Does Wave Reflection Dominate Age-Related Change in Aortic Blood Pressure Across the Human Life Span?

Mayooran Namasivayam, Barry J. McDonnell, Carmel M. McEniery, Michael F. O’Rourke; on behalf of the Anglo-Cardiff Collaborative Trial Study Investigators

Abstract—Aortic systolic and pulse pressure rise with age because of aortic stiffening. Two factors are responsible: a larger incident wave because of increased aortic characteristic impedance and premature return of wave reflection from peripheral sites. This study aimed to determine the relative contribution of each factor before and after age 60 years. Aortic pressure waveforms were generated for 3682 healthy subjects using a generalized transfer function applied to radial pressure waveforms recorded by applanation tonometry. Linear regression and product of coefficient mediation analysis were performed in the cross-sectional cohort to determine the yearly contribution of the incident and reflected waves (waves measured as first systolic peak and augmented pressure, respectively) to aortic systolic and pulse pressure elevation with age. This was done separately for subjects ≤60 and >60 years of age, with both sexes initially pooled and subsequently separated. Analyses were repeated with correction for height, weight, heart rate, and mean arterial pressure. Before age 60 years, the reflected wave was a greater \( P<0.05 \) contributor to age-related aortic systolic and pulse pressure elevations, with no significant contribution of the incident wave in this age group in sex-pooled analysis. After age 60 years, both incident and reflected waves were significant \( P<0.05 \) and comparable contributors \( P \) difference >0.05) to age-related aortic systolic and pulse pressure elevations. This general pattern was observed in both sexes and persisted after correction for confounders. Wave reflection is important across the life span, whereas aortic characteristic impedance contributes significantly only beyond age 60 years. (Hypertension. 2009;53:979-985.)

Key Words: aging ▪ blood pressure ▪ arterial stiffening ▪ hypertension ▪ aorta

Age-related increases in systolic and pulse pressures\(^1\,^2\) contribute to progressively rising cardiovascular risk and cardiovascular morbidity and mortality.\(^3\,^4\) As part of the normal aging process, the aorta undergoes structural changes, progressively stiffening because of cyclic strain, causing fracture of elastin lamellae in the tunica media and fibrous remodeling of the aortic wall.\(^5\) Aortic stiffening is deemed responsible for age-related increases in systolic and pulse pressures\(^6\,^6\) and exerts direct and indirect effects.\(^7\) Directly, aortic stiffness increases aortic characteristic impedance and, therefore, increases the magnitude of the peripherally traveling (incident) pressure wave generated by ventricular ejection. Indirectly, increased aortic stiffness alters the timing and magnitude of wave reflection from the periphery, such that the aorta is subjected to progressively early return of a larger reflected pressure wave with advancing age. The phenomenon of wave reflection forms the traditional view regarding age-related blood pressure elevation.\(^8\,^9\) Mitchell et al,\(^10\,^11\) however, have suggested that wave reflection is irrelevant in women over age 60 years and minor in men over age 60 years and propose that the incident wave (aortic characteristic impedance) is more important. Such a view has been questioned, and there has been debate as to the relative importance of the incident and reflected arterial pressure waves to age-related arterial pressure elevation.\(^12\,^15\) This study, therefore, aimed to quantify the contribution of the incident and reflected arterial pressure waves to age-related arterial pressure elevation, before and after age 60 years, in a cohort of healthy subjects. We chose age 60 because of the aforementioned debates, as well as previous observations of reduction in the rate of increase in augmentation index with age beyond age 60 years\(^13\) and the finding that the relationship between coronary disease and wave reflection is mediated primarily by patients under the age of 60 years.\(^16\) This study focused on aortic systolic and pulse pressures, not brachial pressure, because recent work has shown that central pressure (as compared with peripheral pressure) rises to a proportionately greater extent with age,\(^17\) may be a better predictor of cardiovascular outcome,\(^18\,^19\) and causes independent adverse cardiac, renal, and cerebral events.\(^20\)

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Methods

Subjects
This study was composed of a healthy subset of subjects from the Anglo-Cardiff Collaborative Trial (ACCT) database. The details of subject selection have been published previously.1 From this cohort, 319 subjects who were missing required data were excluded from analysis, leaving 3682 subjects with a complete data set. There were no significant differences in the variables analyzed in this study between the original cohort and the cohort postexclusion. All of the subjects gave written informed consent, and all of the studies were approved by local research ethics committees.

Data Collection
All of the subjects had height, weight, and brachial cuff blood pressure recorded. Seated blood pressure was measured in the dominant arm using a validated oscillometric device (HEM-705CP, Omron Corporation). Radial arterial sphygmoscopy (pressure pulse waveform recording) was performed via applanation tonometry using a high-fidelity piezoelectric tonometer (SPT-301, Millar Instruments). Aortic pressure waveforms were then generated for all of the subjects using a validated,22 generalized transfer function (SphygmoCor, AtCor Medical; FDA K002742 and K012487). All of the measurements were made in duplicate by trained investigators, and mean values were used in subsequent analysis. Interobserver variability was low, in line with previously published studies on radial tonometry and transfer function use.23–25 The radial waveforms were processed with the SphygmoCor device to yield measurements of aortic systolic pressure (SBPao), aortic pulse pressure (PPao), incident wave pressure (P1 height), and reflected pressure wave (augmentation pressure) according to established protocols.26–27 Heart rate was determined from the waveform using cardiac cycle length (period), whereas mean arterial pressure was determined by integration of the pressure waveform.

Statistical Procedures
We observed changes in augmented pressure (AP) and P1 height (P1h) with age, before and after age 60 years, using linear regressions. Using linear regressions, we also observed ∆SBPao per unit ∆AP, as well as ∆SBPao/∆P1h per unit ∆P1h before and after age 60 years. The same analysis was repeated for PPao. We subsequently extended our study by using product of coefficient mediation analysis28 to combine the results of these regressions to determine the changes in SBPao and PPao per year of life attributed to AP and P1h, respectively. This was done by multiplication of regression coefficients, as illustrated by the following example. The regression coefficient (slope) for the regression (AP versus age) represents the ∆AP per year of life. Suppose it has a value of x. The regression coefficient (slope) for the regression SBPao versus AP represents the ∆SBPao/∆AP. Suppose it has a value of y. From these 2 regression coefficients, we know that AP increases per year of life by x units and that for every unit increase in AP, SBPao increases by y units, as per year of life, AP must cause SBPao to increase by (x*y)=xy units. This value (xy) tells us the yearly contribution of wave reflection (as measured by AP) to aortic systolic pressure elevation with age. Note that, for accuracy, the second regression (ie, [SBP versus AP], with slope=x) must be adjusted for age, such that the potential influence of age (the key independent variable) is not accounted for twice as an independent variable in the multiplicative series.28–29 This line of analysis may be repeated with P1h substituted for AP to determine the yearly contribution of the incident wave (as measured by P1h) to aortic systolic pressure elevation with age. We may also substitute PPao for SBPao to determine the yearly contribution of the incident and reflected waves to aortic pulse pressure elevation with age.

Although, to our best knowledge, such a means of statistical analysis has not heretofore been used in arterial pressure waveform analysis, it is based on the principles of mediation analysis, which are used widely in other fields. Mediation analysis accounts for hierarchical causal structures,28–30 and our incorporation of this technique is in line with recent calls for better appreciation of data structure in epidemiological studies.31 A hierarchical, or multilevel, structure exists in the causal relationships analyzed in this study, as shown in Figure 1. That is, age causes AP and P1h to change (level 1), and because of these changes, SBP and PP rise (level 2). The causal structures work at different levels.28,32 The relationship between age and aortic pressure (systolic and pulse) is mediated by AP and P1h. The structure to our multiplicative analysis is outlined in Table 1.

We repeated our analysis with potential confounders (height, weight, heart rate, and mean arterial pressure) added as covariates to the linear regressions. AP and P1h were analyzed together (ie, in the same model) for level 2 regressions, in accordance with recent recommendations for effective analysis of multiple mediators (ie, AP and P1h) representing competing theories.33

To permit statistical inference, we calculated 95% CIs for the potential location of the coefficient products. This is the recommendation for multiplicative linear regression analysis, because it is superior to hypothesis testing alone.26,34,35 CI limits for coefficient products were determined by multiplying 95% confidence bounds for level 1 and 2 regression coefficients (β). That is, minimum coefficient product 95% confidence bounds were obtained by multiplying the minimum 95% confidence bounds for level 1 and 2 β. Similarly, maximum bounds for the coefficient products were determined by multiplying maximum bounds for level 1 and level 2 β. The CIs for coefficient products, thus, represent the potential location of the coefficient product at the 95% confidence level. Significance was taken when the 95% CI did not cross 0 (ie, P<0.05).35 Similarly, significant differences between the coefficient products for the incident and reflected waves (at the P<0.05 level) were observed when 95% CIs did not overlap.

All of the analyses were performed for subjects ≤60 years and >60 years of age. Studies were initially performed with both sexes pooled, and subsequent analyses were repeated separately for men and women. All of the regression coefficients and 95% CIs for β were calculated using SPSS version 14.0 for Windows (SPSS Inc).

Results
Table 2 shows the characteristics of study subjects ≤60 and >60 years of age. Older subjects were, on average, slightly

Table 1. Structure of Regression Coefficient Multiplication in Multilevel Analysis

<table>
<thead>
<tr>
<th>Level 1 β.</th>
<th>Level 2 β.</th>
<th>Coefficient Product, mm Hg/yr</th>
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<tr>
<td>mm Hg/yr*</td>
<td>mm Hg/yr †</td>
<td></td>
</tr>
<tr>
<td>∆AP/∆age</td>
<td>∆SBPao/∆AP</td>
<td>(∆SBPao/∆age) because of AP</td>
</tr>
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<td>∆PPao/∆P1h</td>
<td>(∆PPao/∆age) because of P1h</td>
</tr>
<tr>
<td>∆AP/∆age</td>
<td>∆PPao/∆P1h</td>
<td>(∆PPao/∆age) because of AP</td>
</tr>
<tr>
<td>∆P1h/∆age</td>
<td>∆PPao/∆P1h</td>
<td>(∆PPao/∆age) because of P1h</td>
</tr>
</tbody>
</table>

*Level 1 β represents the base level regression coefficients.
†Level 2 β represents the next level regression coefficients. Level 2 regressions are adjusted for age by adding age as a covariate.
‡Coefficient product represents ([level 1 β]×[level 2 β]).
shorter and lighter than younger subjects. As expected from previous findings, they had higher systolic and pulse pressures and a lower diastolic pressure than younger subjects. This was seen in the brachial artery and the aorta. Older subjects also had a higher AP and P1h, as well as a lower heart rate. Both cardiac ejection duration and mean arterial pressure were greater in older compared with younger subjects. This was seen in the brachial artery and the aorta. Older subjects also had a higher AP and P1h, as well as a lower heart rate. Both cardiac ejection duration and mean arterial pressure were greater in older compared with younger subjects. As expected from previous knowledge of vascular aging, older subjects also had a shorter reflected wave transit time, a greater augmentation index, and a lower pulse pressure amplification ratio.

The regression coefficients for level 1 and level 2 linear regressions (without confounder correction) are shown in Table S1 (available in data supplement online at http://hyper.ahajournals.org). These regressions show that, before age 60 years in sex-pooled analysis, AP increases with age, whereas P1h does not change significantly with age. After age 60 years, however, AP and P1h increase with age at a comparable rate. This confirms the observation of changes in the incident and reflected waves across the life span, as shown in Figure 2.

The yearly contribution of the incident and reflected waves to aortic systolic pressure elevation, before and after age 60, is shown in Figure 3. This shows that, irrespective of sex, before age 60 years the key contributor is wave reflection (P<0.05). In sex-pooled analysis before age 60 years, wave reflection contributes 0.302 mm Hg per year (95% CI: 0.266 to 0.339 mm Hg/y; P<0.05) to aortic systolic pressure elevation, whereas the incident wave does not contribute significantly (−0.003 mm Hg per year; 95% CI: −0.016 to 0.012 mm Hg/y; P value not significant). After age 60 years, both the incident and reflected waves are significant (P<0.05) and comparable (P value for difference not significant) contributors to age-related aortic systolic pressure elevation in both sexes. These findings are expected when the changes in AP and P1h with age before and after age 60 years are considered (Figure 2 and Table S1).

The same results are seen for the yearly contribution of the incident and reflected waves to aortic pulse pressure (Figure S1). Before age 60 years, wave reflection is the key factor in men and women (P<0.05). In sex-pooled analysis before age 60 years, wave reflection raises aortic pulse pressure by 0.299 mm Hg per year (95% CI: 0.271 to 0.327 mm Hg/y; P<0.05), and the incident wave has no significant role (−0.003 mm Hg/y; 95% CI: −0.020 to 0.013 mm Hg/y; P value not significant). After age 60 years, the contribution of the incident and reflected waves is significant (P<0.05) and comparable (P value for difference not significant) in men and women (and, hence, sex-pooled analysis).

When potential confounders (height, weight, heart rate, and mean arterial pressure) were added as covariates to the regressions, the changes in AP and P1h with age (Table S2) and the pattern of results for the yearly contribution of the incident and reflected waves to aortic systolic and pulse pressure elevations persisted (Figures 4 and S2, respectively).

**Discussion**

**Changes in Blood Pressure and Aortic Hemodynamics With Age**

The rise in systolic and pulse pressures with age is well established, as is the associated cardiovascular risk and disease.1–5 The rise in systolic and pulse pressures is also responsible for the overwhelming predominance of isolated
systolic hypertension in older subjects. Although aortic stiffening is known to be the underlying factor behind these observed changes with age, it has not been previously clear as to how progressive stiffening of the aorta generates hemodynamic changes that elevate systolic and pulse pressures.

This study provides insight into this dilemma. First, increased aortic characteristic impedance increases the magnitude of the peripherally traveling (incident) pressure wave generated by ventricular ejection. In our findings, this phenomenon contributes primarily over age 60 years, with little or no contribution before age 60 years in either sex. Second, aortic stiffening alters aortic pulse wave velocity, which permits early return of wave reflection. In a stiffened aorta, the incident wave may reach peripheral reflecting sites sooner and, subsequently, commence reflection back toward the heart earlier. The reflected wave will also travel at a greater velocity when it returns toward the heart. Our findings show that wave reflection contributes across the life span (ie, before and after age 60 years). Additional studies are required to determine the relative contribution of wave reflection magnitude and timing. Some insight may be gained by combining our results with previous findings. Given that aortic pulse wave velocity changes little before age 60 years, we can expect reflected wave timing to contribute to a greater degree after age 60 years. In addition, because reflected wave magnitude depends on incident wave magnitude (law of conservation of energy), and we have shown incident wave magnitude changes little with age before age 60 years (Figure 2 and Table S1), then reflected wave magnitude cannot be expected to contribute much before age 60 years. This is unless the proportion of the incident wave that is reflected back to the heart (ie, the reflection coefficient) also contributes. If reflection coefficient increases with age before age 60 years, it may add to the contributions of changes in aortic pulse wave velocity to generate increases in augmentation pressure (a composite measure of wave reflection magnitude

Figure 3. Contribution of incident and reflected waves to aortic systolic pressure elevation with advancing age (per year of life) in 3682 healthy subjects, before and after age 60 years. Bars represent 95% CIs. A, Results of sex-pooled analysis. B, Results for men and women separately.

Figure 4. Corrected contribution of incident and reflected waves to aortic systolic pressure elevation with advancing age (per year of life) in 3682 healthy subjects, before and after age 60 years with control for height, weight, heart rate, and mean arterial pressure. Bars represent 95% CIs. A, Results of sex-pooled analysis. B, Results for men and women separately.
and timing), which may, in turn, raise aortic systolic and pulse pressures. Additional studies are required to evaluate changes in the reflection coefficient with age and in hypertension.

There has recently been considerable debate as to the relative importance of the incident and reflected pressure waves. This study has evaluated the contribution of both factors and shown that each has a role in systolic and pulse pressure elevations with age: the reflected wave across all ages and the incident wave beyond age 60 years. The results presented here have illustrated that wave reflection is important over age 60 years, a concept previously questioned. In showing the contribution of wave reflection across the human life span, our study has affirmed the preceding work of Marey and Mahomed, who identified the importance of a late systolic peak in the radial pulse waveform, as well as the work of Murgo et al and Kelly et al, who first observed central pressure augmentation attributed to wave reflection, and the work of Wojciechowska et al, who compared changes in radial and aortic augmentation indices with age. The pattern of contribution for the incident and reflected waves sheds some light onto the observed pattern of change in the aortic augmentation index with age, which has generated much discussion. Dominance of the reflected wave explains the observed age-related stability of the augmentation index in subjects over age 60 years.

Our results also draw attention to the importance of central arterial versus peripheral arterial pressure, an increasingly common finding in the literature. Our cohort was composed solely of conventionally defined “normotensive” individuals. Despite this, there was a significant increase in aortic systolic and pulse pressures because of wave reflection, across the life span, and because of aortic characteristic impedance over age 60 years. Our findings have, therefore, highlighted the need to focus cardiovascular risk assessment on central elastic arteries, where hemodynamic changes occur that are at worst missed or at best underestimated, by the brachial cuff sphygmomanometer. The current attention being given to central pressure is well warranted. Sex differences may also be seen in Figures 3 and 4 (and in Figures S1 and S2). These are particularly noted in subjects under the age of 60 years, where, in women, both the incident and reflected waves are seen to make a greater contribution to age-related aortic pressure elevation than in men. This finding is consistent with known sex differences related to aortic characteristic impedance and wave reflection, which are partly explained by anthropometric differences.

Therapeutic Implications

The results of this study explain the hemodynamic pathophysiology of age-related blood pressure elevation, and, therefore, also suggest logical avenues for therapeutic intervention. As wave reflection contributes before and after age 60 years and is easily treated by peripheral arterial vasodilatation, it would appear that these drugs would be useful across the life span. The recent Hypertension in the Very Elderly Study found that there was benefit in blood pressure reduction over age 80 years. Although there may also be a role for pursuing therapies targeting aortic characteristic impedance in those over age 60 years, the comparative weight of evidence for drugs aiming to alter proximal aortic structure is somewhat limited.

Study Strengths, Limitations, and Assumptions

The strengths of this study include the fact that it is the first to account statistically for the multilevel causal framework inherent to this field and to subsequently determine the yearly contribution of the incident and reflected waves to age-related aortic blood pressure elevation. In addition, our cohort was large and free from the confounders of disease or treatment. In addition, measurements were made in duplicate by trained observers. Finally, we conducted analyses separately by sex to account for potential differences in arterial hemodynamics, which have been observed previously.

Limitations of this study include the fact that we used a cross-sectional cohort to infer longitudinal changes. Longitudinal studies are required to confirm the findings presented here. In addition, exclusion of hypertensives may have altered the observed changes in blood pressure with age in a cross-sectional cohort. Future studies should evaluate whether the same patterns are observed when hypertensives are included in analyses. Our cohort was predominantly white in background. Additional studies are required to determine whether our findings are more broadly applicable to other ethnic backgrounds.

Although we accounted for height in multivariate analyses, it is acknowledged that simple adjustment within a model may not be sufficient to account for the complex effects of height on arterial hemodynamics. For instance, arterial length increases and/or becomes tortuous with decreasing body height and age, which may cause effects that exceed the limits of statistical adjustment.

Our analyses are subject to the assumptions of linear regression analysis. First, all relationships subjected to this analysis are indeed linear in nature and are homoscedastic (i.e., contain a similar degree of error along the regression line). Separation of subjects by sex has been used. From observation of the change in the incident and reflected waves across the life span in our cohort, it is seen that this dichotomization is valid (Figure 2). Had different/multiple cutoffs been used, the results presented here would have been altered had a different age cutoff been used. From observation of the change in the incident and reflected waves at comparable rates. Figure 2 also shows that the use of 2 separate linear regressions before and after age 60 years is valid. It may be, however (as suggested by Figure 2), that the equal contribution of the incident and reflected waves commences slightly earlier than age 60 years, perhaps age 55.
The fact that our article continually implicates age 60 years is partly because of our a priori selection of this cutoff for subgroup creation. This is an inherent limitation of creating predefined subgroups and running separate linear regressions over an extended variable range and was recognized by the pioneering work of Chau et al\textsuperscript{56} in the field of hemodynamics and the statistical work of Kastenbaum\textsuperscript{59} and Quandt,\textsuperscript{60} who showed that this concept could be a limiting factor in determining exactly where changes begin to occur, if not considered in tandem with the entire regression range (ie, the whole life span, as per Figure 2).

Finally, mediational analysis assumes that the causal structure presented in Figure 1 is an accurate interpretation of physiological relationships. Such a structure is a reasonable approach to a first approximation, given existing knowledge\textsuperscript{27,61} and given that the statistical criteria for mediation analysis\textsuperscript{29} were met in this study.

**Perspectives**

The rise in aortic blood pressure with age is mediated by changes in aortic hemodynamics. Wave reflection from peripheral sites contributes across the life span, whereas increased aortic characteristic impedance contributes over age 60 years. The future of blood pressure assessment and management must incorporate the emerging concepts of central pressure and aortic hemodynamics to effectively understand and address age-related increases in cardiovascular risk and cardiovascular disease.

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**Disclosures**

M.F.O. is a founding director of AtCor Medical, a manufacturer of systems for pulse waveform analysis. The remaining authors report no conflicts.

**References**

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ONLINE SUPPLEMENT

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<th>Level</th>
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<th>95% Confidence Interval for Beta</th>
<th>Sig.</th>
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<td>(1.108-1.221)</td>
<td>p&lt;0.001</td>
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* Level 2 regressions adjusted for age

Abbreviations: AP = augmented pressure; P1h = P1 height; SBP_{a0} = aortic systolic pressure; PP_{a0} = aortic pulse pressure; NS = not significant
Table S2. Level 1 and 2 multiple linear regressions in gender-pooled analysis with confounder correction

All ≤ 60 years  n = 2311

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<td>P1h</td>
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<td>-0.021</td>
<td>(-0.038 - -0.004)</td>
<td>p&lt;0.05</td>
</tr>
<tr>
<td>2</td>
<td>SBPao</td>
<td>AP†</td>
<td>0.568</td>
<td>(0.555 - 0.581)</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td></td>
<td></td>
<td>P1h†</td>
<td>0.607</td>
<td>(0.596 - 0.617)</td>
<td>p&lt;0.001</td>
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<tr>
<td>2</td>
<td>PPao</td>
<td>AP†</td>
<td>0.938</td>
<td>(0.930 - 0.946)</td>
<td>p&lt;0.001</td>
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<tr>
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<td>P1h†</td>
<td>1.032</td>
<td>(1.025 - 1.038)</td>
<td>p&lt;0.001</td>
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</table>

All > 60 years  n = 1371

<table>
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<tr>
<th>Level</th>
<th>Dependent Variable</th>
<th>Independent Variable</th>
<th>Beta</th>
<th>95% Confidence Interval for Beta</th>
<th>Sig.</th>
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<td>1</td>
<td>AP</td>
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<td>(0.588 - 0.615)</td>
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<td></td>
<td>P1h†</td>
<td>0.639</td>
<td>(0.626 - 0.654)</td>
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<tr>
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<td>PPao</td>
<td>AP†</td>
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<td>(0.994 - 0.997)</td>
<td>p&lt;0.001</td>
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<tr>
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<td>P1h†</td>
<td>1.001</td>
<td>(0.999 - 1.003)</td>
<td>p&lt;0.001</td>
</tr>
</tbody>
</table>

* Level 1 regression : height, weight, heart rate and mean arterial pressure added as covariates
† Level 2 regression : age, height, weight, heart rate and mean arterial pressure added as covariates

Abbreviations: AP = augmented pressure; P1h = P1 height; SBP_{ao} = aortic systolic pressure; PP_{ao} = aortic pulse pressure
Figure S1: Contribution of incident and reflected wave to aortic pulse pressure elevation with advancing age (per year of life) in 3682 healthy subjects, before and after age 60. Bars represent 95% confidence intervals. Panel A shows results of gender-pooled analysis, Panel B shows results for males and females separately. $P_{1h}$ = $P_1$ height (incident wave); $AP$ = augmented pressure (reflected wave).
Figure S2: Corrected contribution of incident and reflected wave to aortic pulse pressure elevation with advancing age (per year of life) in 3682 healthy subjects, before and after age 60. Corrections were made for height, weight, heart rate and mean arterial pressure. Bars represent 95% confidence intervals. Panel A shows results of gender-pooled analysis, Panel B shows results for males and females separately. $P_{1h}$ = $P_1$ height (incident wave); AP = augmented pressure (reflected wave).