OBJECTIVES  This study sought to identify determinants of the exercise rise in plasma levels of cardiac natriuretic peptides (NPs) in patients with coronary artery disease (CAD).

BACKGROUND  During stress, there is a variable rise in the plasma level of NPs, but this rise frequently reaches levels that are known to lower the cardiac load and that thus might be beneficial to CAD patients.

METHODS  Plasma venous concentrations of atrial natriuretic peptide (ANP) and brain natriuretic peptide (BNP) were determined at rest and peak exercise in 104 patients with chronic CAD who were referred to exercise thallium-201 (201Tl) single-photon emission computed tomography (SPECT) and radionuclide angiography.

RESULTS  The extent of scarred myocardium by 201Tl-SPECT and patient age were the best independent predictors of NP concentrations at rest, but also of increases in NP concentration during exercise (all \( p < 0.001 \)). Moreover, beta-blocking treatment was an additional and strong independent predictor of the increase in NP concentrations at exercise (\( p < 0.001 \) for ANP; \( p = 0.001 \) for BNP). On average, exercise increases in NP concentrations were more than twice as high in patients with (\( n = 55 \)) than in those without (\( n = 49 \)) beta-blocker treatment (ANP: \( +49 \pm 63 \) vs. \( +22 \pm 25 \) ng/l, \( p = 0.01 \); BNP: \( +24 \pm 5 \) vs. \( +11 \pm 15 \) ng/l, \( p = 0.04 \)), whereas NP concentrations at rest were equivalent in the two groups (ANP: \( 34 \pm 34 \) vs. \( 30 \pm 33 \) ng/l, \( p = \text{NS} \); BNP: \( 85 \pm 152 \) vs. \( 57 \pm 101 \) ng/l, \( p = \text{NS} \)).

CONCLUSIONS  Patients with chronic CAD exhibit much higher exercise releases of ANP and BNP when they are treated with beta-blockers. This enhanced secretion of potent vasodilating and natriuretic agents constitutes an original therapeutic mechanism for further protecting diseased hearts against stress. (J Am Coll Cardiol 2004;43:353–9) © 2004 by the American College of Cardiology Foundation

Resting plasma concentrations of atrial and brain natriuretic peptide (ANP and BNP, respectively) are enhanced at long-term in a number of cardiac diseases in which these two peptides exert beneficial effects through promotion of vasodilation and natriuresis, as well as inhibition of the renin–angiotensin aldosterone and sympathetic nervous systems (1,2). In addition, during stress, a prompt release from cardiac stores leads to an abrupt rise in plasma levels of BNP and especially of ANP (1,2). However, this rise is highly variable (3–6), although it is generally high for both peptides in patients with heart failure and much more limited in normal subjects (5), in whom a clearly significant rise was documented at exercise for the plasma level of ANP but not BNP (3). Nevertheless, when high levels of cardiac natriuretic peptides (NPs) are released at exercise, their prompt vasodilator and diuretic effects may be expected to lower cardiac load (7–9) and thus beneficial to patients with coronary artery disease (CAD). Up to now, however, the magnitude of this exercise release of NPs has only been poorly analyzed in CAD patients. Therefore, this study was aimed at identifying the main determinants of the exercise rise in plasma concentrations of NPs in patients with chronic CAD.

METHODS  

Study population. We prospectively and consecutively included all patients: 1) who had a proven history of CAD; 2) who had been referred to our department for the performance of both exercise thallium-201 (201Tl) single-photon emission computed tomography (SPECT) and rest equilibrium radionuclide angiography (RNA); and 3) who gave informed consent to participate. Diagnosis of CAD was based on the presence of one or more significant (>50%) coronary narrowings on a previous angiogram.

The exclusion criteria were congenital or valvular heart disease, hypertrophic or idiopathic dilated cardiomyopathy, atrial fibrillation, and noncardiac diseases known to enhance...
the natriuretic peptide system (renal insufficiency and uncontrolled systemic hypertension).

**Radionuclide investigations.** The way to perform and analyze exercise 201Tl-SPECT images has already been described in detail elsewhere (10,11). Briefly, an exercise test was performed in the upright position on a bicycle ergometer; the protocol was started at 20 W and increased by 20 W every 2 min. Exercise end points were physical exhaustion, angina pectoris, >2-mm ST-segment depression, sustained ventricular tachyarrhythmia, ≥10 mm Hg fall in systolic pressure, or achievement of the maximal predicted heart rate (HR) (220 − age). At peak exercise, 37 MBq 201Tl per 25 kg body weight was injected intravenously, and 201Tl activity, corresponding to one-third of that given at exercise, was injected 10 min before rest imaging. Reconstructed slices were scored visually by a blinded observer using both a 20-segment division of the left ventricle (LV) and a 4-point grading system.

The extent of predominantly scarred myocardium (nonviable myocardium) was determined as the percentage of LV segments showing fixed defects with <50% uptake at rest re-injection, and the extent of ischemic and viable myocardium was determined as the percentage of LV segments showing either reversible or fixed defects with >50% uptake at rest re-injection (10,11).

Multigated equilibrium RNA was performed at rest in the supine position, just after the end of 201Tl acquisitions. As previously described (12), 740 to 1,110 MBq technetium-99m (99mTc)-pertechnetate was injected intravenously, and the camera head was set to maximize ventricular separation in the left anterior oblique orientation. Repetitive sampling of cardiac cycle, subdivided into 16 frames, was acquired until a minimum of 300,000 counts/frame was obtained. The LV ejection fraction (LVEF) was calculated using a conventional count-based method; end-systolic, end-diastolic, and background-count regions of interest were drawn manually (12).

**Blood sampling and biochemical measurements.** For each patient, three venous blood samples of 5 ml were drawn in the seated position from a catheter inserted into the antecubital vein: 1) immediately before starting the exercise test, patients having previously observed an at least 20 min rest; 2) at the maximal work load of bicycle exercise; and 3) at the end of the exercise SPECT acquisition, corresponding to a time interval of 20 min from the end of exercise. These samples were collected in polystyrene tubes containing EDTA and aprotinin (500 kallikrein inactivator U/ml); they were placed on ice and then centrifuged at 3,000 g, and plasma was stored at −70°C.

The ANP and BNP concentrations were determined using commercially available kits (Shionoria, Shionogi, Osaka, Japan) (13) using two monoclonal antibodies binding either human ANP or human BNP. Minimal detectable concentrations are 5 pg/ml for ANP and 2 pg/ml for BNP, and the inter- and intra-assay coefficient of variations is <6% for both ANP and BNP.

**Statistical analysis.** Continuous variables are expressed as the mean value ± SD; they were compared using nonparametric tests. The Wilcoxon rank-sum test was used for paired series, and the Mann-Whitney U test was used for two-group unpaired comparisons. Discrete variables are expressed as percentages; they were compared using the chи-square or Fisher exact test when the smallest expected frequency was ≤5. A p value <0.05 was considered to indicate a significant difference. Multivariate analyses were performed stepwise using ascending linear regression analyses (SPSS version 10.0). At each step, the limit for significance to enter a variable was 0.05, and the limit to remove a variable was 0.10.

**RESULTS**

**Characteristics of study patients.** The main characteristics of patients are listed in Table 1. A recent history of chest pain was documented in 48 patients (46%), among whom 34 had typical angina. The remainder had been referred to exercise SPECT for viability assessment (18%) or assessment of the evolution of CAD in the absence of any sign or symptom of ischemia (36%).

Daily-life medical treatment included beta-blockers in 78 patients, among whom 23 had stopped these medications to enhance the sensitivity of exercise SPECT (=2 days before). Clinical data and results of radionuclide investigations were not significantly different between these 23 patients and the others. Therefore, only 55 patients underwent the tests while on their beta-blocking medications: 26 had atenolol, 10 had metoprolol, 3 had celiprolol, 3 had acebutolol, 4 had carvedilol. At exercise, compared with the 49 patients not treated with beta-blockers, the 55 who received beta-blockers had lower values (mean ± SD) of maximal HR (116 ± 19 vs. 141 ± 19 beats/min, p < 0.001), HR increase (difference between maximal and resting values: +46 ± 17 vs. +58 ± 17 beats/min, p = 0.001), maximal systolic pressure (171 ± 30 vs. 186 ± 28 mm Hg, p = 0.003), and systolic pressure increase (difference between maximal and resting values: +49 ± 21 vs. +58 ± 20 mm Hg, p = 0.04).

At 201Tl-SPECT, an ischemic area was documented in 63 patients (61%), and a predominantly scarred area was...
found in 47 (45%). The rest radionuclide LVEF was abnormal (<0.50) in 41 patients (39%).

**Evolution of NP concentrations at exercise.** At rest, the plasma concentration of ANP was lower than that of BNP (32 ± 34 vs. 72 ± 131 ng/l, p < 0.001). However, the increase in plasma concentrations during exercise was higher for ANP than for BNP (difference between peak exercise and rest concentrations: +36 ± 51 vs. +18 ± 32 ng/l, p < 0.001), and the subsequent decrease after exercise was also higher for ANP than for BNP (difference between 20-min recovery and peak exercise concentrations: −19 ± 44 vs. −11 ± 32 ng/l, p = 0.005). The total concentration of peptides, expressing a plasma concentration of both peptides as an overall, exhibited a 74 ± 77% increase during exercise.

**Correlates of resting plasma concentrations of NPs.** Univariate predictors of NP concentrations at rest (extracted from the parameters listed in Table 1) are displayed in Table 2. High NP concentrations at rest were associated with aging and variables reflecting: 1) the presence and severity of necrosis (history of infarction, extent of scarred area on 201Tl-SPECT); 2) the severity of LV dysfunction (LVEF); 3) symptoms and treatments of cardiac insufficiency (New York Heart Association functional class ≥II dyspnea, diuretics, and enzyme-converting inhibitors); and 4) weaker adaptation at exercise (maximal work load, maximal HR, and increase in blood pressure).

In contrast, rest concentrations were not significantly different between patients with and those without beta-blocker treatment for both ANP (34 ± 35 vs. 30 ± 33 ng/l, p = NS) and BNP concentrations (85 ± 152 vs. 57 ± 101 ng/l, p = NS) and for the total concentration of NPs (120 ± 177 vs. 87 ± 130 ng/l, p = NS).

By multivariate analysis, the sole best independent predictors of the total rest concentration of NPs were: 1) the extent of scarred myocardium on 201Tl-SPECT (p < 0.001); and 2) patient age (p < 0.001). As detailed in Table 3, similar results were obtained when rest concentrations of ANP and BNP were considered separately. Figure 1 illustrates the strong correlation between the plasma venous

### Table 1. Main Characteristics of the Study Patients

<table>
<thead>
<tr>
<th>Clinical data</th>
<th>Age (yrs)</th>
<th>Male gender (%)</th>
<th>Diabetes mellitus (%)</th>
<th>Hypertension (%)</th>
<th>Q-wave on ECG (%)</th>
<th>History of infarction (%)</th>
<th>Chest pain (%)</th>
<th>Typical angina (%)</th>
<th>Dyspnea (NYHA class ≥ II) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ANP and BNP</td>
<td>59 ± 11</td>
<td>98 (94%)</td>
<td>15 (14%)</td>
<td>26 (25%)</td>
<td>73 (70%)</td>
<td>83 (80%)</td>
<td>48 (46%)</td>
<td>34 (33%)</td>
<td>22 (21%)</td>
</tr>
</tbody>
</table>

**Main medications**

- Beta-blockers: 55 (53%)
- Calcium antagonists: 15 (14%)
- Nitrates or molsidomin: 29 (28%)
- Enzyme-converting inhibitors: 46 (44%)
- Diuretics: 16 (15%)

**Exercise testing**

- Maximal work load (W): 126 ± 33
- Maximal heart rate (beats/min): 128 ± 22
- Increase in heart rate (beats/min): 51 ± 18
- Maximal systolic pressure (mm Hg): 178 ± 31
- Increase in systolic pressure (mm Hg): 54 ± 25
- Maximal rate–pressure product (×100): 231 ± 68
- Increase in rate–pressure product (×100): 136 ± 56
- ≥1-mm ST-segment depression: 22 (21%)
- Angina or ST-segment depression: 24 (23%)
- Maximal heart rate (beats/min): 128 ± 22
- Maximal systolic pressure (mm Hg): 178 ± 31
- Increase in rate–pressure product (×100): 231 ± 68
- Increase in blood pressure: 54 ± 25
- Increase in heart rate: 136 ± 56
- Increase in rate–pressure product: 231 ± 68
- Increase in blood pressure: 54 ± 25
- Increase in heart rate: 136 ± 56
- Increase in rate–pressure product: 231 ± 68
- Increase in blood pressure: 54 ± 25
- Increase in heart rate: 136 ± 56
- Increase in rate–pressure product: 231 ± 68
- Increase in blood pressure: 54 ± 25
- Increase in heart rate: 136 ± 56
- Increase in rate–pressure product: 231 ± 68
- Increase in blood pressure: 54 ± 25
- Increase in heart rate: 136 ± 56
- Increase in rate–pressure product: 231 ± 68
- Increase in blood pressure: 54 ± 25

**Correlates of resting plasma concentrations of NPs.** Univariate predictors of NP concentrations at rest (extracted from the parameters listed in Table 1) are displayed in Table 2. High NP concentrations at rest were associated with aging and variables reflecting: 1) the presence and severity of necrosis (history of infarction, extent of scarred area on 201Tl-SPECT); 2) the severity of LV dysfunction (LVEF); 3) symptoms and treatments of cardiac insufficiency (New York Heart Association functional class ≥II dyspnea, diuretics, and enzyme-converting inhibitors); and 4) weaker adaptation at exercise (maximal work load, maximal HR, and increase in blood pressure).

By multivariate analysis, the sole best independent predictors of the total rest concentration of NPs were: 1) the extent of scarred myocardium on 201Tl-SPECT (p < 0.001); and 2) patient age (p < 0.001). As detailed in Table 3, similar results were obtained when rest concentrations of ANP and BNP were considered separately. Figure 1 illustrates the strong correlation between the plasma venous

### Table 2. P Values for Univariate Predictors (p < 0.1 on Univariate Analysis) of the Rest and Exercise Plasma Concentrations and of the Increase in Concentrations Between Rest and Exercise for Natriuretic Peptides

<table>
<thead>
<tr>
<th>Variable</th>
<th>ANP + BNP</th>
<th>ANP</th>
<th>BNP</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Rest</td>
<td>Exercise</td>
<td>Increase</td>
</tr>
<tr>
<td>Age</td>
<td>0.001</td>
<td>0.003</td>
<td>0.088</td>
</tr>
<tr>
<td>History of infarction</td>
<td>0.001</td>
<td>0.003</td>
<td>NS</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>0.003</td>
</tr>
<tr>
<td>Beta-blockers</td>
<td>0.011</td>
<td>0.011</td>
<td>NS</td>
</tr>
<tr>
<td>Enzyme-converting inhibitors</td>
<td>0.040</td>
<td>0.013</td>
<td>0.070</td>
</tr>
<tr>
<td>Diuretics</td>
<td>0.006</td>
<td>0.006</td>
<td>0.021</td>
</tr>
<tr>
<td>Exercise 201Tl-SPECT</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maximal work load</td>
<td>&lt;0.001</td>
<td>0.009</td>
<td>NS</td>
</tr>
<tr>
<td>Maximal heart rate</td>
<td>0.022</td>
<td>0.060</td>
<td>NS</td>
</tr>
<tr>
<td>Increase in heart rate</td>
<td>0.058</td>
<td>NS</td>
<td>0.065</td>
</tr>
<tr>
<td>Maximal systolic pressure</td>
<td>0.098</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Increase in systolic pressure</td>
<td>0.003</td>
<td>0.009</td>
<td>NS</td>
</tr>
<tr>
<td>Maximal rate–pressure product</td>
<td>0.037</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Increase in rate–pressure product</td>
<td>0.015</td>
<td>NS</td>
<td>0.092</td>
</tr>
<tr>
<td>SPECT extent of scarred area</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Rest radionuclide LVEF</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>0.002</td>
</tr>
</tbody>
</table>

ANP and BNP = atrial and brain natriuretic peptide, respectively; NS = nonsignificant; other abbreviations as in Table 1.
concentrations of NPs, determined at rest, and the combined information provided by aging and the extent of scarred myocardium.

Correlates of exercise increase in plasma concentrations of NPs. The exercise increase in plasma concentration of NPs, determined by the difference between peak exercise and rest values, was strongly dependent on the rest concentration of NPs (p < 0.001). Other univariate predictors are displayed in Table 2.

A higher exercise increase in NP concentration was significantly related to variables previously identified as predictors of a higher NP concentration at rest: SPECT extent of scarred area, LVEF, dyspnea, and diuretic treatment. In contrast, beta-blocking treatment was a predictor of exercise increase in NP concentration, although it was not a predictor of NP concentration at rest. On average, the exercise increase in peptide concentration was more than twice as high in patients with than in those without beta-blocker treatment for both ANP (+49 ± 60 vs. +22 ± 25 ng/l, p = 0.01) and BNP (+24 ± 40 vs. +11 ± 15 ng/l, p = 0.04).

By multivariate analysis, the best independent predictors of the exercise increase in the total concentration of NPs were: 1) rest concentration of NPs (p < 0.001); 2) exercise increase in HR (p < 0.001); and 3) beta-blocking treatment (p < 0.001). The same parameters were selected when multivariate analysis was applied to predict the plasma level of NPs that was reached at peak exercise. In addition, as detailed in Table 4, similar results were obtained in the multivariate prediction of exercise increase of ANP only. However, predictors of exercise increase in BNP only were slightly different: the rest concentration of BNP was selected in place of total rest concentration of NPs, and exercise increase in rate–pressure product was selected in place of exercise increase in HR; LVEF became an additional predictor.

Moreover, when beta-blocking treatment was initially excluded from the multivariate analyses, it could always be subsequently included within the selected models (p = 0.001 for prediction of exercise increase in NP concentration, p = 0.001 for that of ANP, and p = 0.04 for that of BNP).

Figure 2 illustrates the specific impact of beta-blockers on the exercise increase in NP concentrations. This figure shows the evolutions of NP concentrations at exercise, according to the presence or absence of either beta-blocking treatment or scarred area on SPECT. Although both variables were associated with higher levels of NPs at peak exercise, only the scarred area was additionally associated with higher levels of NPs at rest. Patients treated with beta-blockers had the particularity of exhibiting more abrupt changes: higher exercise increase and higher post-exercise decrease in NP concentrations.

Figure 3 illustrates the additional predictive information provided by exercise increase in HR and beta-blocking treatment. Patients were separated into two groups according to the mean value of increase in HR at exercise (51 beats/min). The exercise increase in NP concentration was consistently higher in patients with than in those without
Natriuretic Peptides

Amounts of ANP than BNP (15,16). This last point explains patients with heart failure (14) although they also develop within ventricular myocytes in is likely to allow a prompt rise in the blood levels of NPs.

Enhanced in patients on beta-blockers.

Shown to induce a prompt rise in the venous concentrations present study conrm previous reports where exercise was

**DISCUSSION**

In a general population of patients with chronic CAD, the present study confirms previous reports where exercise was shown to induce a prompt rise in the venous concentrations of NPs (1–6), but we also found that this rise was markedly enhanced in patients on beta-blockers.

During exercise, a release of NPs from secretory granules is likely to allow a prompt rise in the blood levels of NPs. These granules are mainly located within atrial myocytes, although they also develop within ventricular myocytes in patients with heart failure (14–18), and they contain higher amounts of ANP than BNP (15,16). This last point explains our observation that the exercise rise in the plasma concentration of ANP was twofold higher than that of BNP, on average.

**Influence of resting plasma levels of NPs.** The amount of NPs stored within the secretory granules is known to rise in parallel to the resting blood concentrations of NPs (15–18). That is why the exercise increase in NP concentration was strongly correlated to the rest concentration of NPs. Indeed, peptide storage is most important in patients with the highest blood levels of NPs at rest. Therefore, it is also in these patients that exercise is expected to trigger the highest peptide release from storage granules.

On multivariate analysis, the sole best independent predictors of NP concentrations at rest were aging and the extent of scarred LV area. This age dependence had already been established (19,20), but no previous study has given evidence of the dramatic influence of the extent of scarred myocardium, as determined by myocardial SPECT. The rationale of this observation is that, in patients with chronic CAD: 1) scarred territories are known to secrete high amounts of BNP (21); and 2) the presence of large scarred areas is a main cause of chronic cardiac overload, which is a strong determinant of the increase in the rest concentrations of NPs (1,2,18,22).

**Combined influences of HR and beta-blockers.** The exercise increase in NP concentration was related to the increase in HR at exercise. Previous studies performed during spontaneous tachycardia or ventricular pacing have already provided evidence that a prompt rise in HR was a potent trigger of the acute release of BNP and especially of that of ANP (23,24).

However, the present study shows that this impact of HR is not the same when patients are treated with beta-blockers. As illustrated in Figure 3, for a given range of exercise increase in HR, the patients on beta-blockers had much higher exercise increases in NP concentrations. The main consequence was that, during exercise, the patients on beta-blockers reached higher blood levels of NPs, despite lower increases in HR.

The difference in the exercise increase in NPs, which was observed between patients with and without beta-blockers, was as much as 40 ng/l, on average, and this is in the range ≥51 beats/min, but this relationship was shifted to higher NP levels in patients on beta-blockers.

On average, the difference in exercise increase in NPs, which was documented between patients with and those without beta-blockers, was as much as 40 ng/l in the overall population. However, similar to what was observed for the exercise increase in NPs, this difference was markedly dependent on the rest level of NPs; for instance, it was only 13 ng/l in the half of population with the lowest levels of NPs at rest (<52 ng/l).

### Table 4. Multivariate Analysis: Best Independent Predictors of the Exercise Increase in the Plasma Concentration of Natriuretic Peptides

<table>
<thead>
<tr>
<th>ANP + BNP</th>
<th>ANP</th>
<th>BNP</th>
</tr>
</thead>
<tbody>
<tr>
<td>All variables included</td>
<td>All variables included</td>
<td>All variables included</td>
</tr>
<tr>
<td>Rest level of both peptides (p &lt; 0.001)</td>
<td>Rest level of both peptides (p &lt; 0.001)</td>
<td>Rest level of BNP (p &lt; 0.001)</td>
</tr>
<tr>
<td>Increase in heart rate (p &lt; 0.001)</td>
<td>Increase in heart rate (p &lt; 0.001)</td>
<td>Increase in rate–pressure product (p &lt; 0.001)</td>
</tr>
<tr>
<td>Beta-blockers (p &lt; 0.001)</td>
<td>Beta-blockers (p &lt; 0.001)</td>
<td>Beta-blockers (p = 0.001)</td>
</tr>
<tr>
<td>Exclusion of peptide dosages</td>
<td>Exclusion of peptide dosages</td>
<td>Exclusion of peptide dosages</td>
</tr>
<tr>
<td>Extent of scarred area (p &lt; 0.001)</td>
<td>Increase in heart rate (p &lt; 0.001)</td>
<td>Extent of scarred area (p &lt; 0.001)</td>
</tr>
<tr>
<td>Increase in heart rate (p &lt; 0.001)</td>
<td>Beta-blockers (p = 0.001)</td>
<td>Increase in rate–pressure product (p = 0.001)</td>
</tr>
<tr>
<td>Beta-blockers (p = 0.001)</td>
<td>LVEF (p = 0.038)</td>
<td>Beta-blockers (p = 0.013)</td>
</tr>
<tr>
<td>Age (p = 0.025)</td>
<td>Diuretics (p = 0.041)</td>
<td>Age (p = 0.016)</td>
</tr>
<tr>
<td>Exclusion of increase in heart rate</td>
<td>Exclusion of increase in heart rate</td>
<td>Exclusion of increase in rate–pressure product</td>
</tr>
<tr>
<td>Rest level of both peptides (p &lt; 0.001)</td>
<td>Rest level of both peptides (p &lt; 0.001)</td>
<td>Rest level of BNP (p &lt; 0.001)</td>
</tr>
<tr>
<td>Increase in rate–pressure product (p &lt; 0.001)</td>
<td>Increase in rate–pressure product (p = 0.001)</td>
<td>Maximal rate–pressure product (p &lt; 0.001)</td>
</tr>
<tr>
<td>Beta-blockers (p &lt; 0.001)</td>
<td>Beta-blockers (p = 0.007)</td>
<td>Beta-blockers (p &lt; 0.001)</td>
</tr>
<tr>
<td>Exclusion of beta-blockers</td>
<td>Exclusion of beta-blockers</td>
<td>Exclusion of beta-blockers</td>
</tr>
<tr>
<td>Rest level of both peptides (p &lt; 0.001)</td>
<td>Rest level of both peptides (p &lt; 0.001)</td>
<td>Rest level of BNP (p &lt; 0.001)</td>
</tr>
<tr>
<td>Increase in heart rate (p = 0.001)</td>
<td>Increase in heart rate (p = 0.001)</td>
<td>Increase in rate–pressure product (p &lt; 0.001)</td>
</tr>
<tr>
<td>Diuretics (p = 0.009)</td>
<td>Diuretics (p = 0.009)</td>
<td>LVEF (p = 0.010)</td>
</tr>
<tr>
<td>Maximal work load at exercise (p = 0.020)</td>
<td>Maximal work load at exercise (p = 0.031)</td>
<td></td>
</tr>
<tr>
<td>Maximal heart rate (p = 0.042)</td>
<td>Maximal heart rate (p = 0.042)</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations as in Tables 1 and 2.
of plasma levels reported to induce a clear decrease in cardiac load during the intravenous infusion of BNP or ANP (7,25–28). However, this difference was much lower in patients with a low level of NPs at rest and therefore for whom the physiologic impact of beta-blockers is more debatable. Nevertheless, it is likely that the enhanced release of NPs might be an additional mechanism by which beta-blockers lower cardiac work during stress, at least in patients with diseased hearts and a high level of NPs at rest.

Mechanism of impact of beta-blockers. Beta-blockers have been shown to enhance the resting plasma levels of NPs in patients with hypertension (29) and in those with chronic heart failure (30). Up to now, however, no study has analyzed the effect of these drugs on the exercise secretion of NPs. Exercising under beta-blockers leads to an increase cardiac preload, as evidenced by larger LV cavities at end diastole (31,32); thus, it may be wondered whether this also leads to an increase in wall tension or pressure high enough to trigger enhanced peptide release.

However, experimental studies have also shown that the acute secretion of ANP was decreased by beta-agonists and enhanced by alpha-agonists, even in the absence of any hemodynamic changes (studies on cultured myocytes [33] or with selective intracoronary injection of agonists [34]). These experimental findings indicate direct but opposite effects of alpha- and beta-stimulation, which could explain our observations. First, alpha-stimulation enhances the acute secretion of NPs, but in patients on beta-blockers, this may not be counterbalanced by the opposite effect of beta-stimulation. Second, this unbalance between alpha- and beta-stimulation is likely to be exacerbated during the sympathetic stimulation associated with exercise, thereby explaining our observation that beta-blockers had a clear impact on exercise release but not on rest concentration of NPs.

Further studies are required to clarify the underlying physiologic mechanism. In addition, a limitation is that this is only an observational study. Thus, further studies are required where the exercise release of NPs could be compared between before and after the referral to beta-blockers. Up to now, such studies have never been conducted in patients or normal subjects.
Nevertheless, this study shows that patients with chronic CAD exhibit higher exercise release of both BNP and ANP when their daily-life treatment includes beta-blockers. This enhanced secretion of potent vasodilating and natriuretic agents might constitute an additional and original mechanism of these drugs for further protecting diseased hearts against stress.

Acknowledgments

The authors acknowledge Jean-Marc Gravier and Henri Boutlet for their work in SPECT images analysis. The authors acknowledge Jean-Marc Gravier and Henri Boutlet for their work in SPECT images analysis. The authors acknowledge Jean-Marc Gravier and Henri Boutlet for their work in SPECT images analysis. The authors acknowledge Jean-Marc Gravier and Henri Boutlet for their work in SPECT images analysis.

REFERENCES