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HYPERTENSION

A Meta-Analysis of the Mechanism of Blood Pressure Change With Aging

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Objectives We undertook a meta-analysis to determine whether changes in wave reflection substantiate the consensus explanation of why blood pressure (BP) changes with aging.

Background Consensus documents attribute the aging changes in BP to wave reflection moving progressively from diastole into systole. However, the extensive quantitative data on this phenomenon have never been systematically reviewed. Individual studies have been small, and limited to a narrow age range.

Methods Using PubMed, Cochrane, and Web of Science databases, we identified 64 studies (including 13,770 subjects, age range 4 to 91 years) reporting the timing of wave reflection, defined as the time from the onset (foot) of the pressure waveform to the shoulder point (anachrotic notch).

Results In subjects of all ages, reflection times were well within systole. There was a small tendency for younger subjects to have later reflection, but this was only 0.7 ms per year, whereas the weighted mean reflection time was 136 ms (99% confidence interval: 130 to 141 ms) and the mean duration of systole was 328 ms (99% confidence interval: 310 to 347 ms). At this rate of change with age, arrival of wave reflection would only be construed to be in diastole at an extrapolated age of −221 years.

Conclusions These findings challenge the current consensus view that a shift in timing of wave reflection significantly contributes to the changes in the BP waveform with aging. We should re-evaluate the mechanisms of BP elevation in aging. (J Am Coll Cardiol 2009;54:2087–92) © 2009 by the American College of Cardiology Foundation

Despite many years of research and treatment, high blood pressure (BP) remains the leading cause of mortality worldwide (1), and the hemodynamic mechanisms underlying hypertension remain contentious (2–8). Current consensus (2) explains the arterial pressure waveform in terms of 2 components: an initial rise in pressure due to left ventricular ejection and a secondary rise in pressure caused by reflections returning from distal sites. These components can be divided into forward and reflected waves (9,10).

Most of the additional rise in BP in aging and disease is attributed to the increased magnitude and earlier return of the reflected waves. However, this consensus view has never been formally verified, because the individual studies that might have provided the necessary data have generally been small and limited to narrow age groups.

We undertook a systematic review to test the established hypothesis used to explain the increase in BP with aging; specifically, that the reflected wave arrives in diastole in young healthy persons and, with aging, arrives earlier, ultimately advancing into systole and augmenting systolic pressure.

Methods

Identification of trials. We undertook a systematic review of the literature to identify the time of arrival of the reflected wave as reported in studies between January 1, 1990, and August 1, 2008. This search was carried out twice by 2 investigators independently. Data abstraction was done by 1 investigator and verified independently by the other. We searched PubMed, the Cochrane Collaboration's Database of Systematic Reviews, and Web of Science, using the following search strings and MeSH terms: aorta AND

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Abbreviations and Acronyms

BP = blood pressure

CI = confidence interval

hemodynamics AND wave, aortic wave reflection, augmentation AND systole, augmentation AND timing, augmentation AND diastole, reflected wave AND systole, reflected wave AND timing, wave reflection AND timing, reflected wave AND diastole, time of arrival of reflected wave, peak AND reflected wave, peak systole AND tonometry.

Figure 1 shows the inclusion and exclusion criteria for the studies, each of which was evaluated for quality. Care was taken not to include any study population more than once when it featured in >1 publication. The data were graded according to whether it was invasively or noninvasively acquired.

The arrival time of waves was calculated from the time of the shoulder on the pressure waveform, and the end of systole was estimated to be synchronous with the dicrotic notch (Fig. 2). When we refer to waves, we are referring to the bulk of the traveling wave, which may be composed of multiple waves. Augmentation index is defined as the percentage ratio of augmentation pressure/pulse pressure, where augmentation pressure is the pressure difference between the shoulder and the late peak of BP, and pulse pressure is the difference between systolic and diastolic pressure (Fig. 2).

Statistical analysis. We used data from all the publications to calculate the weighted mean for each time parameter and also the line of regression with respect to age for arrival of the reflected wave. Regression relationships were calculated using SPSS version 15.0 (SPSS, Chicago, Illinois) and Statview version 5.0 (SAS Institute, Cary, North Carolina). Means of data are presented with their 99% confidence intervals (CIs). Regression relationships were calculated by the weighted Pearson method. A p value <0.05 was taken as statistically significant. A sensitivity analysis was performed by repeating the statistical analysis after independently removing cohorts at the extremes of age and then extremes of reflection time.

Results

The search strings returned 2,654 results with 720 unique articles. After limiting this to English language publications and original studies in humans, the remaining 245 studies were individually reviewed. From these, 64 studies describing 134 cohorts met the inclusion criteria. As a result, a total of 13,770 subjects (mean age 53 years, range 4 to 91 years) were included. A table showing the yields from search strings used in this analysis and the references for all cohorts included are provided in the Online Appendix.

The weighted mean for the arrival time of the reflected wave was 136 ms (99% CI: 130 to 141 ms). In comparison, the end of systole occurred at 328 ms (99% CI: 310 to 347 ms). All reflection times were in the first two-thirds of systole, and no study reported an arrival of reflected waves in diastole (Fig. 3).

Similar results were observed from studies using both invasively and noninvasively acquired data. No difference was observed with any individual methodological acquisition technique (Table 1).

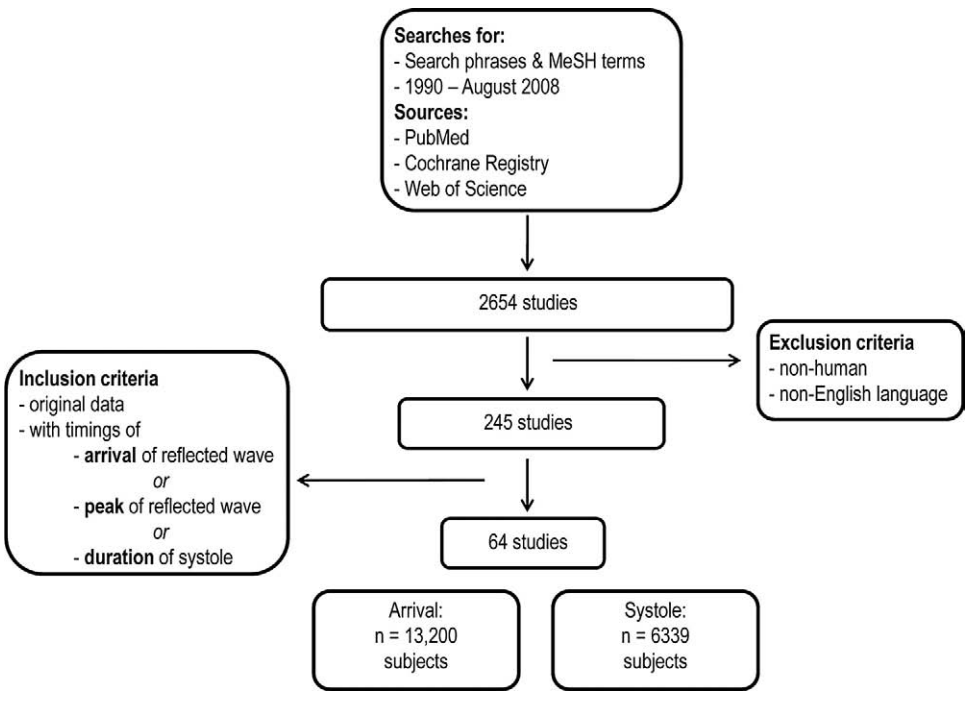

Figure 1 Summary of Trial Identification and Selection

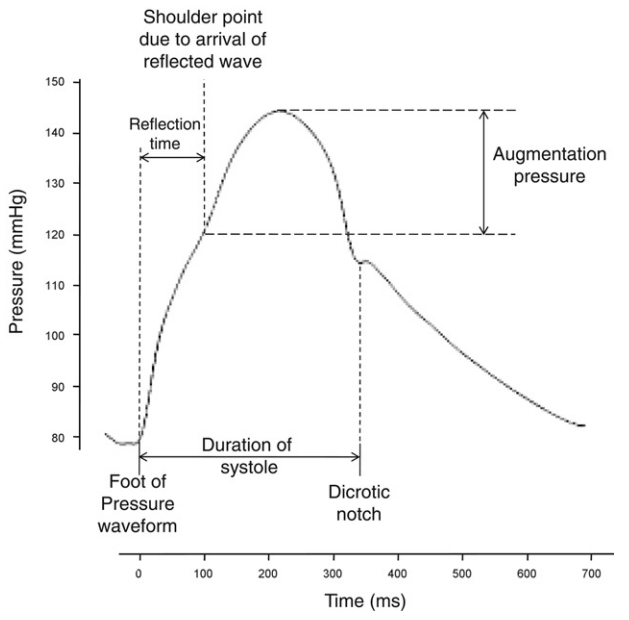

Figure 2 **Annotated Human Arterial Pulse Pressure Waveform**

Arterial pressure waveform recorded from the human proximal aorta showing the foot of pressure waveform and a shoulder point due to arrival of a reflected wave. The time interval between these 2 points is the reflection time. The duration of systole is calculated as the time interval between the foot of the pressure waveform and the dicrotic notch. Augmentation pressure is the rise in pressure from the shoulder point to peak pressure.

The regression relationship of the mean time of arrival of the reflected wave with age is that the reflected wave arrives only 0.71 ms earlier with each 1-year increase in age. At this rate of change, the arrival of the reflected wave would only be expected to be in diastole at an extrapolated age of −221 years.

The results of the sensitivity analyses suggest that there is little change in these findings on exclusion of cohorts at extremes of age or reflection time. The regression coefficient varied between −0.69 and −0.80 ms/year.

The augmentation index was found to markedly increase with age (β = 0.46, 95% CI: 0.36 to 0.56, $p < 0.0001$; r = 0.736, $p < 0.0001$) as expected, despite only a modest shift in the timing of arrival of the reflected wave (r = −0.57, $p < 0.0001$) (Fig. 4). The relationship between augmentation index and age appeared linear, and use of a nonlinear second-order polynomial function to fit the data resulted in a negligible difference in explained variance (linear model r^2 = 0.542; second-order polynomial r^2 = 0.543). The augmentation index was also found to increase with systolic BP (r = 0.386, p = 0.0007). In 25 cohorts, pulse wave velocity was reported; this was also found to increase considerably with age (r = 0.557, p = 0.0032).

Discussion

This systematic review of the literature examining mechanisms contributing to age-related changes in the BP waveform shows that the reflected wave always returns in systole across an age range encompassing almost the entire life course. These findings conflict with the current consensus that emphasizes the mechanistic importance of progressively earlier reflection timing in the development of increased BP and particularly isolated systolic hypertension with aging.

Increased stiffness of the aorta with age and disease has traditionally been used to explain the mechanisms of systolic hypertension by both direct and indirect mechanisms (11). An indirect mechanism attributes higher systolic pressure to the earlier return of reflected waves. In youth, the reflected wave has been postulated to arrive in the proximal aorta in diastole, augmenting coronary flow without increasing cardiac afterload. With increasing age, the timing of wave reflection was proposed to advance into systole, detrimentally increasing afterload without augmenting diastolic coronary perfusion. This change in reflection timing has been used to explain the changes in shape of the respective pressure waveforms (12). However, our analysis finds no evidence to support this hypothesis. Furthermore, the "snail's pace" advancement of 7.1 ms per decade, even viewed over 60 years of aging, moves the reflected wave no more than 43 ms earlier, a movement far smaller than the

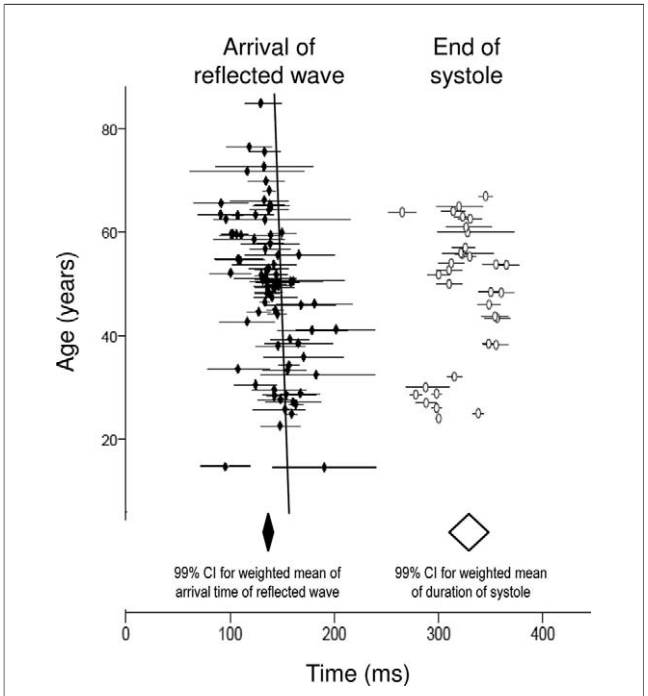

Figure 3 **The Mean Timings Obtained From Each Cohort and 99% CI by Mean Age**

This figure shows the mean time of arrival of the reflected wave **(solid diamonds)** and the mean duration of systole **(open diamonds)** for each cohort plotted by mean age. The **horizontal bars** denote 1 standard deviation. The regression line for the time of arrival of reflected wave with age is shown. The **large solid diamond** describes the mean and the 99% confidence interval (CI) for the weighted mean time of arrival of the reflected wave, and the **large open diamond** shows the mean and the 99% CI for the weighted mean time for the duration of systole.

Table 1 Consistency of Results Between Techniques

	Time of Arrival of Reflected Wave				Duration of Systole			
	Cohorts	n	Mean Age (yrs)	Arrival Time (ms)	Cohorts	n	Mean Age (yrs)	Systolic Duration (ms)
Invasive	13	702	50.7	121 ± 20	9	337	62	310 ± 34
Noninvasive								
SphygmoCor	79	8,699	53.4	131 ± 11	28	3,105	58.8	314 ± 9
Other	26	4,047	50.8	147 ± 30	14	2,897	47.7	345 ± 28
Combined		13,448	52.5	136		6,339	56.2	328

Time of arrival of reflected wave and duration of systole subdivided by data acquistion method. Most papers (88% of all cohorts) stated measurements of the arrival time of the reflected wave, whereas a smaller number (38% of all cohorts) presented data of the duration of systole.

192-ms interval between the mean time of arrival of reflected wave and the end of systole.

In addition to changes in reflection timing, increases in the magnitude of reflected waves themselves may also contribute to higher pressure. In children (13), the magnitude of wave reflection has been shown to be negligible, whereas in older subjects, particularly those with cardiovascular disease, the magnitude of reflection increases markedly (14). Our meta-analysis of augmentation index is consistent with this. Therefore, the results of this meta-analysis should not be interpreted as excluding wave reflection from contributing to elevated BP or hypertension. However, it is important to stress that in the 2,063 subjects studied in the CAFE (Conduit Artery Function Evaluation) study, not only did the reflected wave arrive in systole in all subjects, but the estimated peak of the reflected wave was also found to occur in systole (15), suggesting that the major effects of wave reflection in hypertension occur in systole. Further, since published data largely report the time of arrival of reflection rather than its duration, it is quite possible that reflections extend into diastole. Further studies using approaches that can separate forward and backward waves (6,16,17), and also explore the role of aortic compliance (18), would be valuable in better defining the precise contribution of reflection to diastolic pressure changes with aging.

An alternative, direct mechanism attributes higher systolic pressure with aging to increased aortic stiffness and the implicit loss of aortic compliance. In youth, the elastic aorta is very compliant, converting the phasic left ventricular ejection pattern into a more damped aortic pressure waveform. With increasing age, this elastic compliance is lost (19–21), and the buffering capacity of the aorta to absorb pulsatile left ventricular ejection becomes diminished. This loss of arterial compliance is strongly associated with the development of systolic hypertension (2,11). The impact of changes to the compliance of the proximal aorta is evident in Figure 4, where a cohort of control subjects under the age

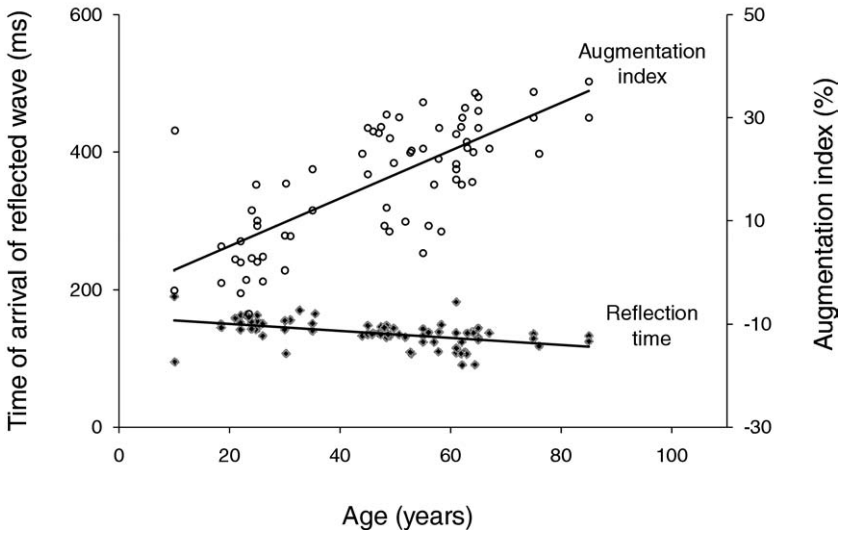

Figure 4 Large Increase in Augmentation Index Despite Only Modest Advance in Time of Arrival of Reflected Wave With Age

This figure shows the mean time of arrival of the reflected wave **(solid diamonds)** and the augmentation index **(open circles)** for each cohort plotted by mean age. The regression lines through these data show that relative to the duration of the cardiac cycle, the time of arrival of the reflected wave advances very little with increasing age, in comparison with augmentation index (shown relative to the theoretical maximum value of 50%), which increases >10-fold over the age range studied.

of 20 years had a mean augmentation index of −3.47% compared with an age-matched cohort who had undergone aortic arch repair that reduced aortic compliance and had a mean augmentation index of 27.5% (22). It should be noted that the inclusion of these latter subjects gives the appearance of a rather wide scatter in the data for younger persons. It was considered inappropriate to exclude these data from the primary analysis, but sensitivity analysis showed that eliminating this cohort did not significantly change the overall results.

The link between the loss of aortic compliance and the development of systolic hypertension has been widely studied in animal models. Ioannou et al. (23) reduced compliance by applying a 3-cm rigid band to the proximal elastic aorta and showed that systolic BP increased significantly, with the morphology of the pressure waveform changing from the textbook pattern of youth to that of old age, despite minimal changes in reflection timing. In the light of our analysis of wave reflection times, we suggest that it is loss of aortic compliance, rather than changes in reflection timing, that is more important in the development of systolic hypertension.

Although a deeper understanding of mechanisms underlying changes in BP with aging is scientifically important, it is also of fundamental relevance to the targeting of appropriate therapeutic strategies (24). If it is loss of compliance of the aorta that is central to the development of systolic hypertension, then perhaps the focus of rational therapeutic development should be on drugs that directly alter the structural characteristics of the aorta (25), rather than on those specifically designed to alter reflection. Furthermore, correct understanding of pathophysiology is critical to the correct interpretation and explanation of clinical trials. Large landmark trials (26,27) have provided us with a wealth of outcome data, but adequate explanations for mechanisms of systolic hypertension remain elusive.

Study limitations. A limitation of this study is the reliance on published data. Suitable data for inclusion in the analysis were not available from many studies. This highlights the need for better reporting of data in publications, possibly as online supplements. Another limitation may be that much of the data relies on the use of pressure augmentation in estimating timing of arrival of the reflected wave, an approach that has been questioned (17). Nevertheless, it is both a weakness and a strength of this analysis that there were a number of techniques utilized by different groups, each with advantages and disadvantages (17). The results of this analysis were nevertheless consistent between the numerous studies, and independent of the specific technique utilized (Table 1).

Conclusions

This study shows that there is no evidence in the published literature to support a substantial shift in wave reflection timing to account for the development of hypertension.

The importance of a correct understanding of the physiological mechanisms underlying arterial pressure and its changes with age and disease should be emphasized. In the race to find ever more sensitive and specific measures of cardiovascular disease, perhaps we should revisit the fundamental physiology.

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Key Words: arteries ■ blood pressure ■ aging ■ wave reflection.

APPENDIX

For a table on the yields from search strings and MESH terms used in analysis and on the references for all cohorts included in the analysis, please see the online version of this article.