Elevated Pulse Pressure Is Associated With Low Renal Function in Elderly Patients With Isolated Systolic Hypertension

Jacobien C. Verhave, Pierre Fesler, Guilhem du Cailar, Jean Ribstein, Michel E. Safar, Albert Mimran

Abstract—In the past decade, pulse pressure has emerged as a strong predictor of cardiovascular morbidity and mortality. During aging, elevation of pulse pressure is a consequence of stiffening of the arterial wall. The relationship between pulse pressure and the renal aging process was studied in a cohort of 212 patients with never-treated isolated systolic hypertension. Glomerular filtration rate and effective renal plasma flow were measured using constant infusion of technetium 99m (99mTc)-DTPA and 131I-ortho-iodohippurate, respectively, and timed urine collections. The relationship between pulse pressure and renal function was studied using a linear regression model in the total population and in 40 to 49, 50 to 59, and 60 years and older age categories. In the whole population, there was an inverse relationship between pulse pressure and glomerular filtration rate; however, this relation did not persist after adjustment for age. In fact, the inverse relationship between pulse pressure and glomerular filtration rate was only present in patients 60 years of age or older. This relationship in elderly patients remained after adjustment for age, gender, MAP, and cardiovascular risk factors ($P=0.006$). It is suggested that pulse pressure, a marker of arterial stiffening, may have a detrimental influence on the age-related decline in glomerular filtration rate, after 60 years of age in patients with never-treated isolated systolic hypertension. (Hypertension. 2005;45:586-591.)

Key Words: age ■ glomerular filtration rate ■ hypertension ■ pulse

In the past decade, pulse pressure (PP), defined as the difference between systolic and diastolic blood pressure (DBP), emerged as a strong predictor of cardiovascular and cerebrovascular mortality.1,2 In the Framingham study of 1924 individuals 50 to 79 years of age, higher PP increased the risk of coronary heart disease.3 A high PP was also a predictor of all-cause, cardiovascular, and, especially, coronary mortality in 19 083 men (40 to 69 years of age) with relatively low cardiovascular risk.4 Interestingly, it was reported that although PP predicts coronary heart disease in subjects older than 60 years, DBP was the strongest predictor in subjects younger than 50 years.5

The increase in PP is considered in subjects older than 40 years of age as a consequence of stiffening of the arterial system, as shown by its correlation with aortic pulse wave velocity.6,7 The relationship between PP and age is J-shaped, being negative in subjects aged younger than 40 years and becomes positive after age 40, thus suggesting a different signification of PP in younger versus older subjects.8 In subjects with preserved ejection fraction aged younger than 40, PP may be related to hyperdynamic cardiovascular condition,9 whereas after age 60, the contribution of arterial stiffening is probably crucial. In fact, after 60 years of age, PP increases because of a decrease in DBP and the continuous increase in systolic blood pressure (SBP).10 Evidence is presently accumulating that renal function impairment is an independent contributor of cardiovascular risk.11–13 In the Multiple Risk Factor Intervention Trial (MRFIT) population, a high risk of end-stage renal disease was found in patients with isolated systolic hypertension (ISH), who are those with a normal DBP and an elevated PP.14

The relationship between arterial stiffening and renal function is unclear and the possibility that modification of vascular compliance could participate or eventually enhance the age-related decline in glomerular filtration rate (GFR) deserves investigation. Longitudinal studies conducted in elderly subjects with ISH suggest that in patients with increased PP but nearly normal mean arterial pressure (MAP), the increase in PP may be preferentially be transmitted to the glomerulus and thus favor arteriolosclerosis and reduced renal function.15 This hypothesis, which has never been tested, requires human investigations, which may be obtained in cross-sectional studies and using adequate and reliable measurements of renal hemodynamics and function. In the present study, the relationship between precisely measured intrarenal hemodynamics and PP was assessed in never-treated patients with ISH.

Received November 19, 2004; first decision December 27, 2004; revision accepted January 27, 2005.
From the Department of Internal Medicine (J.C.V., P.F., G.d.C., J.R., A.M.), CHU Montpellier, France; Diagnosis Center (M.E.S.), Hôtel-Dieu Hospital, Paris, France.
Correspondence to A. Mimran, Department of Internal Medicine, Hôpital Lapeyronie, 34295 Montpellier Cedex 5, France. E-mail amimran@wanadoo.fr

© 2005 American Heart Association, Inc.
Hypertension is available at http://www.hypertensionaha.org DOI: 10.1161/01.HYP.0000158843.60830.cf
Materials and Methods

Study Population

The study population consisted of 212 patients with ISH selected from a cohort of 658 patients with never-treated essential hypertension aged 40 years or older. ISH was defined as a SBP of \( \geq 140 \) mm Hg and a DBP of \( <90 \) mm Hg.\(^{16}\) Patients were recruited from the outpatient clinic of the department of internal medicine, where patients came directly or were referred by general practitioners for detection or investigation of their cardiovascular risk profile. Patients came to the ward with 2 consecutive 24-hour urine collections for the determination of urinary sodium (as an index of sodium intake), urinary urea (as an index of protein intake), and urinary albumin excretion (radioimmunoassay; Beckman Coulter Company, Immunocheck). Body mass index (BMI) was calculated as weight (kg) divided by square of height (m\(^2\)). Microalbuminuria was defined as a urinary albumin excretion of 20 to 199 \( \mu g/\)min. Patients with clinical evidence of atherosclerosis (stroke, coronary and peripheral artery disease), heart failure, renal failure (serum creatinine \( >130 \) \( \mu mol/L \)), clinical proteinuria (dipstick-positive), diabetes mellitus (fasting glucose level \( \geq 7.0 \) mmol/L), a history of alcohol abuse (\( >5 \) drinks per day), and secondary hypertension were excluded. All subjects gave informed consent and the local medical ethics committee approved the study.

Blood Pressure Measurement

After 10 minutes of rest, blood pressure was automatically measured every 3 minutes in the supine position (Model 8800; Colin).\(^{17}\) Reported blood pressure values are the mean of at least 10 successive measurements. PP was calculated as the difference between SBP and DBP. MAP was calculated as DBP plus one-third (SBP−DBP). In addition, blood samples for the measurement of serum creatinine (enzymatic method; Randox, Mauguio), glucose, lipids, and plasma renin activity (RIA using the CEA Sorin kit) were obtained.

Measurements of Renal Function

GFR and effective renal plasma flow (ERPF) were estimated by urinary clearance techniques—labeled diethylenetriaminopentaacetic acid (\(^{99m}\)Tc-DTPA) and \(^{111}\)I-ortho iodohippurate, respectively. The constant infusion technique with timed urine collections was used as previously described.\(^{18}\) Renal hemodynamic values were expressed as mL/min per 1.73 m\(^2\). Filtration fraction was calculated as GFR/ERPF. The reproducibility of measurements of renal hemodynamics was obtained in 20 subjects; the variation coefficient of GFR and ERPF was 6.4% and 6.3%, respectively.

Statistical Analysis

Data are presented as mean \( \pm \) standard deviation (SD) or median and interquartile range when variables were not normally distributed. The population was stratified by age into 3 groups: 40 to 49, 50 to 59, and 60 years and older, and characteristics of age groups were compared by Student \( t \) test or \( \chi^2 \) test. In the total population of 212 patients, the relationship between PP and renal function was studied by a linear regression model with, respectively, GFR, ERPF, and filtration fraction as dependent variables and PP as an independent variable. The linear regression model of PP and renal function was also constructed after stratification for the 3 age categories. In the multivariate analysis, MAP, age, gender, smoking, BMI, total cholesterol, and fasting glucose were also included in the model. In a secondary analysis, urinary sodium and urea excretion and albuminuria were added to the multivariate model to substantiate their influence on the relationship between PP and renal function. To obtain optimal distribution of residuals, urinary albumin excretion was log-transformed.

Each age category was divided into tertiles of PP, and a comparison between renal function parameters was assessed by analysis of variance or covariance with Bonferroni post hoc test. Covariates were MAP, age, gender, smoking, BMI, total cholesterol, and fasting glucose.

All probability values are 2-sided and \( P<0.05 \) was considered statistically significant (SPSS, Chicago version 11.5).

Results

Characteristics of the Population

The present cohort of 212 patients consisted of 33% men and mean age was 52 years (range, 40 to 99). Obesity (BMI \( \geq 30 \) kg/m\(^2\)) was present in 20% of patients. The characteristics of every age category are presented in Table 1. SBP was higher and DBP lower, and as a consequence PP was higher in the older group. MAP and heart rate were not different between age groups. Lower mean values of GFR and ERPF were found in the elderly as compared with the other age groups, and no difference in filtration fraction was detected. Urinary sodium, urea, and albumin excretion were not different over the age categories; however, microalbuminuria was present in 12.5% of the patients in the elderly group versus 5% in patients 40 to 49 years of age (\( P<0.05 \)).

Relationship Between PP and Renal Hemodynamics

When the whole population was considered, GFR and ERPF (dependent variables, indexed to 1.73 m\(^2\) of body surface area) were inversely correlated with PP; however, this relationship did not persist after adjustment for age. When analysis was performed within each age group, the negative relationship between PP and GFR and ERPF was only found in the older (60 years and older) age group (model \( r^2=0.17 \); beta coefficient \( -0.690 \) mL/min per 1.73 m\(^2/mm\) Hg of PP; \( P=0.001 \) for GFR; and model \( r^2=0.12 \); beta coefficient \( -2.51 \) mL/min per 1.73 m\(^2/mm\) Hg of PP; \( P=0.007 \) for ERPF). In patients aged 60 or older, the inverse correlation between PP and GFR remained after adjustment for MAP, heart rate, age, gender, smoking, BMI, total cholesterol, and fasting glucose (model \( r^2=0.49 \); beta coefficient \( -0.727 \) mL/min per 1.73 m\(^2/mm\) Hg of PP; \( P=0.006 \)). When ERPF instead of GFR was introduced as the dependent variable, the relationship with PP was consistently weaker (model \( r^2=0.45 \); beta coefficient \( -1.913 \) mL/min per 1.73 m\(^2/mm\) Hg of PP; \( P=0.096 \)). Of interest, in the older age group, the inverse relationship between PP and GFR was maintained when urinary sodium, urea, and albumin excretions were entered into the model. When GFR and ERPF were expressed as mL/min, all relationships between GFR or ERPF and PP were maintained after inclusion of body weight and height instead of BMI into the model. No relationship between PP and filtration fraction was detected.

In patients 60 years of age or older, PP was inversely correlated with measured creatinine clearance; however, this relationship was not independent of age. No univariate relationship between PP and other estimates of renal function using the Modification of Diet in Renal Disease (MDRD)\(^{19} \) or the Cockcroft-Gault formula\(^{20} \) was detected.

Tertiles of PP and Renal Function Within Each Age Category

Renal hemodynamics according to tertiles of PP within each age group are shown in Table 2 and Figure 1. As compared with the lowest tertile, GFR and ERPF were significantly
lower in the second and third tertiles of PP only in the 60 and older age group. No difference in filtration fraction across tertiles of PP in each age category was detected.

In patients 60 years and older only, the mean value of GFR in the highest tertile of PP was still significantly lower than the lowest tertile after correction for MAP, age, gender, smoking, BMI, total cholesterol, and fasting glucose ($P=0.008$). Also, adjustment for serum high-density lipoprotein cholesterol and triglycerides instead of total cholesterol did not change the relationship between PP and GFR. The

### TABLE 2. Renal Hemodynamics According to Tertiles of Pulse Pressure in Each Age Group

<table>
<thead>
<tr>
<th>Age Categories, y</th>
<th>40 – 49 (n=64)</th>
<th>50 – 59 (n=85)</th>
<th>60+</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Tertile of Pulse Pressure</strong></td>
<td><strong>I</strong></td>
<td><strong>II</strong></td>
<td><strong>III</strong></td>
</tr>
<tr>
<td>Pulse Pressure (mm Hg)*</td>
<td>56 (52–59)</td>
<td>62 (59–65)</td>
<td>73 (65–103)</td>
</tr>
<tr>
<td>Gender (male), %</td>
<td>47.6</td>
<td>31.8</td>
<td>19.0</td>
</tr>
<tr>
<td>Age, y</td>
<td>44.5±2.9</td>
<td>45.2±2.6</td>
<td>45.5±2.6</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>25.8±4.8</td>
<td>25.0±3.1</td>
<td>28.6±6.1§</td>
</tr>
<tr>
<td>MAP, mm Hg</td>
<td>105±2</td>
<td>106±3</td>
<td>108±5†</td>
</tr>
<tr>
<td>GFR, mL/min/1.73 m²</td>
<td>108.4±15.2</td>
<td>104.0±13.4</td>
<td>108.1±22.5</td>
</tr>
<tr>
<td>ERPF, mL/min/1.73 m²</td>
<td>477±66</td>
<td>471±76</td>
<td>451±107</td>
</tr>
<tr>
<td>Filtration fraction, %</td>
<td>22.9±3.1</td>
<td>22.4±3.0</td>
<td>24.2±2.4</td>
</tr>
<tr>
<td>Plasma renin activity, ng/mL/hr*</td>
<td>0.82 (0.40–1.21)</td>
<td>1.00 (0.63–1.56)</td>
<td>0.65 (0.21–2.21)</td>
</tr>
<tr>
<td>Urinary sodium, mmol/24 h</td>
<td>143±87</td>
<td>144±58</td>
<td>129±69</td>
</tr>
<tr>
<td>Urinary urea, mmol/24 h</td>
<td>387±160</td>
<td>400±129</td>
<td>400±201</td>
</tr>
<tr>
<td>Urinary albumin, μg/min</td>
<td>5.5 (3.7–7.7)</td>
<td>5.1 (3.0–7.2)</td>
<td>7.1 (5.3–14.1)</td>
</tr>
</tbody>
</table>

Values are mean±SD or mean (interquartile range).
* $P<0.05$ vs age category 40 – 49.
† Mean and interquartile range.
‡ $P<0.05$ vs first tertile of pulse pressure.
§ $P<0.05$ vs second tertile of pulse pressure.
difference in ERPF over tertiles of PP did not persist after correction for all confounders when urinary sodium, urea, or albumin excretions were entered into the regression model. Our observation of a lower GFR in the oldest age group with the highest PP was confirmed when GFR was not corrected for body surface area (mL/min) or corrected for height (GFR mL/min per meter) (an expression of GFR known to minimize the influence of obesity).

No significant effect of PP on renal function estimated by creatinine clearance, the MDRD, or the Cockcroft-Gault formula was detected.

Although plasma renin activity progressively decreased with increasing age, despite no difference in natriuresis, no between-tertile difference in mean values of plasma renin activity were found within each age group.

**Albuminuria and PP**

As shown in Table 2, urinary albumin excretion was not significantly influenced by PP in the 40 to 49 and 50 to 59 age groups. In patients older than 60, there was a trend for an increase in albuminuria with increasing PP; however, albuminuria expressed as albumin-to-creatinine ratio was higher in the highest tertile of PP compared with the lowest tertile (2.1 versus 0.8 mg/mmol). Univariate analyses of the determinants of log-transformed UAE showed positive correlations with SBP and PP; no relationship was observed with MAP, DBP, or renal function parameters. In a multivariate model, UAE remained positively correlated only with PP and SBP. Nevertheless, this correlation disappeared after introduction of cardiovascular risk factors.

**Discussion**

In the present study conducted in 212 patients with never-treated isolated systolic hypertension, it was observed that only in the group of subjects aged 60 or older was PP inversely related to GFR, independently of age, MAP, and known cardiovascular risk factors. The influence of PP was still present after additional adjustment for natriuresis and urinary urea excretion (ie, taken as indicators of dietary sodium and protein intake), 2 important factors known to influence GFR. Such a finding was not obtained in subjects aged 40 to 49 and 50 to 59 years. These results suggest that PP, an accepted marker of arterial stiffening in elderly patients, may have a detrimental effect on renal hemodynamics and function. Of crucial importance, PP was presently measured using a widely accepted tracer and timed urine collections.

The fact that in the oldest age category the negative influence of PP on GFR was confirmed after adjustment for age suggests that an increasing PP may accelerate the aging process of GFR and renal plasma flow. Although it was demonstrated that a high level of blood pressure accelerates the age-associated decline in GFR measured as creatinine clearance or the Tc-DTPA technique, the present observation persisted after adjustment for MAP.

In 1290 untreated subjects with normal or high blood pressure, it was reported that only in the lowest tertile of calculated renal function calculated by the Cockcroft-Gault formula was there a negative association between pulse wave velocity (a parameter highly correlated with PP) and renal function independently of age, gender, MAP, and classical risk factors. Nevertheless, the relationship between pulse wave velocity and renal function was stronger in subjects younger than 55 years of age than in older people. In the Gubbio population of non-diabetic subjects aged 45 to 64 years, PP was not associated with GFR as measured by creatinine clearance. In 4736 subjects with ISH and older than 65 years of age included in the Systolic Hypertension in the Elderly Program (SHEP), it was observed that SBP, and to a lower extent, PP, and MAP were significant predictors of a decline in kidney function corresponding to an increase in serum creatinine of ≥0.4 mg/dL within 5 years of follow-up. Although the present results were obtained in a cross-sectional study and using a precise measurement of GFR, they are in agreement with the SHEP longitudinal study.

In patients older than 60 years of age, the lower GFR found in the highest tertile of PP was associated with a proportionally lower ERPF; as a consequence, no modification in filtration fraction was found. These results are suggestive of a renal blood flow-dependent influence of PP on GFR, probably resulting from an increase in preglomerular resistance. The primary cause in favor of such a proposition could be the existence of structural changes (hypertrophy or remodeling) within intrarenal vessels in elderly subjects. However, the possibility of functional vascular changes in addition to stiffening of intrarenal vessels remains. When perfusion pressure increases, autoregulation of renal blood flow is mediated by an increase in afferent arteriolar tone to maintain a constant glomerular hydrostatic pressure and subsequently a constant GFR. In fact, myogenic tone of the afferent arteriole, which modulates most of the autoregulatory process, is affected by pressure pulsatility. Consequently, when PP increases out of proportion to MAP, as seen in isolated systolic hypertension, renal blood flow would decrease and result in a decline in GFR. In experimental studies conducted

**TABLE 2. Continued**

<table>
<thead>
<tr>
<th></th>
<th>I (n=147)</th>
<th>II (n=147)</th>
<th>III (n=148)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>62 (55–66)</td>
<td>72 (66–77)</td>
<td>86 (77–101)</td>
</tr>
<tr>
<td>19.0</td>
<td>28.6</td>
<td>28.6</td>
<td>28.4</td>
</tr>
<tr>
<td>63.9±3.7</td>
<td>70.2±10.2‡</td>
<td>67.2±6.0</td>
<td>69.3±6.0</td>
</tr>
<tr>
<td>25.5±4.2</td>
<td>26.3±3.9</td>
<td>27.7±5.2</td>
<td>29.1±5.2</td>
</tr>
<tr>
<td>104±4</td>
<td>105±7</td>
<td>112±5§</td>
<td>114±5§</td>
</tr>
<tr>
<td>95.1±18.2</td>
<td>79.9±18.3‡</td>
<td>76.9±12.4‡</td>
<td>78.6±12.4‡</td>
</tr>
<tr>
<td>413±64</td>
<td>354±82‡</td>
<td>342±77‡</td>
<td>349±77‡</td>
</tr>
<tr>
<td>23.0±2.8</td>
<td>22.7±3.3</td>
<td>23.0±3.3</td>
<td>23.2±3.3</td>
</tr>
<tr>
<td>0.38 (0.12–0.52)</td>
<td>0.30 (0.13–0.54)</td>
<td>0.32 (0.16–0.91)</td>
<td>0.33 (0.18–0.91)</td>
</tr>
<tr>
<td>128±52</td>
<td>142±62</td>
<td>132±76</td>
<td>132±76</td>
</tr>
<tr>
<td>345±117</td>
<td>367±127</td>
<td>299±173</td>
<td>299±173</td>
</tr>
<tr>
<td>5.1 (3.2–8.0)</td>
<td>8.3 (4.3–13.7)</td>
<td>9.5 (4.6–19.7)</td>
<td>10.2 (5.5–20.0)</td>
</tr>
</tbody>
</table>
in the remnant kidney model, in the presence of reduced afferent arteriolar resistance, the increase in PP rather than MAP is more selectively transmitted to the glomerulus and thus favors glomerulosclerosic changes.27

It is of interest that in the present study, the decrease in GFR and ERPF associated with increasing PP was present only in subjects older than 60 years. Among suggested mechanisms operative in elderly patients are the presence of an impairment in the production of endogenous substances with vasodilator capacity such as nitric oxide through accelerated degradation by anion superoxides28 or the presence of an increased concentration of an endogenous inhibitor of nitric oxide such as asymmetrical dimethylarginine.29 Circulating concentration of asymmetrical dimethylarginine was shown to be higher in elderly subjects, to correlate with a decreased ERPF, and finally to act as a potent vasoconstrictor when infused in healthy subjects.30 In addition, it has been shown that nitric oxide-mediated dilatation declines with aging, becoming particularly apparent during the sixth decade, at the time when PP tends to increase markedly.31 In experimental studies using isolated microperfused rabbit renal vessels, it was demonstrated that nitric oxide exerts its vasodilator effect preferentially on the afferent arteriole.32

Adjusted values of GFR (A), ERPF (B), and filtration fraction (C) according to tertiles of pulse pressure in each age category. *P\textless 0.05.

It was recently reported that low (but within the normal range) GFR, as determined by the MDRD formula, was associated with reduced vasodilator response to acetylcholine in the forearm circulation in patients with uncomplicated never-treated essential hypertension.33 Nevertheless, there is no unequivocal evidence that endothelial dysfunction of the forearm circulation is paralleled by a similar alteration of the renal circulation. Of interest, a blunted response of renal blood flow to L-arginine (the substrate for nitric oxide generation) infusion was observed in essential hypertension.34,35

In the present study, albuminuria was elevated in the highest tertile of PP only in patient older than 60 years of age; in contrast, no modification of albuminuria with increasing PP was observed in younger patients. Although the observed increase in albuminuria may result from the increase in systolic pressure (the main mechanism of albuminuria) in normotensive and hypertensive subjects,18 the hypothesis that increased albuminuria may be a marker of intrarenal lesions and subsequent accelerated decline in GFR deserves further longitudinal studies.

The present observation that the higher the PP, the lower the GFR only in patients with ISH and older than 60 years of age is of interest. As recently mentioned by Mitchell,36 evaluation of the relationship between aortic stiffness and GFR requires direct assessment of GFR rather than estimates of renal function by serum creatinine-based formulas. Along this line, no relationship between PP and GFR was observed when estimates of renal function by creatinine clearance or MDRD or Cockcroft-Gault formula were used.

Perspectives

PP is a predictor of cardiovascular morbidity and mortality. In aging subjects, PP increases, partly because of stiffening of the arterial vessel wall. In the present cross-sectional study conducted in 212 patients with isolated systolic hypertension, increasing PP was related to lower GFR only in subjects 60 years of age or older when compared with younger groups of patients. This suggests that the age-related decline in GFR may be accelerated in the presence of elevated PP. Whether the lower GFR value with respect to age may predict further accelerated renal function decline remains to be documented. Study of the effect of long-term control of PP would be of great interest.

References


Adjusted values of GFR (A), ERPF (B), and filtration fraction (C) according to tertiles of pulse pressure in each age category. *P\textless 0.05.
Elevated Pulse Pressure Is Associated With Low Renal Function in Elderly Patients With Isolated Systolic Hypertension

Jacobienc C. Verhave, Pierre Fesler, Guilhem du Cailar, Jean Ribstein, Michel E. Safar and Albert Mimran

Hypertension. 2005;45:586-591; originally published online February 28, 2005;
doi: 10.1161/01.HYP.0000158843.60830.cf
Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2005 American Heart Association, Inc. All rights reserved.
Print ISSN: 0194-911X. Online ISSN: 1524-4563

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://hyper.ahajournals.org/content/45/4/586

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Hypertension can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Hypertension is online at:
http://hyper.ahajournals.org//subscriptions/