C-Reactive Protein Elevation Predicts Pulse Pressure Reduction in Hypertensive Subjects

Jacques Amar, Jean-Bernard Ruidavets, Jean-Claude Peyrieux, Jean-Michel Mallion, Jean Ferrières, Michel E. Safar, Bernard Chamontin

Abstract—Cross-sectional studies have shown a positive association between increased pulse pressure (PP) and an increased likelihood of a C-reactive protein (CRP) level >3 mg/L. In a retrospective subgroup analysis of the hypertensive subjects of the multicenter double-blind study, REASON (PREterax in Regression of Arterial Stiffness in a ContrOlled Double-BliNd), in which fixed first-line antihypertensive combination therapy with an angiotensin converting enzyme (ACE) inhibitor, perindopril (2 mg), and a diuretic, indapamide (0.625 mg), proved significantly more effective than atenolol in normalizing PP, we sought to determine whether perindopril plus indapamide was also more effective than atenolol in lowering CRP levels and, if so, whether this effect correlated with a preferential reduction in PP. At the final visit (12 months) in the 269 patients studied, the decrease in PP was greater, and the proportion of patients with CRP >3 mg/L lower (17.9% versus 28.9%, P = 0.03; adjusted odds ratio, 1.02 to 4.08, P = 0.01), in the perindopril plus indapamide group than in the atenolol group. After adjustment for confounders, patients with a baseline CRP >3 mg/L displaying the greatest decrease in PP were more likely (P = 0.04) to have a CRP ≤3 mg/L at 12 months. No such relationship was found with systolic or diastolic blood pressure. Perindopril–indapamide combination therapy is more effective than β-blockade in lowering elevated CRP in hypertensive subjects. This effect is significantly associated with a more effective PP reduction in patients with baseline CRP >3 mg/L. (Hypertension. 2005; 46:151-155.)

Key Words: clinical science ■ antihypertensive drugs ■ clinical trials

Pulse pressure (PP) and C-reactive protein (CRP) levels are each independently associated with cardiovascular risk.1-5 and are also, according to studies in large population-based samples and hypertensive subjects in Europe and the United States, positively associated with each other.6,7-8 Because these studies were mostly cross-sectional, the mechanisms underlying the association remain largely unknown. However, we recently reported that the association remains significant after adjusting for age, mean blood pressure (BP), presence of atherosclerotic plaques, and pulse wave velocity, ie, it is not fully explained by any of these major determinants of PP, not even by aortic stiffness.8 It was, therefore, tempting to hypothesize that in hypertensive subjects, inflammation mediates parallel long-term changes in PP and CRP. Furthermore, because, in vitro, there is a threshold relationship between the concentration of CRP and inflammatory response9-11 and because the association between CRP and PP (like that between CRP and cardiac, vascular, or noncardiovascular disease)12 is clearly nonlinear, the statistically significant association between the changes in the 2 parameters in humans was more likely to be observed at high CRP levels, namely >3 mg/L.13,15

From a pathophysiological viewpoint, the BP curve in subjects with hypertension is attributable to the summation between a forward wave coming from the heart and propagating along the arterial tree and a backward wave returning toward the heart after reflections, which occur mainly at the origin of arterioles and within the microvascular network.16 In hypertension, the structural changes of arterioles and microcirculation may modify PP through changes in wave reflection coefficients.17,18 Drug treatment of hypertension may reduce structural vascular change19 and improve reflection coefficient17-19 through various mechanisms already described in the literature20 and including, particularly, the role of inflammatory factors. In hypertensive subjects, the drugs most effective at blocking or reducing inflammatory pathways may be those that block the renin-angiotensin system. Indeed, angiotensin II mediates a wide variety of inflammatory processes21 by stimulating the production of vascular cell adhesion molecule-1,22 chemokine monocyte chemotactic protein (MCP)-1,23 the cytokine interleukin 6 (IL-6),24,25 which, in turn, may be involved in the development of vascular hypertrophy. On the other hand, it has been shown...
that PP interacts, via endothelial function, with the expression of various molecules such as reactive oxygen species or cytokines, which, in turn, may generate an inflammatory process causing an increase in CRP.26–29

In a recent large 12-month study, Preterax in Regression of Arterial Stiffness the Controlled Double-Blind Study (REASON),30 we compared the antihypertensive effect of low-dose combination of an angiotensin converting enzyme (ACE) inhibitor, perindopril (Per), and a diuretic, indapamide (Ind), with the \( \beta \)-blocker, atenolol. At doses achieving the same reduction in mean arterial pressure and diastolic BP (DBP), Per/Ind induced significantly greater reductions in systolic BP (SBP) and PP than atenolol. This reduction was more pronounced in central (carotid) than in peripheral (brachial) arteries as a consequence of attenuation of wave reflection and, additionally, reduction of arterial stiffness.30,31

With respect to the possible direct antiinflammatory effect of ACE inhibitors and to the greater decrease in PP observed under Per/Ind, the aim of the present analysis was, therefore, to determine whether Per/Ind is more effective than atenolol in lowering CRP levels in hypertensive subjects and whether in patients with a high baseline CRP this effect is associated with a reduction in PP.

### Materials and Methods

#### Study Design

The REASON project30 was a multicenter, controlled, randomized, double-blind, parallel-group study in 13 countries comparing Per (2 mg) + Ind (0.625 mg) (Per/Ind) with atenolol (50 mg) in essential mild-to-moderate and uncomplicated hypertension. The inclusion criteria was an essential hypertension defined as a supine SBP \( >160 \text{ mm Hg} \) and/or diastolic, and/or PP \( >90 \text{ mm Hg} \) in all cases, hypertension was uncomplicated.30 After a 4-week washout on placebo, 469 hypertensive patients 18 to 84 years of age were randomized to Per/Ind (1 tablet) or atenolol (50 mg; 1 tablet) as a single oral morning dose over 12 months. The dose was then adjusted to the BP response, being doubled after 3 months if SBP was \( >160 \text{ mm Hg} \) and/or DBP was \( >90 \text{ mm Hg} \). No other antihypertensive drugs were allowed, although investigators remained free to prescribe lipid-lowering medication: 34 patients received lipid-lowering therapy at baseline and 37 throughout the study. Adverse events and concomitant treatments were recorded.30 The study was performed in accordance with the Declaration of Helsinki, the protocol was approved by local institutional review boards according to national regulations, and all patients provided written informed consent.

#### Blood Samples and Pulse Wave Analysis

MDS Pharma Services centralized the laboratory investigations for all countries. CRP levels at baseline (M0) and end of follow-up (M12) were measured in sera stored at \(-20^\circ\text{C}\). The sensitivity of the immunonephelometry assay (Dade Behring Marburg GmbH, Marburg, Germany) was 0.2 mg/L. Of the 469 participants in the REASON study, only 325 from 9 of the 13 countries (Austria, Belgium, France, Germany, Ireland, Italy, Netherlands, Spain, and Switzerland) had blood samples for both M0 and M12. Of these 325, only 269 were included in the present analysis for one or more of the following reasons: frozen samples were unavailable (n = 23), serum volume was insufficient (n = 16), the CRP level exceeded 50 mg/L, an infectious or inflammatory adverse event was present, or treatment with nonsteroidal antiinflammatory drugs, steroids, or antibiotics was ongoing at sampling or had been given within the preceding 2 weeks (n = 17). Of the remaining 269 subjects included in the retrospective statistical analysis, 134 belonged to the Per/Ind group and 135 to the atenolol group.

#### Data Analysis

The distribution of CRP values was highly skewed, with most values \(<1 \text{ mg/L}\). Following the practice reported in previous population-based CRP studies6–8 in coronary disease,5 stroke,12 and noncardiovascular disease,13 we decided that it was inappropriate to analyze CRP as a continuous outcome. Instead we analyzed CRP as a dichotomous outcome (CRP \( \geq 3 \text{ mg/L} \) or CRP > 3 mg/L) in logistic regression models. This threshold was determined by the pattern of the relationship between PP and CRP previously found in population-based samples8 and by its clinical relevance.14,15

We first compared the effects of Per/Ind and atenolol on BP and CRP levels using ANOVA and the \( \chi^2 \) test. We then analyzed the relationships between PP and CRP at baseline. Lastly, having observed (in agreement with previous reports5,6) a nonlinear relationship at baseline between the increase in PP and the proportion of patients with a high CRP (the proportion with CRP \( \geq 3 \text{ mg/L} \) remained stable to PP 65 mm Hg, then increased sharply; Figure), we tested the hypothesis that of the patients with baseline CRP > 3 mg/L and independently of assigned treatment (Per/Ind or Atenolol) those displaying the greatest decrease in PP were more likely to exhibit a fall in CRP below the 3 mg/L threshold. We, therefore, analyzed the relationship between the changes in PP and CRP in patients with baseline CRP > 3 mg/L. For this purpose, we defined 2 groups of change in PP with respect to the median decrease in PP (\( \geq \text{median} \) and \( < \text{median} \)) and 2 groups of change in CRP with respect to the 3 mg/L threshold (\( \geq 3 \text{ mg/L} \), \( < 3 \text{ mg/L} \)). For this analysis, the likelihood-ratio statistic test was used to build models through backward stepwise elimination. The variables entered into the
The baseline data showed a positive association (P = 0.03; Table 1). After adjustment for baseline characteristics (age, sex, overweight status [body mass index ≥ 25 kg/m²], use of lipid-lowering drugs throughout the study, and use of randomly assigned antihypertensive treatment. The variable of interest, BP, was entered into the model when the P value of the test reached 0.05. The analysis was performed using SAS statistical software (SAS Institute, Cary, NC).

### Results

#### Treatment Effect: Overall Substudy Population

Two hundred and sixty-nine patients were analyzed. At baseline, demographic, clinical, hemodynamic characteristics, and CRP levels were well balanced between the 2 groups, except PP, which tended to be higher in Per/Ind group (P = 0.05). At M12, the absolute decreases in SBP and PP were significantly greater with Per/Ind than with atenolol (P = 0.008 and P < 0.001; Table 1). DBP did not differ between the groups nor did mean CRP values. However, significantly fewer patients at M12 had CRP levels that were > 3 mg/L in the Per/Ind group than in the atenolol group (18% versus 29%, P = 0.03; Table 1). After adjustment for baseline characteristics (age, sex, overweight status [body mass index ≥ 25 kg/m²], baseline CRP [≥ 3 mg/L versus ≤ 3 mg/L], current smoking) and, because statins are known to improve CRP levels, after adjustment for lipid-lowering therapy, Per/Ind patients were twice as likely as their atenolol counterparts to have CRP levels ≤ 3 mg/L at M12. The odds ratio was 2.04 (95% CI: 1.02 to 4.08; P = 0.04).

The baseline data showed a positive association (P = 0.03; Figure) between a CRP value > 3 mg/L and a high PP (third tertile: ≥ 65 mm Hg) versus a low PP (first tertile: < 55 mm Hg). No comparable finding was observed for SBP or DBP. The relationship remained significant (P = 0.01) in multivariate logistic regression analysis after adjusting for confounders.

#### Relationship Between Changes in PP and CRP in Patients With High Baseline

Seventy-seven patients (36 in the Per/Ind group and 41 in the atenolol group) had baseline CRP > 3 mg/L. Among these 77 subjects, those displaying the greatest decrease in PP (> median decrease) were more likely to show a fall in CRP to ≤ 3 mg/L than those with the lowest decrease in PP (≤ median decrease, P = 0.007; Table 2): n = 22 of 39 (56.2%) versus n = 10 of 38 (26.3%), respectively. This difference remained significant in multivariate analysis (P = 0.02; Table 3) after adjustment for baseline CRP and overweight and independently of antihypertensive treatment (Table 3). The adjusted odds ratio was 2.97; 95% CI, 1.07 to 8.28. No significant association was observed with SBP or DBP.

#### Discussion

This REASON substudy confirms the results in the overall intention-to-treat population, namely that Per/Ind induces greater decreases in SBP and PP than atenolol given the same decrease in DBP. The novel findings in the substudy are 2-fold: (1) Per/Ind patients were twice as likely as their atenolol counterparts to have a CRP ≤ 3 mg/L at M12 (adjusted odds ratio, 2.04; 95% CI, 1.02 to 4.08); and (2) of the patients with a high baseline CRP, those displaying the greatest decrease in PP were more likely to show a fall in CRP to < 3 mg/L (adjusted odds ratio, 2.04; 95% CI, 1.02 to 4.08).

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**Table 1: Baseline and End-of-Study BP and CRP**

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Per/Ind (n = 134)</th>
<th>Atenolol (n = 135)</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>52.4 ± 11.1</td>
<td>50.5 ± 10.7</td>
<td>0.16</td>
</tr>
<tr>
<td>Sex, male (%)</td>
<td>85 (63.43)</td>
<td>91 (67.41)</td>
<td>0.49</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>26.6 ± 2.8</td>
<td>26.8 ± 2.6</td>
<td>0.74</td>
</tr>
<tr>
<td>Overweight, %</td>
<td>72.4</td>
<td>74.0</td>
<td>0.75</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>M0</td>
<td>162.0 ± 11.6</td>
<td>159.6 ± 13.4</td>
<td>0.11</td>
</tr>
<tr>
<td>Final visit</td>
<td>139.3 ± 14.1</td>
<td>142.8 ± 19.1</td>
<td>0.08</td>
</tr>
<tr>
<td>Change</td>
<td>−22.7 ± 14.7</td>
<td>−16.8 ± 17.1</td>
<td>0.008</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>M0</td>
<td>99.6 ± 5.8</td>
<td>100.2 ± 5.2</td>
<td>0.35</td>
</tr>
<tr>
<td>Final visit</td>
<td>85.7 ± 9.3</td>
<td>86.2 ± 10.9</td>
<td>0.74</td>
</tr>
<tr>
<td>Change</td>
<td>−13.9 ± 9.7</td>
<td>−14.0 ± 10.3</td>
<td>0.86</td>
</tr>
<tr>
<td>Pulse pressure, mm Hg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>M0</td>
<td>62.4 ± 12.6</td>
<td>59.4 ± 13.1</td>
<td>0.05</td>
</tr>
<tr>
<td>Final visit</td>
<td>53.6 ± 10.7</td>
<td>56.6 ± 14.1</td>
<td>0.04</td>
</tr>
<tr>
<td>Change</td>
<td>−8.8 ± 11.5</td>
<td>−2.8 ± 13.3</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>C-reactive protein, mg/L</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>M0</td>
<td>2.66 ± 3.52</td>
<td>2.87 ± 3.11</td>
<td>0.60</td>
</tr>
<tr>
<td>Final visit</td>
<td>2.08 ± 2.54</td>
<td>2.76 ± 3.58</td>
<td>0.07</td>
</tr>
<tr>
<td>Change</td>
<td>−0.58 ± 2.73</td>
<td>−0.11 ± 3.50</td>
<td>0.21</td>
</tr>
<tr>
<td>Patients with CRP &gt; 3 mg/L, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>M0</td>
<td>36 (26.9)</td>
<td>41 (30.4)</td>
<td>0.52</td>
</tr>
<tr>
<td>Final visit</td>
<td>24 (17.9)</td>
<td>39 (28.9)</td>
<td>0.03</td>
</tr>
</tbody>
</table>

*Between-group comparison. All values except percentages are mean (SD)
versus a fixed low-dose combination of an ACE inhibitor and a diuretic over 1 year the antiinflammatory effect of a combination of a
addition, this study was, to our knowledge, the first to compare
power was offset by the fact of double-blind data evaluation. In
50% of the REASON patients. However, this loss of statistical
ie, at M0 and M12. These conditions were met by a little over
measuring each parameter before and after long-term treatment,
the decrease in PP paralleled that in CRP, a well-known marker
other hand, in randomized trials conducted over a short period of
association exerted a significant influence on CRP levels. In patients
in cytokines and endothelial dysfunction. PP is positively asso-
pulsatile stress per se may help to lower CRP, following changes
A second hypothesis is that put forward by Abramson et al: pulsatile stress per se may help to lower CRP, following changes in cytokines and endothelial dysfunction. PP is positively associated with increased production of the reactive oxygen species hydrogen peroxide, which, in turn, can stimulate inflammatory signaling pathways. It has also been shown that oscillatory shear with flow reversals increases adhesion molecule expression. In line with this hypothesis, our study found that, among patients with baseline CRP >3 mg/L, those displaying the greatest decrease in PP were more likely to have a decrease in CRP to <3 mg/L. Also we showed that this relationship was independent of antihypertensive treatment. These results suggest that change in PP per se plays a key role in change in CRP levels among hypertensive patients with microinflammation.
Hypertension is a risk factor for the development of atherosclerosis. Although the mechanisms of this interaction have yet to be fully elucidated, they probably involve vessel wall inflammation, as found in atherosclerosis. In this respect, it is worth noting that an observational study has identified PP as a predictor of coronary heart disease mortality but not (or at least to a lesser extent) of cerebrovascular mortality. In line with this observation, therapeutic trials show a greater reduction in coronary events in patients with isolated systolic hypertension (ie, high PP) than in those with systolic-diastolic hypertension. In these trials, antihypertensive therapy prevented 40% of strokes and did so equally in patients with isolated systolic hypertension and those with systolic-diastolic hypertension. Because CRP is a potent predictor of coronary heart disease, our results may help to identify some of the links between elevated PP and atherosclerotic coronary disease.

**Perspectives**

This study has shown that Per/Ind is more effective than atenolol in decreasing elevated CRP levels in hypertensive subjects. With respect to the links between PP and inflammatory pathways, these data not only begin to account for some important relationships among PP, ACE inhibition, and the beneficial influence of ACE inhibitor on CRP level. These results suggest that change in PP per se plays a key role in change in CRP levels among hypertensive patients with microinflammation.

### TABLE 2. Decrease in CRP and Decrease in BP in Patients With Baseline CRP >3 mg/L (n=77)

<table>
<thead>
<tr>
<th>Decrease in PP</th>
<th>Decrease in SBP</th>
<th>Decrease in DBP</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;Median Decrease</td>
<td>&gt;Median Decrease</td>
<td>&gt;Median Decrease</td>
</tr>
<tr>
<td>(n=39)</td>
<td>(n=38)</td>
<td>(n=38)</td>
</tr>
<tr>
<td>≤Median Decrease</td>
<td>≤Median Decrease</td>
<td>≤Median Decrease</td>
</tr>
<tr>
<td>(n=38)</td>
<td>(n=39)</td>
<td>(n=39)</td>
</tr>
</tbody>
</table>

- **Decrease in CRP to <3 mg/L, n (%):**
  - 22 (56.4%)
  - 10 (26.3%)*
  - 19 (50.0%)
  - 13 (33.3%)
  - 18 (47.4%)
  - 14 (35.9%)

Median decreases: PP, 7.7 mm Hg; SBP, 22.7 mm Hg; DBP, 13.4 mm Hg; *P=0.007

### TABLE 3. Likelihood of CRP Decreasing From >3 mg/L to ≤3 mg/L With Respect to Decrease in BP

<table>
<thead>
<tr>
<th>Decrease</th>
<th>Odds Ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulse pressure</td>
<td>2.97</td>
<td>1.11–12.03†</td>
</tr>
<tr>
<td>Systolic blood pressure</td>
<td>1.92</td>
<td>0.71–5.52</td>
</tr>
<tr>
<td>Diastolic blood pressure</td>
<td>1.57</td>
<td>0.57–4.27</td>
</tr>
</tbody>
</table>

Multivariate logistic regression adjusted for baseline CRP and overweight (body mass index<25 kg/m²).

- >Median vs ≤median decrease (PP, 7.7 mm Hg; SBP, 22.7 mm Hg; DBP, 13.4 mm Hg); †P=0.04.

**ratio, 2.97; 95% CI, 1.07 to 8.28.** These findings were specific to PP and not observed for either SBP or DBP.

The REASON project was a randomized controlled trial comparing the antihypertensive regimens Per/Ind and atenolol over 1 year. The present retrospective substudy confirms, in a smaller population, the BP changes observed in the overall intention-to-treat population. The substudy hypothesis was that the decrease in PP paralleled that in CRP, a well-known marker of cardiovascular inflammation. It could be tested only by measuring each parameter before and after long-term treatment, ie, at M0 and M12. These conditions were met by a little over 50% of the REASON patients. However, this loss of statistical power was offset by the fact of double-blind data evaluation. In addition, this study was, to our knowledge, the first to compare over 1 year the antiinflammatory effect of a combination of a fixed low-dose combination of an ACE inhibitor and a diuretic versus a β-blocker: atenolol. Unlike atenolol, the fixed combination exerted a significant influence on CRP levels. In patients with angiographic coronary artery disease or stroke, cohort studies have found that drug treatment by ACE inhibitor is associated with reduced plasma concentration of CRP. On the other hand, in randomized trials conducted over a short period of time (from 4 to 24 weeks) in subjects with uncomplicated essential hypertension, ACE inhibitor failed to show any significant influence on CRP, although a positive effect on intercellular adhesion molecule 1 has been reported. In light of these data, the current results suggest that in primary prevention of hypertension the antiinflammatory effect of ACE inhibitor may be enhanced by the presence of a diuretic compound like indapamide and/or that a long time period is required to observe the beneficial influence of ACE inhibitor on CRP level. The study design offers no elucidation of the possible causal relationship between changes in CRP and those in PP. However, several hypotheses may be advanced to explain the parallelism on ACE inhibitor plus indapamide therapy. First, the antiinflammatory effect of Per/Ind currently observed may help to reduce the structural microvasculature changes commonly observed in hypertensive subjects; indeed, Per/Ind are already well-recognized as reducing these changes, unlike atenolol. This, in turn, may modify the reflection sites, resulting in a selective decrease in SBP and PP. In line with this hypothesis, an earlier REASON study showed that the selective reduction of SBP and PP in response to Per/Ind was attributable not to decreased pulse wave velocity but rather to attenuation of wave reflection. Thus, reduction of inflammation may reduce PP through regression of structural changes of the microvasculature and resulting changes in wave reflections.

A second hypothesis is that put forward by Abramson et al: pulsatile stress per se may help to lower CRP, following changes in cytokines and endothelial dysfunction. PP is positively associated with increased production of the reactive oxygen species hydrogen peroxide, which, in turn, can stimulate inflammatory signaling pathways. It has also been shown that oscillatory shear with flow reversals increases adhesion molecule expression. In line with this hypothesis, our study found that, among patients with baseline CRP >3 mg/L, those displaying the greatest decrease in PP were more likely to have a decrease in CRP to <3 mg/L. Also we showed that this relationship was independent of antihypertensive treatment. These results suggest that change in PP per se plays a key role in change in CRP levels among hypertensive patients with microinflammation.
CRP levels but also make the case for further elucidation in a prospective controlled trial.

Acknowledgments

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References


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