The heart as an endocrine organ secretes natriuretic peptides that allow homeostasis and control of the volume of circulating blood (1). The levels of atrial and brain natriuretic peptides (ANPs and BNPs, respectively) are increased in patients with congestive heart failure (CHF) (2,3), especially in those with severe hemodynamic impairment (1,4,5), and are strong predictors of prognosis in patients with previous myocardial infarction (6) and CHF (7).

Because CHF is frequent (8) and associated with high mortality (8,9), early treatment is essential, emphasizing the need for early diagnosis before the occurrence of overt heart failure (10). This, in turn, has raised the hope that the hormonal activation associated with heart failure (10), in particular that of natriuretic peptides, could be used for the early diagnosis of left ventricular (LV) dysfunction (11). N-terminal ANP (N-ANP), which has a prolonged half-life (12), and BNP levels are increased in patients with LV dysfunction (11,13–15), even if asymptomatic (11). However, the diagnostic use of these hormonal levels remains controversial (16), in particular because other cardiac diseases associated with aging (17) and atrial overload (18) may also result in their activation.

Atrial fibrillation (A-Fib) is a frequent disease among the elderly, who represent the same population affected by CHF (19). Previous studies have suggested that C-terminal ANP levels are elevated in patients with A-Fib (20,21). Regarding N-ANP or BNP levels, specific information has been limited or lacking (22,23), and A-Fib was either acute (23) or associated mostly with concomitant left-sided heart disease, such as cardiomyopathy or mitral stenosis (22,24,25). Therefore, it is unclear whether chronic A-Fib in and by itself, rather than left atrial (LA) enlargement (18), hemodynamic impairment (23) or other hormonal alteration, can result in elevation of N-ANP or BNP levels.
An independent association would have major implications for the utilization of hormonal levels in the diagnosis of LV dysfunction and would raise important questions regarding the significance of hormonal activation in A-Fib.

To analyze the intrinsic effect of A-Fib on natriuretic peptides, it is essential to compare patients with A-Fib and sinus rhythm with similar clinical characteristics and ranges of atrial volume, hemodynamics and LV function. Therefore, natriuretic peptide levels and comprehensive Doppler echocardiography were obtained prospectively and simultaneously in patients with LA overload in sinus rhythm or A-Fib to verify the hypothesis that A-Fib is a major determinant of natriuretic peptide levels, independently of LA volume, LV function or hemodynamic alterations.

**METHODS**

The patients were enrolled prospectively. Patient inclusion criteria were 1) sinus rhythm with either primary (i.e., not caused by valve or pericardial disease or acute myocardial infarction) LV dysfunction (ejection fraction \[EF\] <50%) or organic mitral regurgitation (due to intrinsic valvular disease) or 2) chronic A-Fib, idiopathic (lone) or due either to primary LV dysfunction or to organic mitral regurgitation. The duration of overt A-Fib ranged from six months to 13 years (mean, 49 ± 50 months). The underlying cardiac disease was defined on the basis of history, clinical examination and Doppler echocardiography. The methodologic inclusion criteria were 1) comprehensive quantitative Doppler echocardiographic assessment and 2) simultaneous venous blood sampling for measuring hormonal levels. Exclusion criteria were as follows: 1) relatively recent onset (<6 months) of A-Fib; 2) high heart rate (>120 beats/min); 3) associated aortic valve disease, pericardial disease or congenital heart disease as determined by Doppler echocardiography; and 4) known major comorbid condition such as stroke or extensive atherosclerosis or renal, liver, or respiratory failure or malignancy. No exclusions were made on the basis of gender, race, age, degree of mitral regurgitation or degree of hemodynamic impairment. A total of 100 patients were enrolled in the study. These patients were referred to the echocardiographic laboratory for systolic murmur or history of mitral regurgitation (n = 58), for heart failure or LV dysfunction (n = 24) or for A-Fib (n = 18). The mean age was 70 ± 8 years, and 37% were female. The symptoms of heart failure (according to the New York Heart Association [NYHA] class), the treatment received and associated comorbid conditions were noted. Fourteen gender, and age-matched subjects in sinus rhythm, with no history of heart disease and entirely normal echocardiographic findings referred to the echocardiographic laboratory to rule out pericardial disease or for systolic murmurs, were enrolled as a control group.

**Echocardiographic study.** All patients had a complete two-dimensional echocardiographic and Doppler study that used multiple windows, as previously described (26).

The quantitative Doppler study was performed as previously described (27,28), and mitral and aortic stroke volumes were calculated. At least three measurements of each variable were averaged (six in patients with A-Fib). Cardiac output and index were calculated using the aortic stroke volume (27). Both mitral and aortic stroke volumes were used to calculate the mitral regurgitant volume and regurgitant fraction in all patients (28). In the presence of notable mitral regurgitation, the regurgitant volume was also measured by the proximal isovelocity surface area method (29). The measurement of regurgitant volume by these two methods showed close correlation (r = 0.98; p < 0.0001; standard error of the estimate, 8.5 ml). In our laboratory interobserver and intraobserver variabilities for regurgitant volume are low, 3.9 ± 4.8 and 6.0 ± 3.8 ml, respectively. Pulmonary artery systolic pressure was measured using the tricuspid regurgitant jet velocity (30).

Left atrial volume was measured at end-systole (largest atrial volume) with the use of two orthogonal apical views (31). Right atrial volume was measured at end-systole with a single plane method from the apical view. Left ventricular filling was assessed by the E-velocity and deceleration time obtained by pulsed-wave Doppler. Left ventricular end-systolic and end-diastolic volumes were measured by using the biapical Simpson’s rule, as recommended by the American Society of Echocardiography (32), allowing calculation of the LV EF. The total LV stroke volume calculated by this method and by the Doppler method showed close correlation (r = 0.98; p < 0.0001; standard error of the estimate, 5.9 ml).

**Blood sampling.** At the end of the echocardiographic examination and, thus, after the patient had been in a supine position for at least 30 min, a blood sample was drawn from a peripheral vein into edetic acid-coated tubes containing chilled potassium, immediately placed on ice and centrifuged at 2,500 rpm at 4°C. Plasma was separated and stored at −20°C. The N-ANP level was measured after extraction, using a polyclonal antibody to human ANP 26–55. The recovery is 86% and the intra-assay and interassay variabilities are 6% and 9%, respectively. There is no cross-reactivity with C-terminal ANP or BNP. The BNP level was measured using an assay with double antibody-coated beads to

### Abbreviations and Acronyms

- **A-Fib** = atrial fibrillation
- **ANOVA** = analysis of variance
- **ANP** = atrial natriuretic peptide
- **BNP** = brain natriuretic peptide
- **CHF** = congestive heart failure
- **EF** = ejection fraction
- **LA** = left atrium, left atrial
- **LV** = left ventricle, left ventricular
- **N-ANP** = N-terminal ANP
- **NYHA** = New York Heart Association
human BNP. The intra-assay and interassay variabilities are both 11%. The endothelin-1 level was measured after extraction using a polyclonal rabbit antiendothelin-1 antibody. The recovery is 81% and intra-assay and interassay variabilities 9% and 5%, respectively.

**Statistical analysis.** Results are presented as mean value ± SD. The patients were divided into two groups according to cardiac rhythm: sinus rhythm (group 1) and A-Fib (group 2). Differences were also tested between lone (primary) and secondary (to mitral regurgitation or LV dysfunction) A-Fib. Group comparisons were performed using a standard t test or chi-square test and comparison was also stratified according to underlying cardiac disease using analysis of variance (ANOVA). Linear and nonparametric regression was used as appropriate with N-ANP and BNP levels as the dependent variables and age and gender, presence of A-Fib, NYHA class of symptoms, LV EF, LA and right atrial volumes, cardiac index, systolic pulmonary artery pressure and endothelin-1 measurements as independent variables. Correlations were also analyzed separately in each group. Multivariate analysis using stepwise multiple linear regression was performed using the listed variables as candidates to define the independent determinants of the hormonal levels and was repeated with and without inclusion of the control patients; p < 0.05 was considered significant.

**RESULTS**

**Baseline characteristics.** Among the 100 patients, atrial overload was due to organic mitral regurgitation in 58 (regurgitant volume = 74 ± 36 ml, LA volume = 122 ± 60 ml, 49 in sinus rhythm), to LV dysfunction in 24 (EF = 33 ± 8%, LA volume = 112 ± 61 ml, 19 in sinus rhythm) and to lone A-Fib in 18 (EF = 59 ± 7%, LA volume = 106 ± 44 ml). By design, there was no difference in age (p = 0.6) and gender (percentage of women: 37% vs. 43%, p = 0.67) between patients and control subjects. As shown in Table 1 (left part), in comparison to control subjects, the patients showed signs of atrial overload, with significantly higher LA and right atrial volumes, and altered hemodynamics, with reduced cardiac index and higher pulmonary pressure. The difference in LV EF was of borderline significance. The atrial overload was due partly to the high regurgitant volume (50 ± 44 vs. 4 ± 3 ml per beat, p < 0.0001) and fraction (35 ± 21% vs. 4 ± 3%, p < 0.0001) measured in patients, as compared with control subjects. Accordingly, the hormonal measurements showed that N-ANP and BNP levels in patients were significantly and considerably higher than in control subjects. However, no difference was observed for endothelin-1 levels.

**A-Fib versus sinus rhythm.** Patients with sinus rhythm (group 1, n = 68) compared with those with A-Fib (group 2, n = 32) had a higher cardiac index and smaller right atrial volume (Table 1) and were less often treated with digitalis (p = 0.005) or warfarin (p = 0.004). However, no other significant baseline difference was noted. There was no difference in regurgitant volume between patients in sinus rhythm or A-Fib, either in those with organic disease (i.e., mitral regurgitation or primary LV dysfunction) (61 ± 41 vs. 55 ± 52 ml per beat, p = 0.66) or in those with lone A-Fib compared with control subjects (6 ± 4 vs. 4 ± 3 ml per beat, p = 0.23). No difference was observed in LA volume, LV EF and filling characteristics, systolic pulmonary artery pressure or endothelin-1 level (Table 1). No differences between the two groups were noted regarding symptoms of heart failure (Table 1) or treatment with angiotensin-converting enzyme inhibitors, calcium channel blockers, beta-blockers, diuretics and antiarrhythmic drugs (all p > 0.20) or comorbid conditions such as history of hypertension (49% vs. 47%, p = 0.88) or diabetes (16% vs.

### Table 1. Comparison of the Baseline Characteristics of the Study Groups

<table>
<thead>
<tr>
<th></th>
<th>Control Group (n = 14)</th>
<th>Patients (n = 100)</th>
<th>p Value</th>
<th>Sinus Rhythm (Group 1) (n = 68)</th>
<th>A-Fib (Group 2) (n = 32)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>69 ± 8</td>
<td>70 ± 8</td>
<td>0.6</td>
<td>70 ± 7.6</td>
<td>72 ± 7.2</td>
<td>0.18</td>
</tr>
<tr>
<td>NYHA = II (%)</td>
<td>0</td>
<td>44</td>
<td>0.016</td>
<td>45</td>
<td>44</td>
<td>0.9</td>
</tr>
<tr>
<td>LV EF (%)</td>
<td>65 ± 4.5</td>
<td>57 ± 16</td>
<td>0.07</td>
<td>57 ± 17</td>
<td>56 ± 12</td>
<td>0.5</td>
</tr>
<tr>
<td>Cardiac index (L/min/m²)</td>
<td>3.1 ± 0.5</td>
<td>2.7 ± 0.6</td>
<td>0.03</td>
<td>2.8 ± 0.7</td>
<td>2.5 ± 0.5</td>
<td>0.03</td>
</tr>
<tr>
<td>Systolic PAP (mm Hg)</td>
<td>32 ± 6</td>
<td>43 ± 13</td>
<td>0.002</td>
<td>44 ± 13</td>
<td>40 ± 13</td>
<td>0.1</td>
</tr>
<tr>
<td>LA volume (ml)</td>
<td>55 ± 14</td>
<td>117 ± 58</td>
<td>0.0001</td>
<td>111 ± 52</td>
<td>128 ± 66</td>
<td>0.2</td>
</tr>
<tr>
<td>RA volume (ml)</td>
<td>47 ± 9</td>
<td>70 ± 34</td>
<td>0.0001</td>
<td>58 ± 26</td>
<td>93 ± 36</td>
<td>0.0001</td>
</tr>
<tr>
<td>E-velocity (cm/s)</td>
<td>69 ± 15</td>
<td>94 ± 28</td>
<td>0.0001</td>
<td>93 ± 27</td>
<td>97 ± 30</td>
<td>0.5</td>
</tr>
<tr>
<td>Deceleration time (ms)</td>
<td>247 ± 40</td>
<td>192 ± 47</td>
<td>0.0001</td>
<td>192 ± 52</td>
<td>192 ± 34</td>
<td>0.99</td>
</tr>
<tr>
<td>Endothelin-1 (pg/ml)</td>
<td>15.4 ± 6.5</td>
<td>13.5 ± 6.8</td>
<td>0.3</td>
<td>13.5 ± 6.7</td>
<td>13.5 ± 6.9</td>
<td>0.9</td>
</tr>
<tr>
<td>BNP (pg/ml)</td>
<td>29 ± 42</td>
<td>161 ± 239</td>
<td>0.0001</td>
<td>160 ± 26</td>
<td>165 ± 163</td>
<td>0.9</td>
</tr>
<tr>
<td>N-ANP (pg/ml)</td>
<td>910 ± 536</td>
<td>1,961 ± 1,507</td>
<td>0.01</td>
<td>1,654 ± 1,323</td>
<td>2,613 ± 1,681</td>
<td>0.007</td>
</tr>
</tbody>
</table>

A-Fib = atrial fibrillation; BNP = brain natriuretic peptide; EF = ejection fraction; LA = left atrial; LV = left ventricular; N-ANP = N-terminal atrial natriuretic peptide; NYHA = New York Heart Association; PAP = pulmonary artery pressure; RA = right atrium.
19%, $p > 0.75$). Nevertheless, comparison of hormonal levels between groups showed that patients with A-Fib had significantly higher N-ANP levels than those with sinus rhythm ($2,613 \pm 1,681 \, \text{vs.} \, 1,654 \pm 1,323 \, \text{pg/ml}; p = 0.003$) but no difference in BNP level ($165 \pm 163 \, \text{vs.} \, 160 \pm 239 \, \text{pg/ml}; p = 0.92$). Comparison between patients with A-Fib and sinus rhythm stratified according to underlying heart disease (LV dysfunction, mitral regurgitation or neither) confirmed the significant differences for N-ANP (adjusted $p < 0.0001$) and the lack of difference for BNP (adjusted $p = 0.14$).

Within group 2, patients with lone A-Fib (primary, $n = 18$) in comparison to those with secondary A-Fib (with organic disease, $n = 14$) had a lower BNP level ($106 \pm 94 \, \text{vs.} \, 240 \pm 202 \, \text{pg/ml}; p = 0.035$) but a similar N-ANP level ($2,339 \pm 1,542 \, \text{vs.} \, 2,968 \pm 1,841 \, \text{pg/ml}; p = 0.30$). There was a trend, albeit not significant, toward a negative association between duration of A-Fib and levels of N-ANP ($r = -0.34, p = 0.06$) and BNP ($p = 0.20$).

**Determinants of natriuretic peptide levels.** In the overall population of patients and control subjects, the correlation observed between LV EF and BNP ($r = -0.62, p < 0.0001$) was maintained in patients with A-Fib ($r = -0.51, p < 0.003$), whereas that with N-ANP was weak ($r = -0.22, p = 0.017$) and was observed only in those with sinus rhythm ($r = -0.31, p = 0.005$) but not in A-Fib ($r = 0.04, p = 0.81$). A significant correlation was also observed between NYHA class of symptoms and N-ANP level ($r = 0.42, p < 0.0001$) without interaction with the presence or absence of A-Fib ($p$ for interaction = 0.36). Stratified by symptom category, the N-ANP level was higher in patients with A-Fib than in those with sinus rhythm (adjusted $p$ in ANOVA = 0.0004, Fig. 1). Similarly, a significant correlation was observed between NYHA class of symptoms and BNP level ($r = 0.55, p < 0.0001$) without interaction with the presence or absence of A-Fib ($p$ for interaction = 0.20).

Stratified by symptom category, the BNP level was not different between patients with A-Fib and those with sinus rhythm (adjusted $p$ in ANOVA = 0.59, Fig. 2). No other variable demonstrated correlations with N-ANP level with $r \geq 0.40$ in sinus rhythm or in A-Fib. Conversely, BNP correlated significantly with systolic pulmonary artery pressure ($r = 0.53, p < 0.0001$) and LA volume ($r = 0.53, p < 0.0001$).

Of particular interest were variables with values different between patients in A-Fib and those in sinus rhythm. Right atrial volume and cardiac index showed poor correlations with N-ANP ($r = 0.17, p = 0.10$ and $r = -0.30, p = 0.002$, respectively) and BNP ($r = 0.24, p = 0.02$ and $r = -0.36, p = 0.0002$, respectively). Also, digoxin treatment was not associated with higher N-ANP or BNP levels globally and within each group (all $p > 0.05$). Furthermore, right atrial volume, cardiac index and digoxin treatment were not independent predictors of N-ANP and BNP levels in multivariate analysis.

The results of multivariate analysis are presented in Table 2. The independent determinants of higher N-ANP levels were higher NYHA functional class, A-Fib and a higher endothelin-1 level. This result was not altered if the control subjects were removed from the model ($p = 0.0001, 0.0016$ and 0.023, respectively). Conversely, the independent determinants of higher BNP levels were lower LV EF and higher LA volume, systolic pulmonary artery pressure and endothelin-1 level. This result was not altered after removal of the control subjects from the model ($p = 0.0001, 0.00001, 0.03$ and 0.008, respectively).

**DISCUSSION**

The present study shows the following: 1) natriuretic peptide levels are elevated in patients with LA overload; 2) A-Fib is associated with markedly elevated N-ANP levels, independently of symptoms, atrial volumes, LV function,
Atrial fibrillation (A-Fib) is a frequent disease, particularly in the elderly (19). The prognosis of A-Fib is linked to that of the causal disease, usually benign in young patients with lone A-Fib (33), but more often associated in the elderly with relatively high rates of complications, including embolism and heart failure (19). The progressive LA enlargement observed in patients with A-Fib (34) may be partly responsible for these complications. These morphologic alterations also raise the question that A-Fib may be associated with activation of natriuretic peptides. Although the exact trigger for release of natriuretic peptides is still debated, experimental and clinical studies have suggested that atrial volume, pressure and wall stretch are the main determinants of the activation of these peptides and are all potentially altered in A-Fib (1,18,35–37).

Previous studies in small series of patients with A-Fib reported increased levels of the short half-life peptide C-terminal ANP, reflective of the instantaneous activation of ANP (21,38). This activation was not consistently observed (39) and may have been the result of associated heart diseases (mitral stenosis, cardiomyopathy) or altered hemodynamics (22,24,25,40). Little information is available about the longer half-life peptide N-ANP (22,23) or BNP levels (17), and no concomitant information on cardiac function (particularly LA volume [34] and LV function [22]) has been reported. Therefore, the respective role of A-Fib or the underlying cardiac alterations in the potential activation of natriuretic peptides is unclear.

To address these unresolved issues, the present study was designed to compare patients with A-Fib to patients with sinus rhythm with similar cardiac alterations, as determined by an extensive Doppler-echocardiographic assessment. Consequently, patients with sinus rhythm or A-Fib had very similar baseline characteristics, in particular for LA volume, EF and pulmonary pressure but also for symptoms, comorbid conditions and treatment. Using this population, we observed that chronic A-Fib is independently associated with higher N-ANP levels, which, therefore, are not confined to acute A-Fib (23) or A-Fib associated with heart failure (22). This univariate association was confirmed in comparisons stratified to the causal cardiac disease and in multivariate analysis adjusting for baseline determinants of N-ANP, in particular, symptoms and EF. Conversely, despite the association between BNP level and LA volume observed in the present study, there was no independent association of BNP level with A-Fib (17). These results were confirmed after adjustment for the level of endothelin-1, which may stimulate natriuretic peptide secretion independently of hemodynamic alterations (41). These results were also confirmed in lone A-Fib, which is associated with less hemodynamic alteration than secondary A-Fib. In lone A-Fib compared with secondary A-Fib, the N-ANP levels were not significantly different, but the BNP levels were significantly lower. These data confirm that BNP secretion closely reflects hemodynamic alterations (42), but also that any form of A-Fib even without heart failure can lead to high N-ANP levels.

The mechanism of increased N-ANP levels in A-Fib is unknown. Experimental and clinical studies have suggested that in failing myocardium, ANP secretion increases because of the up-regulation of ANP gene expression linked to the hypertrophic process (43–45). The hypothesis of an intrinsic atrial myocardial failure associated with A-Fib is consistent with our observation of no significant correlation between the hemodynamic status and the N-ANP level in patients with A-Fib and is supported by recent histologic data suggesting that A-Fib presents as an isolated atrial cardiomyopathy (46,47). The decrease of natriuretic peptides observed after cardioversion (20,24,25) does not rule out the possibility of intrinsic atrial myocardial alteration and may reflect transient inhibition of ANP secretion, as suggested by the trend for delayed recurrent increase in ANP (20) and by the inhibition of secretion also observed after the Maze procedure (48). Another possible link between A-Fib and excess ANP secretion is through G-protein alterations. As recently demonstrated, G-proteins, which form the switchboard between a family of receptors and intracellular effector molecules, mediate ANP secretion (49) and ion channel regulation (50) and, thus, may influence electrical stability of the myocyte membrane and have a role in generating A-Fib.

Clinical implications. Clinically, the independent association between A-Fib and N-ANP level raises the question of the role of N-ANP level in prognostic stratification. In CHF and ischemic heart disease, higher N-ANP levels are associated with worse outcome (6,7). Although the N-ANP level in A-Fib is not acutely predictive of return to sinus rhythm (23), its large individual variation suggests a potential role as a prognostic indicator that should be evaluated in large long-term studies.

Table 2. Determinants of Natriuretic Peptide Levels in A-Fib

<table>
<thead>
<tr>
<th>Variable</th>
<th>N-ANP</th>
<th>BNP</th>
</tr>
</thead>
<tbody>
<tr>
<td>A-Fib</td>
<td>0.0003</td>
<td>—</td>
</tr>
<tr>
<td>NYHA class</td>
<td>0.0001</td>
<td>—</td>
</tr>
<tr>
<td>LV EF</td>
<td>—</td>
<td>0.0001</td>
</tr>
<tr>
<td>LA volume</td>
<td>—</td>
<td>0.0001</td>
</tr>
<tr>
<td>ET-1</td>
<td>0.032</td>
<td>0.016</td>
</tr>
<tr>
<td>Systolic PAP</td>
<td>—</td>
<td>0.005</td>
</tr>
</tbody>
</table>

A-Fib = atrial fibrillation; BNP = brain natriuretic peptide; EF = ejection fraction; ET-1 = endothelin-1; LA = left atrial; LV = left ventricular; N-ANP = N-terminal atrial natriuretic peptide; NYHA = New York Heart Association; PAP = pulmonary artery pressure.
Another important clinical issue is the use of natriuretic peptides as diagnostic markers for LV dysfunction. Congestive heart failure is the source of high morbidity and mortality (9) and is due most often to LV dysfunction (10). Recognizing LV dysfunction before overt failure is challenging but may allow early treatment (10). Previous studies demonstrated that ANP levels are increased in patients with CHF (3) proportionally to the degree of hemodynamic alteration (2,5). Therefore, several studies have attempted to define the role of natriuretic peptides as markers of LV dysfunction, with or without symptoms (11,13–15). Although all studies found significant diagnostic value of natriuretic peptides as markers of LV dysfunction (11,13–15), some inconsistencies were observed, suggesting that either N-ANP (13) or BNP (14,15) had a superior diagnostic accuracy. These discrepancies suggest that the diagnostic value of natriuretic peptides for LV dysfunction is dependent on the population in which it is applied. This is particularly relevant in the elderly, in whom many interactions are possible (17) and in whom both heart failure and A-Fib are particularly frequent (19). Although our data confirmed a correlation between N-ANP level and LV EF (11), the observation that N-ANP is strongly influenced by A-Fib (40) limits the value of this peptide as a marker of LV dysfunction. This observation is consistent with the most recent large cohort series, which observed a relatively low specificity of N-ANP (14,15). Conversely, BNP is not independently influenced by A-Fib and shows a strong correlation with EF, even in this population with atrial overload, which is a potential explanation for its high sensitivity and specificity as a diagnostic marker for LV dysfunction (14,15).

**Study limitations.** Analysis of the diagnostic value or of all possible hemodynamic determinants of natriuretic peptides would require very large sample sizes, which could not be achieved in a prospective study concomitantly with extensive Doppler echocardiographic assessment. However, these were not the goals of the study, and appropriate adjustment for major hemodynamic variables, comorbid conditions, treatment and other hormonal alterations could be achieved to analyze the independent effect of A-Fib on natriuretic peptides (21). Left atrial overload was specifically analyzed by measuring atrial volume, which reflects atrial remodeling (34) better than the M-mode atrial size used in previous studies (21). By using patients in sinus rhythm with atrial overload for comparison, the bias of major differences in cardiac status observed between patients with sinus rhythm and those with A-Fib was avoided, and most baseline characteristics were identical between the two groups, which is a unique feature of the present study. Right atrial volume was also measured and significant differences were observed between patients with A-Fib and those in sinus rhythm, but because of the wide range of values, these differences could be adjusted for in multivariate analysis. Therefore, these differences do not alter the conclusions of the study regarding the associations of A-Fib with natriuretic peptides.

The control population was referred to the echocardiography laboratory, and bias may be a concern. However, the N-ANP levels were very similar to those obtained in population-based studies (23) and the echocardiographic measurements were similar to those defined by the American Society of Echocardiography (32), in agreement with an appropriate control population.

Although the present study was not designed to address the molecular mechanism of activation of ANP in patients with A-Fib, it could analyze the relationship of natriuretic peptide activation with hemodynamic alterations, atrial overload and LV function. Future experimental and human studies should explore these mechanistic issues as well as the prognostic impact of this association.

**CONCLUSIONS**

Comparison of patients with A-Fib to patients with sinus rhythm with similar clinical characteristics, LA overload, LV EF and filling characteristics, pulmonary pressure and endothelin-1 level showed that A-Fib is independently associated with a higher N-ANP level and blurs the association of N-ANP with reduced LV function. Conversely, the BNP level is not independently affected by A-Fib and remains strongly associated with LV dysfunction, for which it can be used as a marker both in sinus rhythm and A-Fib.

**REFERENCES**


