in PPc and Pf at a decreased HR are accounted for by an enhanced Pb rather than by a prolonged ejection or filling duration and hence flow (Q). These effects at a young-to-middle age are of little clinical significance, but at an older age, are of clinical importance. **(*Hypertension*. 2022;79:435–446. DOI: 10.1161/HYPERTENSIONAHA.121.18271.)**

• **Supplemental Material**

Key Words: cardiovascular disease ■ coronary artery disease ■ heart failure ■ heart rate ■ hypertension

The relationship between a lower heart rate (HR) and an increased central arterial (PPc), but not peripheral pulse pressure (PP), is well recognized.[1–3] The impact of HR on PPc[4,5] accounts in-part for the limited ability of β_1 selective adrenergic receptor blockers to reduce the risk of cardiovascular events in hypertension when employed as first-line agents.[6,7] As a consequence, guidelines recommend that β-blockers should not be used as first-line therapy for uncomplicated hypertension.[8] The impact of β-blockers on outcomes in hypertension and the central arterial effects produced, raise the question of how best to use all HR-reducing agents in cardiovascular disease without producing adverse effects on central arterial pressure, that are not detected at the peripheral pulse. Importantly, in the presence of several cardiac conditions, particularly coronary artery disease and heart failure, β-blockers are beneficial therapeutic agents.[9] However, their benefits in cardiac diseases often associated with hypertension, may be offset by deleterious effects on central arterial pressure. As a number of pharmacological agents employed in cardiovascular diseases reduce HR, identifying the mechanisms of HR effects on PPc is of importance.

Several mechanisms may explain relationships between HR and PPc beyond brachial PP.[1,5,10,11] The impact of increases in stroke volume (SV) produced by

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ORIGINAL ARTICLE

Novelty and Significance

What Is New?

- Whether the inverse relationship between heart rate (HR) and forward wave (Pf) and hence central arterial pulse pressure (PPc) is determined by flow (Q) or re-reflection of backward wave pressures (Pb), is uncertain.

What Is Relevant?

- We determined the relative contribution of increases in Q versus re-reflected wave pressures to the impact of a lower HR on Pf and hence PPc in a community studied across the full adult age range. We showed that increases in Pf and hence PPc at a decreased HR are accounted for by an enhanced afterload (Pb) and hence wave re-reflection. Although a lower HR was associated with an increased ejection duration and stroke volume, increases in Q did not contribute to relationships between HR and Pf or PPc. Although the adverse effects of a lower HR on Pb and hence Pf and PPc were of little clinical significance at a young-to-middle age; these effects, which are undetectable at the brachial pulse, were pronounced in the elderly.

Summary

Increases in Pf and hence PPc at a decreased HR are accounted for by an enhanced afterload generated by Pb and hence wave re-reflection. In contrast, increases in Q produced by a prolonged ejection duration or filling time play no role in contributing to HR relations with Pf and PPc. These adverse effects of HR on afterload are largely noted in the elderly.

Nonstandard Abbreviations and Acronyms

BP	blood pressure
ED	ejection duration
HR	heart rate
Pb	backward wave P
Pf	forward wave pressure
PP	pulse pressure
PPc	central pulse pressure
PQxZc	pressure generated by the product of Q and Zc
RM	reflection magnitude
SV	stroke volume

a prolonged ejection duration (ED) and filling time with consequent increases in volume load (preload), are primary mechanisms used to explain HR effects on PPc.[10] Increases in SV are thought to enhance forward wave pressures (Pf) (Figure S1, left panel) by increasing aortic flow (Q) and hence that component of forward wave pressures generated by the interaction of Q with aortic characteristic impedance (Zc; peak P_{QxZc} and P_{QxZc} at peak PPc; Figure S1, right panel). Increases in SV, although increasing left ventricular stroke work or the peak pressure generated by aortic flow, do not cause cardiac dysfunction beyond brachial PP.[12,13] However, an additional mechanism that may explain HR effects on PPc is that mediated by increases in backward (reflected) wave pressures (Pb) (Figure S1, left panel). In this regard, the inverse frequency dependency of the reflection coefficient and the harmonics of the pulse wave (which moves to a lower frequency at decreasing HR), results in increases in backward wave pressures at a lower HR.[11] As backward wave pressure generates an impedance (resistance in a pulsatile system) to flow, increases in backward wave pressures enhance afterload to the left ventricle and hence promote cardiac dysfunction and heart failure, effects that are independent of brachial blood pressure (BP).[13–15] The question of the primary mechanism responsible for increases in PPc with a lower HR is confounded by the fact that forward wave pressure is not only determined by aortic Q and characteristic impedance, but in-part by wave re-reflection (Figure S1, right panel)[16] and hence backward wave pressures. Thus, in the absence of measures of Q, the assessment of forward wave pressures alone may be a poor index of the effects of Q. In this regard, no previous studies have identified the relative contribution of changes in Q versus re-reflection of backward wave pressures to HR effects on forward wave pressures and hence PPc. In the present study performed in a community sample studied across the full adult age range, we therefore performed central arterial waveform analysis from both flow and pressure assessments (Figure S1).[13,17–19] Making use of the range of physiological resting HR values that occur in any population, we thereby determined the mechanisms responsible for the associations between HR and Pf and hence PPc and the impact of age thereon.

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 (M02-04-72 and renewed as M07-04-69, M12-04-108 and M17-04-01). Participants gave informed, written consent. The data are available from the corresponding

authors upon reasonable request. The present study design has previously been described.[17–20] In this sub-study, 824 participants from randomly recruited (from the population census figures of 2001) families of black African descent (Nguni and Sotho chiefdoms) from the South West Township of Johannesburg, South Africa, with siblings older than 16 years of age with high quality velocity measurements in the outflow tract, were evaluated. Families living in informal dwellings were not included in the census and hence were not recruited for the study. There were no other inclusion criteria, and no participants were excluded from the study for other reasons.

Clinical, Demographic, and Anthropometric Measurements

A questionnaire was administered to obtain demographic and clinical data.[20] Height and weight were measured using standard approaches and overweight or obesity identified from body mass index . Laboratory blood tests of renal function, liver function, blood glucose, hematologic parameters, and percentage glycated hemoglobin were performed. Diabetes was defined as the use of insulin or oral hypoglycemic agents or an glycated hemoglobin value >6.5%. High quality office brachial BP measurements were obtained in the seated position after 5 minutes of rest, by a trained nurse-technician using a standard mercury sphygmomanometer[20] according to guidelines. The mean of 5 measurements obtained at least 30 seconds apart was taken as office BP. Hypertension was defined as mean office BP ≥140/90 mm Hg or the use of antihypertensive medication.

Central Arterial Hemodynamic Assessments

Central arterial hemodynamics were determined from central arterial pressure recordings using pulse wave analysis and aortic velocity and diameter assessments obtained in the outflow tract as previously described.[13,17–19] After participants had rested for 15 minutes in the supine position, arterial waveforms at the radial (dominant arm) pulse were recorded by applanation tonometry and SphygmoCor software (see Supplemental Material for details). Central arterial waveforms were generated from peripheral waveforms using a validated generalized transfer function in SphygmoCor software. Immediately after peripheral and central arterial pressure waveforms were acquired, aortic velocity and diameter measurements were obtained by an experienced observer (A.J. Woodiwiss) in the left lateral decubitus 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 early systole was used to construct the aortic flow waveform.

Central Arterial Waveforms

Central arterial waveforms were constructed as previously described[13,17–19] based on prior studies.[16,21–23] Aortic flow waveforms were generated from aortic velocity and diameter (from which cross-sectional area was calculated) 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. Aortic velocity and cross-sectional area were employed to construct a flow waveform. Characteristic impedance (Zc) was determined in the time domain using approaches previously described[21,22] and validated against invasive pressure measurements.[23] In addition to generating a complete flow waveform, to determine Zc, serial pressures in the cardiac cycle up until the dicrotic notch were extracted from SphygmoCor data and a central arterial pressure waveform was also generated (Figure S1). The volume flow waveform was paired with central arterial pressure waveforms by aligning the foot (t_0) of the respective signal averaged waveforms. The point at which flow achieves 95% of its peak (t_{Q95}) was identified. 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_{Q95}. As the accuracy of this approach is determined by the similarity of EDs in sequential pressure and then flow assessments, we first determined the differences in ED 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 msec difference over an average 320.4 msec period, representing a 0.73% difference in ED.

The pressure wave generated by Q was subsequently determined by calculating the product of Q and Zc (P_{QxZc}) over multiple time points from the foot of the flow wave to the dicrotic notch (Figure S1, right panel).[16] To determine the impact of increases in peak Q (produced by an enhanced filling time and hence SV) to PPc, peak P_{QxZc} was identified (Figure S1, right panel). To assess the contribution of the pressures generated by a prolonged ED to PPc, we determined the extent to which summation of the pressures generated by Q at peak PPc contribute to PPc (P_{QxZc} at peak PPc; Figure S1, right panel).[16] The use of a pressure waveform generated from the product of Q and Zc rather than relying on Pf to identify the impact of changes in Q, excludes the possibility of errors inherent in the use of Pf which includes pressures generated by wave re-reflection (Figure S1, right panel).[16]

Using Zc values and flow and pressure waveforms, wave separation analysis was performed and Pb determined from (aortic PP–QxZc)/2 and Pf from (aortic PP+QxZc)/2 (Figure S1, left panel).[17–19] To assess the impact of Pb independent of Pf, reflection magnitude (RM) was calculated from peak Pb/peak Pf×100. We assessed the contribution of wave reflection ($P_{reflect}$) and re-reflection ($P_{re\text{-}reflection}$) to peak PPc as the difference between peak aortic PPc and Pf ($P_{reflect}$) and the difference between Pf and P_{QxZc} at peak PPc ($P_{re\text{-}reflect}$; Figure S1, right panel).[16] We also determined the time to the peak of Pb (T_{peak} of Pb; Figure S2). Moreover, we assessed the relative proportion of peak Pb that contributes to peak PPc (%Pb at peak PPc/peak Pb; Figure S2). This was determined to identify whether alterations in the timing of peak PPc affected the proportion of peak Pb that contributes to PPc.

Additional Hemodynamic Calculations

ED, SV, HR, end diastolic volume, and systemic vascular resistance were determined using standard approaches (see Supplemental Material).

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 SEM). Dichotomous variables are expressed as percentages. For graphical representation of variables at different HR values, multiple variable adjusted data are shown across septiles of HR. Multiple linear regression analysis was performed to determine the independent relations between HR and hemodynamic variables. Multiple variable adjusted product of coefficient mediation analysis was performed to determine the contribution of hemodynamic factors to HR-PPc relations. In both linear regression and product of coefficient mediation analysis, adjustments were for age, sex, regular alcohol intake, regular tobacco intake, body mass index, diabetes, mean arterial pressure and the use of antihypertensive treatment. To determine the impact of age on the effect of HR on hemodynamic variables, relationships were compared in those < versus ≥50 years of age, the age at which PPc changes sharply (identified from LOESS procedures in SAS software). In addition, relationships between HR and hemodynamic parameters were determined over a young (<40 years), middle (40–59 years) and old (≥60 years) age. To avoid the impact of antihypertensive treatment, sensitivity analysis was performed in those not receiving therapy. As hemodynamic variables may differ between men and women, sensitivity analysis was also performed in sex-specific groups. Probability values <0.05 were considered to be significant.

RESULTS

Participant Characteristics

Table 1 shows the characteristics of the sample. A high proportion of participants had hypertension and obesity. Only half of all hypertensives were receiving therapy. Of the hypertensives 74.6% had uncontrolled BP values despite a number of these individuals receiving antihypertensive medication. No participants were receiving HR-reducing agents including β-adrenoreceptor blockers, cardio-selective calcium channel blockers, centrally acting antihypertensives, ivabradine, or antiarrhythmic agents.

HR-PP Relations

HR was independently and inversely associated with PPc, but not brachial PP (Figure 1, Tables 2, Tables S1 and S2). Independent of the individual terms and additional confounders, an interaction between age and HR determined PPc (P=0.024). Consequently, the slope (β-coefficient) of this relationship was markedly greater in older as compared with younger participants (Figure 2, Table 2). Importantly, as compared with the highest tertile of HR (≥72 beats/min), older participants with HR values lower than this value had a significant increase in the risk of an enhanced central arterial systolic BP (≥130 mm Hg; Figure S3). In contrast, no significant increase in the risk for an enhanced brachial systolic BP (≥140 mm Hg) was noted in these same participants (Figure S3). HR was not associated with an increased risk of either an uncontrolled brachial or central arterial systolic BP in younger participants (Figure S3).

Table 1. Characteristics of Community Participants

n (% female)	824 (68.3)
Age, y	46.3±18.2
Body mass index, kg/m^2	29.7±7.7
% Overweight/obese	25.0/44.5
% Hypertensive	47.3
% Treated for hypertension	27.5
% Uncontrolled hypertension	35.3
% Diabetes	13.1
% Smokers	15.1
% Regular alcohol intake	19.8
Brachial SBP/DBP, mm Hg	128±22/83±12
Brachial pulse pressure, mm Hg	46±16
PPc, mm Hg	36±14
Heart rate, beats/min	68±12
Forward wave pressure and related variables	
Pf, mm Hg	27±9
LV filling time, ms	602±150
EDV, mL	110±28
SV, mL/beat	80±24
Peak aortic flow (Q), mL/s	352±173
Characteristic impedance (Zc), dynes.s/cm^5	86.3±42.3
LV ED, ms*	322±26
LV ED, ms†	321±26
Peak P_{QxZc}, mm Hg	26±8
P_{QxZc} at peak PPc, mm Hg	13±6
Backward wave pressures and related factors	
Pb, mm Hg	13±6
RM, %	48.2±10.3
$P_{reflect}$ at peak PPc, mm Hg	12±7
$P_{re\text{-}reflect}$ at peak PPc, mm Hg	12±7
$P_{reflect\ +re\text{-}reflect}$ at peak PPc, mm Hg	24±13
%Pb at peak PPc/peak Pb	87±21
T_{peak} of Pb, msec	302±33
Time to peak PPc, msec	228±23

Data shown are mean±SD or proportions. DBP indicates diastolic blood pressure; ED, ejection duration; EDV, end diastolic volume; ED, ejection duration; LV, left ventricle; Pb, backward wave P; Pf, forward wave pressure; PPc, central pulse pressure; P_{QxZc}, Pressure generated by the product of Q and Zc; $P_{reflect\ +\ re\text{-}reflect}$, pressure generated by the combined impact of wave reflection and re-reflection; $P_{re\text{-}reflect}$, pressure generated by re-reflection; RM, reflection magnitude; SBP, systolic blood pressure; SV, stroke volume; and T_{peak} of Pb, time to the peak of Pb.

*Calculated from foot of PPc to dicrotic notch.

†Calculated from duration of the velocity wave.

HR-Forward Wave Pressure Relations

Similar to the HR-PPc relations (Figure 1), HR was independently and inversely associated with Pf (Figure 2),

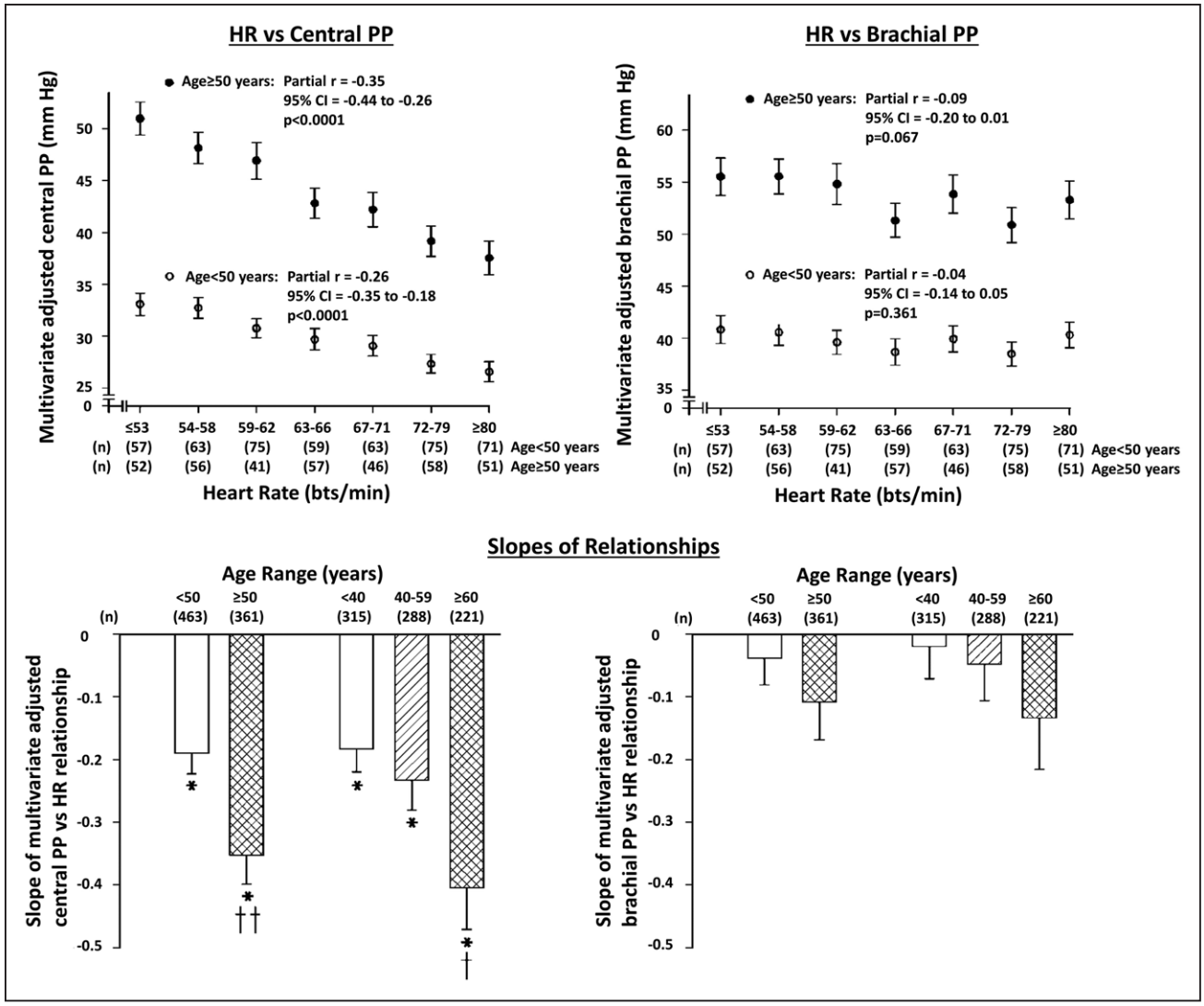

Figure 1. Multivariate adjusted age-dependent relationships between heart rate (HR) and central arterial and brachial pulse pressure (PP) in a community sample (n=824).
Slopes (β-coefficients) are shown in the **lower** parts. See data analysis section for age groups and adjustments. *P<0.0001 for significance of relations and †P<0.05, ††P<0.005 for comparison with younger or young or middle-aged.

and this relation was markedly greater in older as compared with younger participants (Figure 2). HR was also independently and inversely associated with diastolic filling time, end diastolic volume, and SV (Tables 2, Tables S1 and S2). However, HR-SV relations were attributed to increases in ED, rather than peak aortic Q. Indeed, there were no relationships between HR and peak aortic Q (Figure 2, Figure S4, Table 2, Tables S1 and S2) or HR and the peak pressure generated by Q (peak P_{QxZc}; Figure 2 and Figure S4, Table 2, Tables S1 and S2). In product of coefficient mediation analysis, peak aortic Q failed to contribute; and peak P_{QxZc} contributed only modestly to HR-PPc relations (Table 3). In addition, neither peak aortic Q nor peak P_{QxZc} accounted for HR-Pf relations (data not shown).

HR was also independently and inversely associated with a prolonged ED (Tables 2 and Table S1). However, a direct (positive) rather than inverse relationship between HR and the pressure generated by Q at peak PPc (P_{QxZc} at peak PPc) occurred either across the full adult age range or at a younger or older adult age (Figure 2 and Figure S4, Tables 2, Tables S1 and S2). Thus, in product of coefficient mediation analysis, P_{QxZc} at peak PPc contributed to a greater PPc (Table 3) or greater Pf (data not shown) at higher rather than lower HR values (Table 3). The lack of impact of ED and hence P_{QxZc} at peak PPc to HR-Pf and HR-PPc relations was attributed to an extended duration of the time to the peak of Pb (T_{peak} of Pb) and hence to the time to the peak of PPc (Tables 2, Tables S1 and S2).

In contrast to the lack of contribution of Q and hence peak P_{QxZc} or P_{QxZc} at peak PPc to HR-Pf relations; HR-Pf relations were attributed to re-reflected pressure wave effects. Indeed, HR was inversely associated with re-reflected wave

Table 2. Slopes (β-Coefficients) of Relationships Between HR and Hemodynamic Factors in Participants From a Community Sample

	Full adult age (n=824)		<50 years of age (n=463)		≥50 years of age (n=361)	
HR vs	β-coefficient±SEM	*P* value	β-coefficient±SEM	*P* value	β-coefficient±SEM	*P* value
Brachial pulse pressure	−0069±0.037	=0.07	−0.039±0.042	=0.36	−0.109±0.060	=0.07
PPc	−0.266±0.030	<0.0001	−0.190±0.033	<0.0001	−0.352±0.047*	<0.0001
Forward wave pressures and related factors						
Forward wave pressure	−0.093±0.023	<0.0001	−0.052±0.025	<0.05	−0.144±0.039†	=0.0005
LV filling time	−10.7±0.2	<0.0001	−11.0±0.3	<0.0001	−10.3±0.3	<0.0001
End diastolic volume	−0.402±0.086	<0.0001	−0.436±0.106	<0.0001	−0.385±0.141	<0.01
Stroke volume	−0.391±0.117	<0.001	−0.323±0.150	<0.05	−0.487±0.187	<0.01
Peak aortic flow	0.308±0.484	=0.53	0.757±0.613	=0.22	−0.350±0.803	=0.66
Peak P_{QxZc}	−0.029±0.022	=0.19	−0.025±0.024	=0.30	−0.035±0.037	=0.36
LV ejection duration‡	−1.55±0.06	<0.0001	−1.46±0.07	<0.0001	−1.68±0.10	<0.0001
LV ejection duration§	−1.52±0.06	<0.0001	−1.45±0.07	<0.0001	−1.62±0.10	<0.0001
P_{QxZc} at peak PPc	0.094±0.019	<0.0001	0.080±0.023	<0.001	0.093±0.029	<0.005
Backward wave pressures and related factors						
Backward wave pressure	−0.114±0.013	<0.0001	−0.078±0.014	<0.0001	−0.151±0.024†	<0.0001
Reflection magnitude	−0.274±0.028	<0.0001	−0.235±0.037	<0.0001	−0.293±0.043	<0.0001
$P_{re\text{-}reflect}$ or $P_{reflect}$ at peak PPc	−0.160±0.014	<0.0001	−0.117±0.016	<0.0001	−0.203±0.024*	<0.0001
$P_{reflect\ +re\text{-}reflect}$ at peak PPc	−0.320±0.029	<0.0001	−0.235±0.033	<0.0001	−0.407±0.049*	<0.0001
%Pb at peak PPc/peak Pb	−0.504±0.061	<0.0001	−0.520±0.089	<0.0001	−0.501±0.074	<0.0001
T_{peak} of Pb	−1.44±0.08	<0.0001	−1.43±0.09	<0.0001	−1.59±0.12	<0.0001
Time to peak PPc	−1.43±0.05	<0.0001	−1.36±0.07	<0.0001	−1.51±0.08	<0.0001

Adjustments are for age, sex, regular alcohol intake, regular tobacco intake, BMI, diabetes, MAP, and treatment for hypertension. BMI indicates body mass index; HR, heart rate; LV, left ventricle; MAP, mean arterial pressure; Pb, backward wave P; and PPc, central arterial pulse pressure.

*P<0.005 for comparison of β-coefficients (slopes) with younger participants.

†P<0.05.

‡Calculated from foot of PPc to dicrotic notch.

§Calculated from duration of the velocity wave.

pressures ($P_{re\text{-}reflect}$; Figure 2 and Figure S4, Tables 2, Tables S1 and S2), and inverse HR-Pf relations were abolished after adjustments for $P_{re\text{-}reflect}$ at peak PPc (data not shown).

HR-Backward Wave Pressure Relations

HR was independently and inversely associated with RM, Pb, the proportion of Pb that summates with the pressures generated by the product of Q and Zc at peak PPc to determine PPc (%Pb at PPc/peak Pb) and the pressure generated by wave reflection or re-reflection ($P_{reflect}$ or $P_{re\text{-}reflect}$; Figure 3, Tables 2, Tables S1 and S2). No multivariate adjusted relationships between RM or Pb and systemic vascular resistance were noted (P=0.32 and P=0.44, respectively). Adjustments for systemic vascular resistance did not affect the relationships (partial r, 95% CI) between HR and either RM (before, −0.33 [−0.39 to −0.27], P<0.0001 and after, −0.32 [−0.38 to −0.25], P<0.0001) or Pb (before, −0.29 [−0.36 to −0.23], P<0.0001 and after, −0.30 [−0.37 to −0.24], P<0.0001). The increased %Pb at peak PPc/peak Pb was attributed to an inverse relationship between HR and the time to peak Pb and hence peak PPc (Tables 2, Tables S1 and S2). In product of coefficient mediation analysis, the combined pressures generated by $P_{reflect}$ and $P_{re\text{-}reflect}$ accounted for most of the impact of HR on PPc or Pf, respectively, at either a younger or an older age (Table 3). An independent interaction between age and HR was associated with Pb and $P_{reflect}$ or $P_{re\text{-}reflect}$ (P=0.038, P=0.009, and P=0.009, respectively). However, no interaction between age and HR was independently associated with RM or %Pb at peak PPc/peak Pb (P=0.78 and P=0.74, respectively). Consequently, the relationship between HR and Pb (Table 2), $P_{reflect}$ (Figure 3, Table 2) and the combined pressures generated by $P_{reflect}$ and $P_{re\text{-}reflect}$ (Table 2), but not RM or %Pb at peak PPc/peak Pb, was strikingly greater in older as compared with younger persons.

DISCUSSION

In the present study, using approaches to central arterial waveform analysis that account for the contribution to forward wave pressures of not only aortic flow (Q) and characteristic impedance, but also wave re-reflection (Figure S1, right panel as compared with left panel),[16] we explored the primary mechanisms that explain relationships between a lower HR and a higher PPc. We performed these studies in a community sample across the full adult age range to identify HR effects under

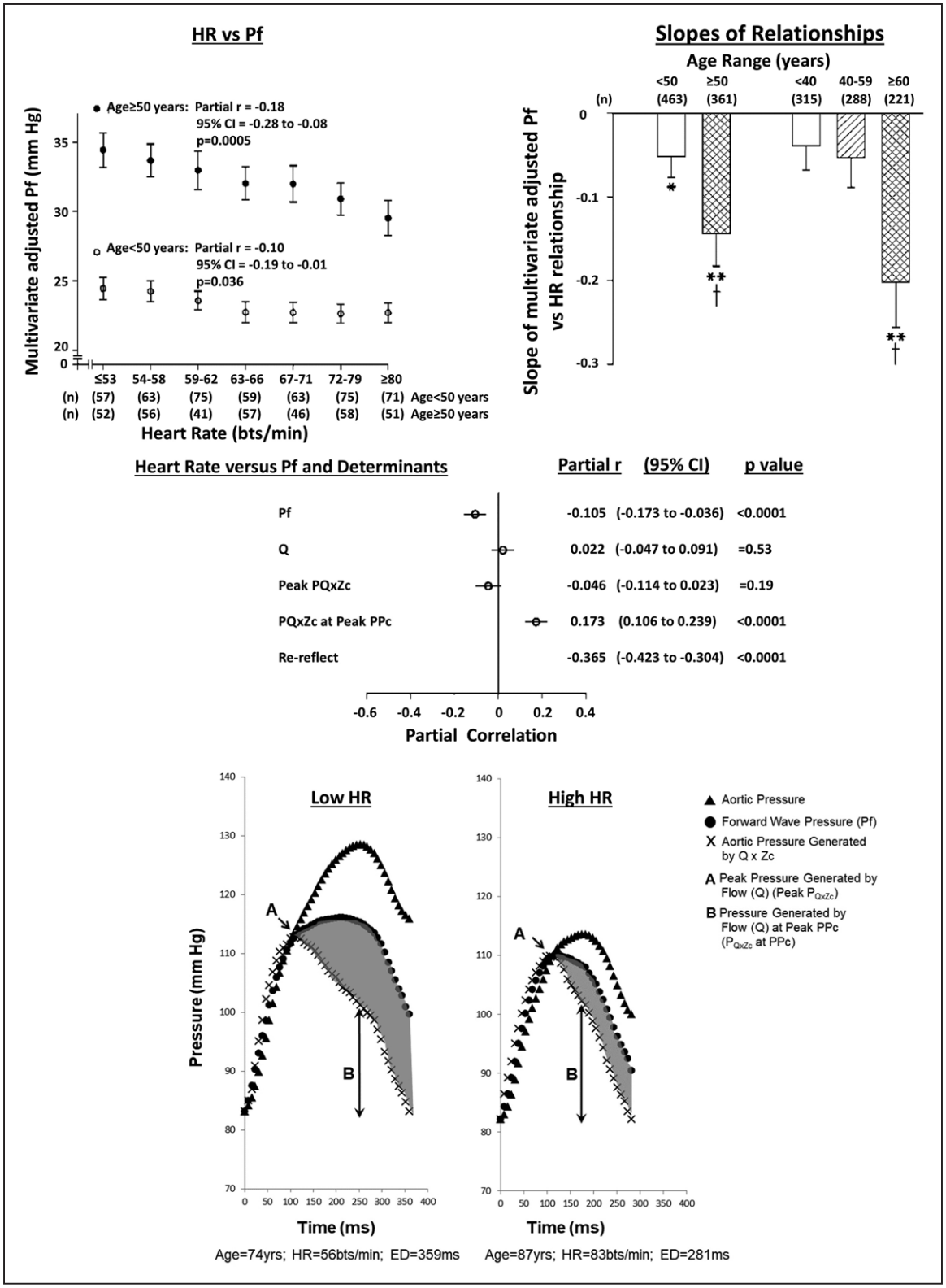

Figure 2. Multivariate adjusted age-dependent relationships between heart rate (HR) and forward wave pressures (Pf; upper and middle parts) or the determinants thereof (middle) in participants from a community sample (n=824).
Lower parts show actual waveforms obtained in participants with different resting HR showing the pressures given in the **middle** part. Peak pressure generated by the product of Q and Zc (P_{QxZc}) and P_{QxZc} at peak PPc are pressures generated by flow that determine pulse pressure. Shaded area is the re-reflected wave pressure ($P_{re\text{-}reflect}$). Figure S1 for waveforms and the data analysis section for age groups and adjustments. *P<0.0001 for significance of relations and †P<0.05, ††P<0.005 for comparison with younger or young or middle-aged.

Table 3. Contribution, in Product of Coefficient Mediation Analysis, of Hemodynamic Factors to HR Relationships With PPc in a Community Sample

	Full adult age (n=824)		<50 years of age (n=463)		≥50 years of age (n=361)	
Hemodynamic factor	One SD effect	*P* value	One SD effect	*P* value	One SD effect	*P* value
One SD effect of HR on PPc→	−3.20±0.36	<0.0001	−2.23±0.39	<0.0001	−4.52±0.60	<0.0001
Contribution of →$P_{reflect + re-reflect}$	−2.55±0.01	<0.0001	−1.67±0.01	<0.0001	−3.71±0.03	<0.0001
Peak Q	−0.004±0.012	=0.53	−0.016±0.018	=0.12	0.037±0.036	=0.56
Peak P_{QxZc}	−0.60±0.01	<0.05	−0.32±0.01	=0.30	−0.97±0.02	<0.05
P_{QxZc} at peak PPc	0.91±0.01	=0.0001	0.59±0.02	<0.001	1.15±0.03	<0.0005

Adjustments are for age, sex, regular alcohol intake, regular tobacco intake, BMI, DM, MAP and treatment for hypertension. BMI indicates body mass index; HR, heart rate; MAP, mean arterial pressure; Pb, backward wave P; PPc, central arterial pulse pressure; P_{QxZc}, Pressure generated by the product of Q and Zc; and $P_{reflect + re-reflect}$, pressure generated by the combined impact of wave reflection and re-reflection.

physiological conditions and to determine the impact of age thereon. In this regard, we show for the first time that HR relations with PPc and forward wave pressures are not explained by an impact of ED or filling time on aortic Q. Importantly, previous studies failed to perform direct assessments of Q and hence did not construct pressure waveforms generated by Q. Although a decreased HR was associated with an extended ED, the pressures generated by Q at peak PPc (P_{QxZc} at peak PPc) did not account for HR-PPc relations. This occurred because of an increase in the time to the peak of Pb and hence PPc with decreases in HR. Furthermore, although a decreased HR was associated with an increased filling period, end diastolic volume and SV, the effects on SV were accounted for by a prolonged ED and not peak Q. Thus, HR was not associated with the peak pressure generated by Q (Peak P_{QxZc}). In contrast, HR was strongly associated with backward (reflected) wave pressures. The pressures generated by the impact of backward wave pressures and thus re-reflection, therefore, accounted for HR relations with forward wave pressures and hence PPc and the impact of age thereon.

The importance of a lower HR as a determinant of a higher PPc beyond brachial PP and the adverse effects thereof, have been highlighted by the impact of β-blockers on PPc.[4,5] These effects are thought to explain the limited benefits of these agents as compared with alternative antihypertensives, on outcomes despite equivalent brachial BP lowering.[6,7] However, if HR effects on PPc are accounted for by increases in flow, this would suggest that HR effects on central beyond peripheral arterial pressure are of little clinical consequence to the left ventricle. Indeed, flow-induced increases in left ventricular stroke work do not produce deleterious effects on the heart,[12] and the adverse effects of forward wave pressures on the left ventricle would be indirect, and detected at the brachial pulse.[13] However, in the present study, we show for the first time that associations between HR and both forward wave pressures and PPc, are driven by increases in backward wave pressures and not by increases in flow. Indeed, HR relations with PPc were dependent neither on ED nor filling time, but rather on the frequency dependency of wave reflection, which also increases wave re-reflection and hence forward wave pressures. As increases in backward wave pressures produce cardiac damage independent of brachial BP,[13–15] these data may, therefore, explain the limited benefits of β-blockers at equivalent brachial BP values, as compared with alternative antihypertensives, on outcomes.[6,7] These data may also be particularly important in explaining the worse outcomes for heart failure despite similar brachial BP lowering in the β-blocker treated group of hypertensive diabetics with electrocardiographic left ventricular hypertrophy in the LIFE study.[24] Further studies are, therefore, required to determine whether the limited benefits of β-blocker therapy on central as compared with peripheral BP are accounted for by HR effects on backward wave pressures and wave re-reflection as opposed to increases in flow. In this regard, the present study does not account for the alternative hemodynamic actions of β-blocker therapy such as effects on myocardial contractility and chamber remodeling. Moreover, whether the benefits of alternative HR-reducing agents on outcomes are also offset by similar adverse central arterial pressure effects that go undetected at the brachial pulse, requires consideration.

In the present study, we show that the relationships between HR and PPc are strongly age-dependent. This is unlikely to be explained by the impact of age-related variations in arteriolar tone on wave reflection, as adjustments for systemic vascular resistance failed to modify relationships between backward wave pressures and HR. Moreover, variation in more proximal arterial tone is also unlikely to explain this finding as interactions between age and HR were independently associated with backward wave pressures and pressures generated by wave reflection or re-reflection, but not with the RM. The impact of age on the HR-backward wave pressure relationship is explained rather by the age-dependence of the harmonic frequencies of the pulse wave in central arteries,[25] an effect that will increase backward wave pressures.[11] In this regard, at a younger age, the elasticity of central arteries

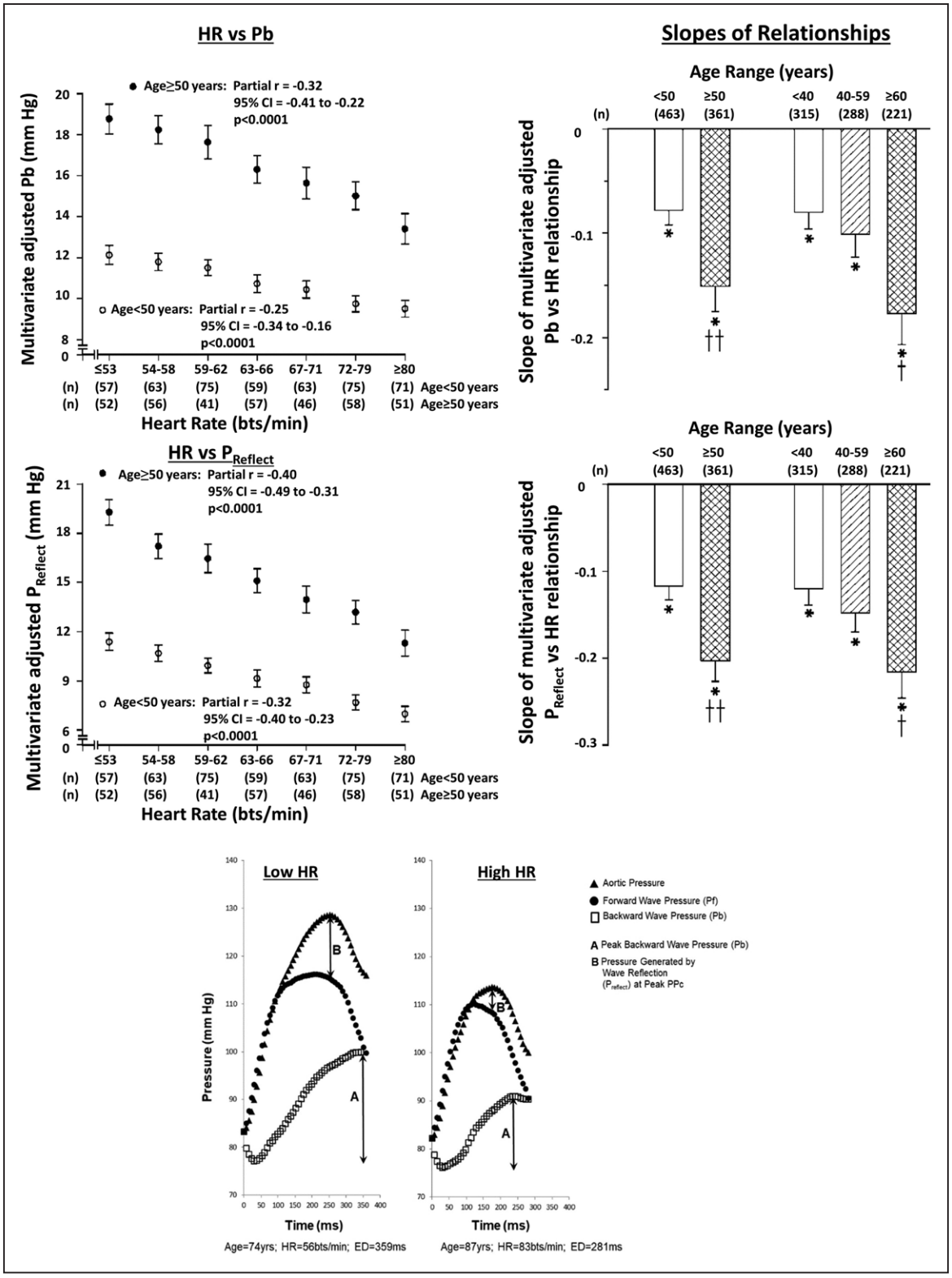

Figure 3. Age-dependent relationships between heart rate (HR) and backward wave pressures (Pb) or the pressures generated by wave reflection at peak aortic pulse pressure ($P_{reflect}$) in participants from a community sample (n=824).
Lower, Actual waveforms obtained in participants with different resting HR with Pb and $P_{reflect}$ indicated. See Figure S1 for waveforms and data analysis section for age groups and adjustments. *P<0.0001 for significance of relations and †P<0.05, ††P<0.005 for comparison with younger or young or middle-aged.

increases harmonic frequencies and hence decreases pulsatile pressures. With aging and a reduction in the elastic properties of central arteries, harmonic frequencies decrease and hence pulsatile pressures are enhanced. As we show that HR effects on backward wave pressures are of little clinical significance at a younger adult age, HR reduction is unlikely to produce important adverse effects on the myocardium in adults under 60 years of age. In-line with our findings, the limited impact of HR on backward wave pressures over a young adult age may explain the possibility of greater benefits of β-blockers for a given brachial BP at a younger as compared with an older adult age.[26] In contrast, in the elderly, the adverse effects of a lower HR on backward wave pressures and PPc are pronounced and importantly are undetectable at the brachial pulse. These effects are, therefore, likely to result in unobserved increases in left ventricular afterload over this age range. This will cause further deterioration of myocardial function produced by backward wave pressures[13–15] in patients with underlying ischemic heart disease or cardiac dysfunction.

As indicated by the present results, reductions in backward wave pressures may be necessary when β-blockers or alternative HR-reducing agents are required at an older age. Since wave reflection indexes are lower in treated versus untreated hypertensives, this would suggest that antihypertensive agents other than β-blockers reduce wave reflection,[10] hence the use of agents with vasodilator properties is a potential solution to this problem. However, meta-analyses of intervention studies[27] and a large intervention study,[28] do not support this notion. The current solution to potential increase in afterload produced by the use of HR-reducing agents at an older age may nevertheless be intense brachial BP lowering, possibly to thresholds (systolic BP <130 mm Hg) currently recommended by guidelines for the United States.[8] Indeed, it is only with intense brachial BP reduction that a normal PPc will be achieved at HR values at the lower end of the normal range. In this regard, any agent which reduces mean arterial pressure will decrease aortic characteristic impedance (through a reduction in distending pressures and hence aortic stiffness) and therefore, forward wave pressures, the consequence being an attenuation in the magnitude of backward waves (backward wave pressures depend of forward wave pressures through inertial effects) and PPc. Our data may, therefore, in-part explain the beneficial effects of intense brachial BP lowering on heart failure observed in the SPRINT trial (age >50 years).[29]

There are several limitations of the present study that require consideration. To assess HR effects under physiological circumstances and over a physiological range (using the range of resting HR values that are noted in adults), the present study was cross-sectional in design. Hence relationships between HR and hemodynamics may be through residual confounding. However, the impact of HR on hemodynamics across the full adult age range can only be more effectively assessed with artificial pacing. This will limit the ability to address this question in a significant number of young participants, as pacemakers are infrequently required at a young adult age. Studies on the mechanisms of the hemodynamic effects of HR-reducing agents per se are also likely to be confounded by vascular or alternative cardiac effects of specific agents. If anything, several of these classes will decrease aortic flow through negative inotropic effects, thus limiting the ability to detect HR effects on flow. Nevertheless, further studies are required to determine the dominant mechanisms responsible for increases in PPc with a reduced HR when employing β-blockers or alternative HR-reducing agents. The present study was also conducted in a single ethnic group. Thus, whether the results are translatable to all populations is unknown. However, age-related increases in characteristic impedance, forward wave pressures, and PP are remarkably similar in the present[17] as compared with alternative[22] ethnic groups. Although backward wave pressures have been demonstrated to contribute far more to age-related increases in PPc in the present population[13] than in the Framingham Heart Study,[22] the contribution of backward wave pressures to age-related increases in PPc in the present study is similar to that noted in the Anglo-Cardiff Study.[30]

PERSPECTIVES

Several mechanisms have been suggested to explain the increase in central arterial BP that occurs with HR reduction, effects that are not detected at the brachial pulse. Although flow-induced increases in forward wave pressures and enhanced backward wave pressures have both been suggested to play an important role, no previous studies have assessed whether forward wave pressure effects are attributed to increases in flow. In the present study, conducted across the full adult lifespan, we show, using analyses of central arterial waveforms that account for all of the factors that determine forward wave pressures,[16] that the relationships between a lower HR and increased forward wave pressures and PPc are not accounted for by preload-induced increases in aortic flow produced by an enhanced ED or filling time. Rather, relations between a lower HR and increased forward wave pressures and PPc are explained, through harmonic effects on the pulse wave at lower HR values, only by the impact on an increased afterload generated by backward (reflected) wave pressures. These changes increase forward wave pressures through pressure wave re-reflection. As the impact of HR on backward waves are age-dependent,

reduction of HR over a young-to-middle (<60 years) adult age, may have no clinically significant effect on afterload. However, HR reduction at an older adult age could have a significant impact on backward wave pressures and hence afterload, effects which are not detectable with peripheral BP measurements. The extent to which these adverse effects on afterload occur with HR-reducing agents such as β-blockers, requires further study.

ARTICLE INFORMATION

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REFERENCES

1. Nichols WW, O'Rourke MF, Vlachopoulos C. *McDonald's Blood Flow in Arteries: Theoretical, Experimental and Clinical Principles*. 6th ed. CRC-Taylor & Francis Group; 2011:1–741.
2. Tan I, Kiat H, Barin E, Butlin M, Avolio AP. Effects of pacing modality on noninvasive assessment of heart rate dependency of indices of large artery function. *J Appl Physiol (1985)*. 2016;121:771–780. doi: 10.1152/japplphysiol.00445.2016
3. Wilkinson IB, MacCallum H, Flint L, Cockcroft JR, Newby DE, Webb DJ. The influence of heart rate on augmentation index and central arterial pressure in humans. *J Physiol*. 2000;525(pt 1):263–270. doi: 10.1111/j.1469-7793.2000.t01-1-00263.x
4. Williams B, Lacy PS, Thom SM, Cruickshank K, Stanton A, Collier D, Hughes AD, Thurston H, O'Rourke M; CAFE Investigators; Anglo-Scandinavian Cardiac Outcomes Trial Investigators; CAFE Steering Committee and Writing Committee. Differential impact of blood pressure-lowering drugs on central aortic pressure and clinical outcomes: principal results of the Conduit Artery Function Evaluation (CAFE) study. *Circulation*. 2006;113:1213–1225. doi: 10.1161/CIRCULATIONAHA.105.595496
5. Williams B, Lacy PS; CAFE and the ASCOT (Anglo-Scandinavian Cardiac Outcomes Trial) Investigators. Impact of heart rate on central aortic pressures and hemodynamics: analysis from the CAFE (Conduit Artery Function Evaluation) study: CAFE-Heart Rate. *J Am Coll Cardiol*. 2009;54:705–713. doi: 10.1016/j.jacc.2009.02.088
6. Wiysonge CS, Bradley HA, Volmink J, Mayosi BM, Opie LH. Beta-blockers for hypertension. *Cochrane Database Syst Rev*. 2017;1:CD002003. doi: 10.1002/14651858.CD002003.pub5
7. Wright JM, Musini VM, Gill R. First-line drugs for hypertension. *Cochrane Database Syst Rev*. 2018;4:CD001841. doi: 10.1002/14651858.CD001841.pub3
8. Whelton PK, Carey RM, Aronow WS, Casey DE Jr, Collins KJ, Dennison Himmelfarb C, DePalma SM, Gidding S, Jamerson KA, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *J Am Coll Cardiol*. 2018;71:e127–e248. doi: 10.1016/j.jacc.2017.11.006
9. Dézsi CA, Szentes V. The real role of β-blockers in daily cardiovascular therapy. *Am J Cardiovasc Drugs*. 2017;17:361–373. doi: 10.1007/s40256-017-0221-8
10. Sluyter JD, Hughes AD, Lowe A, Parker KH, Camargo CA Jr, Hametner B, Wassertheurer S, Scragg RK. Different associations between beta-blockers and other antihypertensive medication combinations with brachial blood pressure and aortic waveform parameters. *Int J Cardiol*. 2016;219:257–263. doi: 10.1016/j.ijcard.2016.06.051
11. Xiao H, Tan I, Butlin M, Li D, Avolio AP. Mechanism underlying the heart rate dependency of wave reflection in the aorta: a numerical simulation. *Am J Physiol Heart Circ Physiol*. 2018;314:H443–H451. doi: 10.1152/ajpheart.00559.2017
12. Bello H, Woodiwiss AJ, Naran R, Peterson VR, Libhaber CD, Mmopi KN, Mthembu N, Masiu M, Da Silva Fernandes D, Bamaiyi AJ, et al. Impact of stroke work on the ability of left ventricular mass to account for pressure effects on function in a community with prevalent systemic flow-dependent hypertension. *J Hypertens*. 2021;39:2092–2102. doi: 10.1097/HJH.0000000000002896
13. Bello H, Norton GR, Peterson VR, Mmopi KN, Mthembu N, Libhaber CD, Masiu M, Da Silva Fernandes D, Bamaiyi AJ, Peters F, et al. Hemodynamic determinants of age versus left ventricular diastolic function relations across the full adult age range. *Hypertension*. 2020;75:1574–1583. doi: 10.1161/HYPERTENSIONAHA.119.14622
14. Chirinos JA, Segers P, Rietzschel ER, De Buyzere ML, Raja MW, Claessens T, De Bacquer D, St John Sutton M, Gillebert TC; Asklepios Investigators. Early and late \ wall stress differentially relate to myocardial contraction and relaxation in middle-aged adults: the Asklepios study. *Hypertension*. 2013;61:296–303. doi: 10.1161/HYPERTENSIONAHA.111.00530
15. Chirinos JA, Kips JG, Jacobs DR Jr, Brumback L, Duprez DA, Kronmal R, Bluemke DA, Townsend RR, Vermeersch S, Segers P. Arterial wave reflections and incident cardiovascular events and heart failure: MESA (Multiethnic Study of Atherosclerosis). *J Am Coll Cardiol*. 2012;60:2170–2177. doi: 10.1016/j.jacc.2012.07.054
16. Phan TS, Li JK, Segers P, Chirinos JA. Misinterpretation of the determinants of elevated forward wave amplitude inflates the role of the proximal aorta. *J Am Heart Assoc*. 2016;5:e003069. doi: 10.1161/JAHA.115.003069
17. Woodiwiss AJ, Mmopi KN, Peterson V, Libhaber C, Bello H, Masiu M, Fernandes DDS, Tade G, Mthembu N, Peters F, Sareli P, Norton GR. Distinct contribution of systemic blood flow to hypertension in an african population across the adult lifespan. *Hypertension*. 2020;76:410–419. doi: 10.1161/HYPERTENSIONAHA.120.14925
18. Motau TH, Norton GR, Sadiq E, Manyatsi N, Kolkenbeck-Ruh A, Robinson C, Tade G, Mabena P, Monareng T, Naran R, et al. Marked arterial functional changes in patients with arterial vascular events across the early adult lifespan. *Arterioscler Thromb Vasc Biol*. 2020;40:1574–1586. doi: 10.1161/ATVBAHA.119.313734
19. Mmopi KN, Norton GR, Bello H, Libhaber C, Masiu M, Da Silva Fernandes D, Sareli P, Peterson V, Woodiwiss AJ. Increased aortic characteristic impedance explains relations between urinary Na+/K+ and pulse or systolic blood pressure. *Hypertension*. 2020;75:1260–1270. doi: 10.1161/HYPERTENSIONAHA.119.14563
20. Woodiwiss AJ, Molebatsi N, Maseko MJ, Libhaber E, Libhaber C, Majane OH, Paiker J, Dessein P, Brooksbank R, Sareli P, et al. Nurse-recorded auscultatory blood pressure at a single visit predicts target organ changes as well as ambulatory blood pressure. *J Hypertens*. 2009;27:287–297. doi: 10.1097/HJH.0b013e328317a78f
21. Segers P, Rietzschel ER, De Buyzere ML, Vermeersch SJ, De Bacquer D, Van Bortel LM, De Backer G, Gillebert TC, Verdonck PR; Asklepios investigators. Noninvasive (input) impedance, pulse wave velocity, and wave reflection in healthy middle-aged men and women. *Hypertension*. 2007;49:1248–1255. doi: 10.1161/HYPERTENSIONAHA.106.085480
22. Mitchell GF, Wang N, Palmisano JN, Larson MG, Hamburg NM, Vita JA, Levy D, Benjamin EJ, Vasan RS. Hemodynamic correlates of blood pressure across the adult age spectrum: noninvasive evaluation in the Framingham Heart Study. *Circulation*. 2010;122:1379–1386. doi: 10.1161/CIRCULATIONAHA.109.914507
23. Kelly R, Fitchett D. Noninvasive determination of aortic input impedance and external left ventricular power output: a validation and repeatability study of a new technique. *J Am Coll Cardiol*. 1992;20:952–963. doi: 10.1016/0735-1097(92)90198-v

24. Lindholm LH, Ibsen H, Dahlöf B, Devereux RB, Beevers G, de Faire U, Fyhrquist F, Julius S, Kjeldsen SE, Kristiansson K, et al; LIFE Study Group. Cardiovascular morbidity and mortality in patients with diabetes in the Losartan Intervention For Endpoint reduction in hypertension study (LIFE): a randomised trial against atenolol. *Lancet*. 2002;359:1004–1010. doi: 10.1016/S0140-6736(02)08090-X
25. Wang SH, Hsu TL, Jan MY, Wang YYL, Wang WK. Age-Related Changes in Specific Harmonic Indices of Pressure Pulse Waveform. In: Lim C.T., Goh J.C.H. (eds) 13th International Conference on Biomedical Engineering. *IFMBE Proceedings*, 2009, vol 23:183–185. Springer, Berlin, Heidelberg. https://doi.org/10.1007/978-3-540-92841-6_44
26. Khan N, McAlister FA. Re-examining the efficacy of beta-blockers for the treatment of hypertension: a meta-analysis. *CMAJ*. 2006;174:1737–1742. doi: 10.1503/cmaj.060110
27. Manisty CH, Hughes AD. Meta-analysis of the comparative effects of different classes of antihypertensive agents on brachial and central systolic blood pressure and augmentation index. *Brit J Clin Pharmacol*. 2012; 75:79–92.
28. Agnoletti D, Zhang Y, Borghi C, Blacher J, Safar ME. Effects of antihypertensive drugs on central blood pressure in humans: a preliminary observation. *Am J Hypertens*. 2013;26:1045–1052. doi: 10.1093/ajh/hpt081
29. The Sprint Research Group. Final report of a trial with intensive versus standard blood-pressure control. *N Engl J Med*. 2021;384:1921–1930. doi: 10.1056/NEJMoa1901281
30. Namasivayam M, McDonnell BJ, McEniery CM, O'Rourke MF; Anglo-Cardiff Collaborative Trial Study Investigators. Does wave reflection dominate age-related change in aortic blood pressure across the human life span? *Hypertension*. 2009;53:979–985. doi: 10.1161/HYPERTENSIONAHA.108.125179