Vascular Stiffness, Wave Reflection

Aortic Diameter, Wall Stiffness, and Wave Reflection in Systolic Hypertension


Abstract—Systolic hypertension is associated with increased pulse pressure (PP) and increased risk for adverse cardiovascular outcomes. However, the pathogenesis of increased PP remains controversial. One hypothesis suggests that aortic dilatation, wall stiffening and increased pulse wave velocity result from elastin fragmentation, leading to a premature reflected pressure wave that contributes to elevated PP. An alternative hypothesis suggests that increased proximal aortic stiffness and reduced aortic diameter leads to mismatch between pressure and flow, giving rise to an increased forward pressure wave and increased PP. To evaluate these two hypotheses, we measured pulsatile hemodynamics and proximal aortic diameter directly using tonometry, ultrasound imaging, and Doppler in 167 individuals with systolic hypertension. Antihypertensive medications were withdrawn for at least 1 week before study. Patients with PP above the median (75 mm Hg) had lower aortic diameter (2.94 ± 0.36 versus 3.13 ± 0.28 cm, P < 0.001) and higher aortic wall stiffness (elastance-wall stiffness product: 161 ± 0.7 versus 157 ± 0.7 ln[dyne/cm], P < 0.001) with no difference in augmentation index (19.9 ± 10.4 versus 17.5 ± 10.0%, P = 0.12). Aortic diameter and wall stiffness both increased with advancing age (P < 0.001). However, an inverse relation between PP and aortic diameter remained significant (P < 0.001) in models that adjusted for age, sex, height, and weight and then further adjusted for aortic wall stiffness, augmentation index, and mean arterial pressure. Among individuals with systolic hypertension, increased PP is primarily attributable to increased wall stiffness and reduced aortic diameter rather than premature wave reflection. (Hypertension. 2008;51:105-111.)

Key Words: hypertension ■ hemodynamics ■ pulse pressure ■ aorta ■ vascular stiffness ■ pulse wave velocity

The strong relation between pulse pressure (PP) and cardiovascular events, and the importance of elevated PP in the pathogenesis of systolic hypertension, has stimulated considerable interest in establishing potential mechanisms of increased PP. Early studies focused on the importance of medial degeneration in the aorta as the principal mechanism for the increase in PP that accompanies aging. One hypothesis asserts that mechanical fatigue and fragmentation of the elastin fibers of the aorta leads to dilatation of the proximal aorta and transfers load to stiffer elements of the aortic wall, such as collagen. As a result, aortic wall stiffness and pulse wave velocity (PWV) increase, resulting in premature arrival of reflected pressure waves from the periphery. According to this hypothesis, premature arrival of the reflected pressure wave during systole is considered to be the primary mechanism contributing to increased PP and development of systolic hypertension. For this hypothesis to be correct, PP should be related closely to the extent of pressure augmentation in the central aorta (augmentation index). Furthermore, elevated PP should be associated with increased aortic diameter and PWV.

We recently reported that characteristic impedance (Zc), which is a measure of the pressure-flow relation of the proximal aorta, was elevated out of proportion to the increase in carotid-femoral PWV in individuals with systolic hypertension. Zc is proportional to local PWV divided by local cross-sectional area. Therefore, we proposed that the observed pattern of a predominant increase in Zc with only a moderate increase in carotid-femoral PWV in individuals with a wide PP suggested a reduction in aortic diameter. In this setting the primary mechanism for increased PP would be the mismatch between aortic flow and diameter leading to increased forward wave amplitude, rather than premature wave reflection. To further assess the validity of these alternative hypotheses, we studied pulsatile hemodynamics and aortic root diameter in individuals with systolic hypertension without clinical evidence of atherosclerotic disease.

Methods

Study Participants
Detailed noninvasive hemodynamic studies were performed after withdrawal of all antihypertensive medications for at least 1 week as
part of a previously reported multicenter clinical trial.\textsuperscript{1}\ Men or women who were 18 years of age or were eligible for the trial if they were in sinus rhythm and had moderate systolic or mixed systolic-diastolic hypertension, defined as a seated systolic blood pressure (SBP) $\geq 160$ mm Hg and $\leq 200$ mm Hg and a seated diastolic blood pressure (DBP) $\leq 110$ mm Hg at the time of the qualifying visit. Heart failure, documented ejection fraction $<45\%$, valvular heart disease, or clinically significant peripheral vascular disease were exclusion criteria. Failure to obtain a technically satisfactory baseline study, as determined by the core laboratory, was an exclusion criterion. Additional exclusion criteria have been presented in detail elsewhere.\textsuperscript{3} To be considered in the present analyses, participants were required to be at least 40 years of age, with a supine SBP $\geq 140$ mm Hg at the time of the hemodynamic study, and no history of atherosclerotic disease. An institutional review board at each clinical center approved the study protocol and each subject gave written informed consent prior to enrollment.

**Hemodynamic Data Acquisition**

Participants were evaluated in the supine position after approximately 10 minutes of rest. Supine auscultatory blood pressures were obtained by using a computer-controlled device that automatically inflated the cuff to a user preset maximum pressure and then precisely controlled deflation at 2 mm Hg/sec. This device digitized and recorded mean and oscillometric cuff pressure and ECG (1000 Hz) and a cuff microphone channel (12 kHz) throughout the inflation and deflation sequence so that all blood pressure measurements could be overread by the core laboratory. Blood pressure was obtained 3 to 5 times at 2-minute intervals with a goal of obtaining 3 sequential readings that agreed to within 5 mm Hg for both SBP and DBP. Arterial tonometry with ECG was obtained from the brachial, radial, femoral, and carotid arteries using a custom transducer. Next, 2-dimensional echocardiographic images of the left ventricular outflow tract and proximal aortic root were obtained from a parasternal long axis view, followed by duplicate acquisitions of instantaneous tonometry of the carotid artery and pulsed Doppler of the left ventricular outflow tract from an apical 5-chamber view. Body surface measurements from suprasternal notch to femoral and carotid recording sites were obtained. All clinical sites underwent a rigorous training and certification procedure under the direction of the core laboratory (Cardiovascular Engineering Inc) before enrolling any participants into the trial. All data were digitized during the primary acquisition, transferred to CD-ROM, and shipped to the core laboratory for analysis.

**Data Analysis**

Tonometry waveforms were signal-averaged using the ECG as fiducial point. Average systolic and diastolic cuff pressures were used to calibrate peak and trough of the signal-averaged brachial waveform. Diastolic and mean brachial pressures were then used to calibrate carotid, radial, and femoral waveforms.\textsuperscript{4} Carotid-femoral PWV was calculated as previously described.\textsuperscript{2} $Z_c$ was computed in the time domain.\textsuperscript{6} Total arterial compliance was estimated by using the diastolic area method applied to the last two-thirds of diastolic.\textsuperscript{6} Augmentation index was assessed from the carotid pressure waveform.\textsuperscript{7} Because augmentation index depends on identification of the inflection point between forward and reflected pressure wave, which theoretically may be obscured in cases with markedly premature arrival of the reflected wave,\textsuperscript{6} we also evaluated an alternative augmentation index that does not require identification of the inflection point on the carotid pressure waveform. The alternative augmentation index was calculated by first calculating forward wave amplitude using a pressure-flow approach.\textsuperscript{6} The difference between central PP and forward wave amplitude, which is the augmented pressure, was then divided by central PP. The traditional definition of augmentation index was used in all analyses except as noted in the text. Aortic annulus diameter was measured just proximal to the aortic leaflets and aortic root diameter was measured just distal to the sinuses of Valsalva. At each location, the largest (systolic) diameter was identified visually from a 5-second loop and measured on-screen from the original digital images. The water hammer equation was used to calculate the proximal aortic PWV, $c_a = (Z_c \times A)/\rho$, where $Z_c$ is characteristic impedance, $A$ is aortic cross-sectional area and the density of blood, $\rho$ is assumed fixed at 1.06 g/cm$^3$. The aortic elastance-wall thickness product (Eh), a measure of wall stiffness, was computed by rearranging the Moens–Korteweg equation to give: $Eh = c_a \times \rho D$, where $c_a$ is central aortic PWV and $D$ is measured aortic root diameter. Eh was highly skewed and was therefore In transformed to normalize variance.

As previously reported in a multicenter setting, our protocol has high reproducibility for measures of central aortic stiffness with intraclass correlation coefficients for repeated measures of $Z_c$ of 0.93 to 0.95.\textsuperscript{5} To evaluate the reproducibility of aortic root diameter measurements, measurements were performed twice in 28 randomly selected cases. The correlation coefficient for these paired measurements was 0.93 and the coefficient of variation was 4.6%.

**Statistical Analysis**

Sample characteristics were tabulated separately by low and high PP groups that were defined according to whether peripheral PP was below or above the approximate median value of 75 mm Hg. Impedance spectra were averaged by harmonic and plotted against the averaged frequency at each harmonic. Regression analysis was used to assess relations between peripheral PP, treated as a continuous variable, and aortic diameter alone and with adjustment for age, sex, height, and weight. Stepwise multivariable regression with age, sex, height, and weight forced into the model was then used to evaluate relations between peripheral PP and aortic properties (diameter and Eh). Carotid-femoral PWV, augmentation index, and mean arterial pressure (MAP). General linear models that adjusted for age, sex, height, weight, and MAP were used to assess differences in aortic diameter and Eh in the low and high PP groups. To evaluate changes in aortic diameter and stiffness with advancing age in high and low PP groups, regression analysis was used to generate aortic diameter and stiffness residuals adjusted for sex, height, weight, and MAP. Aortic diameter and stiffness residuals were then plotted against age. Relations between aortic diameter residuals, age, and PP group were assessed by using a general linear model with age as a continuous variable and low versus high PP as a grouping variable. This procedure was repeated for the aortic stiffness residuals.

Values are presented as mean±SD except as noted. A 2-sided $P<0.05$ was considered significant.

**Results**

Baseline hemodynamic evaluations were performed in 220 individuals, including 18 (9\%) hemodynamic studies that were rejected for technical reasons and repeated. There were 7 (3\%) individuals who did not enter the trial for nontechnical reasons, 9 (4\%) whose data could not be analyzed, 9 (4\%) who were excluded for the purposes of this analysis because their supine SBP was $<140$ mm Hg at the time of the hemodynamic study, 7 (3\%) whose aortic root diameter could not be measured, 19 (9\%) with a history of atherosclerotic coronary or peripheral vascular disease, and 2 (1\%) who were younger than 40 years of age, resulting in a final sample of 167 individuals. Characteristics of the study sample are presented in Table 1. Participants with higher PP were more likely to be women and older, shorter, and lighter, but had a comparable body-mass index. Those with higher PP had higher systolic and lower diastolic pressures and a trend toward higher MAP (Table 1). There were no differences in fasting serum glucose or cholesterol levels, prevalence of diabetes mellitus, or current use of aspirin or lipid lowering medications (Table 1).

Central hemodynamic variables are presented in Table 2. Peripheral resistance tended to be higher in the high PP
group, whereas cardiac output did not differ (Table 2). Zc, carotid-femoral PWV and aortic PWV were higher and total arterial compliance was lower in the high PP group, whereas augmentation index did not differ. Aortic root diameter was smaller and aortic wall stiffness was higher in the high PP group (Table 2).

Average impedance spectra are presented in Figure 1. The modulus of impedance exhibited a parallel upward shift throughout the first 10 harmonics in the high PP group. In contrast, the phase spectrum was relatively unchanged. There was no evidence of a shift in the first minimum of the impedance modulus or the first zero crossing of phase (Figure 1). These spectra suggest that differences in pulsatile load were largely attributable to an increase in Zc rather than a change in timing or amplitude of wave reflections.

Multivariable correlates of PP evaluated as a continuous variable are presented in Table 3. When aortic diameter alone was entered into a model for PP, there was an inverse relation that explained 12% of the variability in PP (Model 1, Table 3). When age, sex, height, and weight were added to the model, the model R² increased to 36% and the inverse relation between aortic diameter and PP remained significant (Model 2, Table 3). We then evaluated a model that included age, sex, height, and weight and offered aortic wall stiffness, aortic root diameter, carotid-femoral PWV, heart rate, augmentation index, and MAP as potential covariates in a stepwise manner. Aortic wall stiffness, aortic root diameter, augmentation index, and MAP entered the model (Model 3, Table 3). We

Table 1. Characteristics of the Sample

<table>
<thead>
<tr>
<th>Variable, Units</th>
<th>Pulse Pressure ≤75 mm Hg (n=81)</th>
<th>Pulse Pressure &gt;75 mm Hg (n=86)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>58±9</td>
<td>65±8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Women, n (%)</td>
<td>19 (23)</td>
<td>48 (56)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Height, cm</td>
<td>172±10</td>
<td>166±10</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>91±16</td>
<td>82±20</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Body-mass index, kg/m²</td>
<td>30.7±5.3</td>
<td>29.4±6.1</td>
<td>0.120</td>
</tr>
<tr>
<td>Heart rate, min⁻¹</td>
<td>65.0±9.4</td>
<td>63.6±8.5</td>
<td>0.284</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>155.7±9.5</td>
<td>173.5±12.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>89.1±9.0</td>
<td>81.6±10.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mean arterial pressure, mm Hg</td>
<td>116.4±9.8</td>
<td>119.3±9.6</td>
<td>0.055</td>
</tr>
<tr>
<td>Pulse pressure, mm Hg</td>
<td>66.6±6.4</td>
<td>91.9±12.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Glucose, mg/dL</td>
<td>101±25</td>
<td>103±29</td>
<td>0.570</td>
</tr>
<tr>
<td>Cholesterol, mg/dL</td>
<td>209±33</td>
<td>209±36</td>
<td>0.921</td>
</tr>
<tr>
<td>Diabetes</td>
<td>9 (11)</td>
<td>7 (8)</td>
<td>0.603</td>
</tr>
<tr>
<td>Current smoker</td>
<td>10 (12)</td>
<td>10 (12)</td>
<td>1.000</td>
</tr>
<tr>
<td>Aspirin</td>
<td>16 (20)</td>
<td>20 (23)</td>
<td>0.707</td>
</tr>
<tr>
<td>Lipid lowering medication</td>
<td>17 (21)</td>
<td>20 (23)</td>
<td>0.852</td>
</tr>
</tbody>
</table>

SD indicates standard deviation; Beta, change in pulse pressure per 1 SD increase in the independent variable; Eh, elastance x wall thickness.
tested Model 3 with the alternative definition of augmentation index, which is not dependent on detection of the inflection point in the carotid pressure waveform. The results were essentially identical to Model 3 (data not shown). To test for effect modification, we ran Model 3 separately in men versus women, in those older versus younger than the median age (61 years), in obese (BMI ≥ 30 kg/m²) versus nonobese participants, and in those shorter or taller than the median height (169 cm) (data not shown). In all models, PP was related inversely to aortic diameter and directly to aortic wall stiffness (P < 0.001 for all models). Augmentation index and MAP were significant in models for women and older or shorter individuals and neither was significant in models for men and younger or taller individuals. MAP was significant and augmentation index was not in obese individuals whereas augmentation index was significant and MAP was not in nonobese individuals.

Changes in aortic diameter and wall stiffness with advancing age are presented in Figure 2. Aortic diameter (Figure 2A) and wall stiffness (Figure 2B) increased with advancing age. However, diameter was lower and wall stiffness was higher in the high PP group.

Partial residual plots corresponding to PP Model 3 are presented in Figure 3. To generate these partial plots, all variables except for the test variable were entered into models that optimized the fit without the effects of the test variable. Residuals from each model were plotted against the excluded variable. After optimizing model fit for all other covariates, a strong inverse relation between PP and aortic diameter remained (Figure 3A). PP increased steeply with increasing wall stiffness (Figure 3B) and modestly with increasing augmentation index (Figure 3C) and MAP (Figure 3D). Figure 3A demonstrates that even when measures of aortic wall stiffness, wave reflection and distending pressure were considered first in a model, a strong inverse relation between PP and aortic diameter was observed.

Aortic diameter and aortic wall stiffness adjusted for age, weight, and MAP are summarized by PP group and sex in Figure 4. Aortic root diameter was lower in women as compared with men and was lower in the high as compared with the low PP group (Figure 4A). Higher body weight was associated with increased aortic diameter (P < 0.001) in this model, which adjusted for age, sex, height, and MAP, suggesting that aortic diameter increased in proportion to an increase in body weight at a given height. Aortic stiffness did not differ significantly by sex but was higher in the high PP group (Figure 4B).

**Discussion**

This study evaluated relations between PP and aortic properties in a sample of individuals with uncomplicated systolic hypertension. Participants spanned a broad age range (40 to 83 years) and were recruited from several centers distributed across North America. We found an inverse relation between PP and aortic diameter that persisted in multivariable models that adjusted for age, sex, height, weight, and other measures associated with increased PP, including aortic wall stiffness, augmentation index, and MAP. Higher PP was associated with increased aortic wall stiffness in a model that included aortic root diameter and other covariates. Our findings suggest that increased wall stiffness and reduced aortic diameter, which are the main components of Zc, each contributed to higher PP in this hypertensive sample. Our findings confirm that with increasing age, the aortic wall stiffens and aortic root diameter increases modestly. However, higher PP was associated with reduced rather than increased aortic root diameter measured directly from echocardiographic images in this sample of individuals with systolic hypertension.

Our findings are not consistent with a paradigm of cyclic stress, elastin fragmentation, and premature wave reflection as the primary mechanism for the genesis of increased PP. The cyclic stress hypothesis posits that elastin fragmentation...
attributable to mechanical fatigue leads to passive aortic dilatation, wall stiffening, and increased PWV. The increase in PWV leads to premature return of reflected pressure waves, which serves as the primary mechanism for increased PP in systolic hypertension. We did find a relation between aortic wall stiffness (Eh product) and PP, indicating that either the aortic wall material was stiffer or the wall was thicker in those with higher PP. However, we found no evidence of increasing aortic diameter in association with increasing PP, which is a hallmark of the cyclic stress hypothesis. Instead, we found an inverse relation between PP and aortic diameter that was confirmed in unadjusted

Figure 3. Partial residual plots for PP in a model that included age, sex, height, weight, and 3 of the following variables: aortic diameter, wall stiffness, augmentation index, and MAP. Residuals were regressed on the omitted variable in each panel.

Figure 4. Aortic diameter (A) and wall stiffness (B) adjusted for age, height, weight, and MAP and grouped according to PP and sex. Aortic diameter remained smaller in women after adjusting for body size and was smaller in those with a higher PP (A). Aortic stiffness did not differ by sex but was higher in those with higher PP (B). Values represent mean ± SEM.
models and in a multivariable model that adjusted for age, sex, height, weight, aortic wall stiffness, wave reflection, and MAP. Furthermore, variability in wave reflection accounted for only a minority of the variance in PP in our sample. Thus, factors other than elastin fragmentation, increased PWV and premature wave reflection are involved in the genesis of increased PP in individuals with systolic hypertension.

Our sample included only individuals with systolic hypertension, suggesting that our observations may not be applicable to the broader community. However, our finding of an inverse relation between aortic diameter and PP is consistent with observations from two community-based studies of the correlates of aortic root diameter. Our finding that augmentation index is less important than forward wave amplitude in explaining variability in PP is also consistent with the results of an analysis of arterial pressure waveforms in a healthy community-based sample.

The observation of an inverse relation between aortic diameter and PP may provide insights into a potential mechanism for increased PP in systolic hypertension. Zc, which is the ratio of the change in pressure and flow in early systole (before return of the reflected pressure wave), describes the pulsatile pressure-flow relation of the proximal aorta. Zc is directly related to aortic wall stiffness and is inversely related to aortic diameter. Increased PP in the setting of increased Zc and reduced aortic diameter is indicative of mismatch between resting pulsatile aortic flow and aortic root diameter. We have shown that individuals with higher PP manifest impaired matching between pulsatile flow and diameter, leading to the observed triad of reduced aortic diameter, increased Zc, and increased PP. Therefore, abnormalities in pathways involved in matching aortic properties to ambient levels of mean and pulsatile flow may be involved in the pathogenesis of systolic hypertension in individuals with elevated PP.

The aorta is a dynamic organ that remodels in response to hemodynamic demands. In animal models, creation of an aorticaval shunt is associated with a marked increase in aortic flow and shear stress followed by a progressive increase in aortic diameter, which tends to restore aortic shear stress to control levels. Similarly, in our study participants, higher body weight, which is associated with increased resting cardiac output, was associated with increased aortic diameter. Thus, experimental models and data from humans suggest that aortic diameter is actively modulated in response to physiological stimuli. Active modulation of aortic diameter was not considered in earlier models of aortic function that portrayed aortic elastin as a long-lived molecule that is deposited once during development and maturation and then monotonically degraded thereafter in the wake of unremitting pulsatile strains.

Wave reflection played a relatively minor role in the genesis of higher PP in our hypertensive sample. It is important to acknowledge that carotid pressure augmentation was highly prevalent in our sample and accounted for nearly 20% of central PP (Table 2). However, variability in central pressure augmentation contributed only modestly to variability in peripheral PP in our hypertensive sample. Furthermore, the relation between peripheral PP and wave reflection remained modest even when wave reflection was quantified using a pressure-flow approach that does not rely on identification of the inflection point between forward and reflected pressure waves. Therefore, contrary to prior suggestions, inaccurate assessment of central pressure augmentation in those with the highest PP is an unlikely explanation for the finding of only modest relations between augmentation index and peripheral PP in this middle-aged to elderly sample.

Higher PP was associated with higher MAP. The association between PP and MAP is generally attributed to the passive mechanical effects of excessive distending pressure leading to increased arterial wall stiffness. Elevated MAP may have contributed to the observed association between PP and aortic wall stiffness in our study. However, increased MAP cannot explain the inverse relation between PP and aortic diameter because aortic diameter should be increased if distending pressure was raised sufficiently to increase passive stiffness of the aortic wall. Furthermore, it is important to underscore that the association between PP and MAP remained significant in a model that included aortic wall stiffness, suggesting that factors other than a passive increase in aortic stiffness may be involved in the cross-sectional relation between MAP and PP. Prior studies have shown that increased pressure pulsatility may trigger rarefaction, remodeling and increased tone in the microcirculation, which could secondarily increase MAP in the setting of unchanged cardiac output. Thus, it is possible that in some individuals, abnormal aortic function, including reduced aortic diameter or increased aortic wall stiffness, may precede and contribute to the development of elevated MAP through secondary effects on microvascular function.

Potential limitations of our study need to be considered. Our measurement of aortic diameter considered only the diameter in the proximal aortic root, just above the sinotubular ridge. In addition, we did not measure aortic wall thickness. A more comprehensive evaluation of aortic root structure including measurement of aortic diameter and wall thickness at multiple levels in the arch may provide additional insights into the role of aortic geometry in the pathophysiology of elevated PP. However, such a detailed assessment of aortic root structure would likely clarify rather than refute the basic observations made in our study. In addition, it is important to note that augmentation index remained a significant predictor of PP in our sample. Thus, while wave reflection does contribute to elevated pulse pressure, it appears that this contribution is modest, although the contribution may be more substantial in a given individual or in particular disease states.

Perspectives
Systolic hypertension is highly prevalent in our aging society and is associated with increased PP and a marked increase in cardiovascular disease risk. To prevent or properly treat systolic hypertension, a better understanding of the pathophysiology of elevated PP is required. There is general agreement that abnormal aortic properties (wall stiffness, wall thickness, or lumen diameter) are involved in the pathogenesis of increased systolic and PP. However, hypotheses that view the aorta as a static, mechanical system that slowly
breaks down as an inevitable and irreversible consequence of simple mechanical fatigue, run counter to the findings of several large studies involving normal and hypertensive individuals. Such concepts must be carefully reevaluated in the context of the present findings and other data showing both adaptive and maladaptive mechanisms for dynamic change in aortic properties.

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Disclosures

G.F.M. is owner of Cardiovascular Engineering Inc, a company that designs and manufactures devices that measure vascular stiffness. The company uses these devices in clinical trials that evaluate the effects of diseases and interventions on vascular stiffness.

References

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