Plasma Atrial Natriuretic Factor and Cyclic GMP in Mitral Stenosis Treated by Balloon Valvulotomy

Effect of Atrial Fibrillation

Jean-Claude Dussaule, MD, Alec Vahanian, MD, Pierre-Louis Michel, MD, Isabelle Soullier, MD, Stanislas Czekalski, MD, Jean Acar, MD, and Raymond Ardaillou, MD

To study the relation between plasma atrial natriuretic factor (ANF) and cardiac pressures, we measured plasma ANF in 24 patients with mitral stenosis 30 minutes before and 20 minutes after balloon mitral valvulotomy. All patients were without physical signs of congestive heart failure. Normal sinus rhythm was present in 15 (group 1), whereas the other nine (group 2) had permanent atrial fibrillation. There were no significant differences between groups for basal mean pressures in right atrium (RA), left atrium (LA), and pulmonary artery (PA). Valvulotomy resulted in a fall in both groups (p<0.001) in LA and PA mean pressures, whereas heart rate, cardiac index, and RA and aorta (AO) pressures did not change significantly. Basal ANF was not different in either group in RA (240 ± 43 vs. 266 ± 35 pg/ml) or AO (441 ± 92 vs. 643 ± 70 pg/ml) but tended to be higher in group 2 in LA (428 ± 88 vs. 682 ± 84 pg/ml; p = 0.059) and PA (488 ± 93 vs. 759 ± 92 pg/ml; p = 0.057). Plasma ANF was the highest in PA, and about 50% ANF was extracted in the systemic circulation. After valvulotomy, plasma ANF was greater (p<0.05) in group 2 (372 ± 90, 755 ± 152, 805 ± 134, and 707 ± 144 pg/ml) than in group 1 (206 ± 36, 386 ± 47, 429 ± 66, and 421 ± 49 pg/ml), regardless of the site of blood collection (RA, LA, PA, and AO, respectively). PA ANF was correlated with LA pressure (p<0.05) in group 1 before as well as after valvulotomy, whereas there was no such correlation in group 2. Cyclic GMP (cGMP) in LA was correlated (p<0.01) with PA ANF in group 1, and LA cGMP (10.0 ± 1.2 and 9.1 ± 1.8 pmol/ml in groups 1 and 2, respectively) was higher (p<0.05) than PA cGMP (9.1 ± 1.0 and 8.0 ± 1.5 pmol/ml in groups 1 and 2, respectively) before valvulotomy, which suggests the presence of ANF receptors in the pulmonary circulation. Taken together, these results indicate that in patients in sinus rhythm with mitral stenosis, there is an increase in ANF secretion depending on LA pressure. ANF secretion is also high in patients with mitral stenosis and atrial fibrillation but does not respond appropriately to changes in LA pressure. cGMP production in the lungs is related to ANF secretion in patients with sinus rhythm, whereas it seems to be independent in those with atrial fibrillation. (Circulation 1988;78:276–285)

It has been clearly established that secretion of atrial natriuretic factor (ANF) was regulated by the atrial stretch,1 which essentially depends on the pressures in both atria. Most studies in humans have been performed in patients with cardiac diseases who are undergoing right heart catheterization.2–6 These studies provided no information on the relation between ANF secretion and the hemodynamic parameters in the left heart. Moreover, pressure variations during the study of a given patient remained in a limited range. Therefore, we thought that patients with mitral stenosis treated by balloon valvulotomy represented a good model to determine 1) what are plasma ANF concentrations in the various cardiac cavities and vessels in humans? 2) How do hemodynamic parameters influence the local secretion of ANF? 3) How do balloon occlusion of the mitral valve and valvulotomy modify this secretion? 4) Is there a relation between plasma ANF and its second messenger, cyclic GMP (cGMP), in the cardiopulmonary circulation? 5) Does atrial contraction (sinus rhythm versus atrial
fibrillation) modify ANF and cGMP responses to changes in cardiac hemodynamic parameters?

The present study provides information on these different points and, in particular, demonstrates that ANF response to changes in left atrial pressure is inappropriate in patients with atrial fibrillation.

**Patients and Methods**

**Patients**

Thirty-four patients with mitral stenosis were treated by balloon mitral valvulotomy over a period of 4 months. They were divided into two groups. Group 1 included 15 patients (two men and 13 women) with normal sinus rhythm at the time of the study, without any history of atrial fibrillation, and who never had been treated with antiarrhythmic drugs. Group 2 included nine patients who had been in permanent atrial fibrillation for at least 6 months. The remaining 10 patients were excluded from the study because of associated disease (one patient with severe emphysema), postvalvulotomy complications (mitral insufficiency in two patients and persistent interatrial communication in one), or history of long-term atrial fibrillation successfully treated by antiarrhythmic drugs that were still being given at the time of the study (six patients). No patient in either group had aortic or tricuspid lesions or exhibited symptoms of mitral regurgitation that would have required valve replacement. Eleven patients (seven in group 1 and four in group 2) were in NYHA Class II, whereas the 13 others (eight in group 1 and five in group 2) were in NYHA Class III. Mitral commissurotomy had been performed in three patients (patients 2, 3, and 6 of group 1) more than 10 years before. The clinical characteristics of the patients are indicated in Table 1. It must be noted that patients of group 2 were older (p<0.05) than those of group 1. Plasma creatinine, although in the normal range, was also higher (p<0.05) in group 2 than in group 1. Left atrium (LA) diameter, which had been measured by echocardiography in M-mode using a transaortic long-axis section, was elevated in both groups compared with the normal values of the laboratory (<40 mm). It tended to be higher in group 2. The difference observed was just above (p = 0.066) the admitted level (p<0.05) of statistical significance.

**Protocol**

The usual treatment of each patient was not modified during the time of the study and is indicated in Table 1. Patients gave an informed consent, and the protocol was approved by the local ethical committee. A peripheral venous blood sample was collected in the supine position 24 hours before balloon dilatation for determination of plasma creatinine, aldosterone, cGMP, ANF, and renin activity (PRA).

Valvulotomy was performed under local anesthesia and mild sedation 2 hours after subcutaneous injection of atropine sulphate (1 mg). From the left groin, a venous catheter (7F, Swan-Ganz, American Edwards Laboratories, Anasco, Puerto Rico) was positioned in the pulmonary artery (PA) and an arterial catheter (8F, pigtail) in the left ventricle. Transseptal catheterization was performed from the right femoral vein using a standard Brockenbrough needle and a Mullins transseptal sheath and dilator (8F, USCI, Galway, Ireland). Heparin (5,000 IU) was administered immediately after transseptal puncture. Then, the sheath was removed, and an 8-mm peripheral angioplasty balloon (Schneider Medintag) was advanced along a guide wire to dilate the atrial septum. Two balloons (Trefoil 3 x 10 mm and a 19-mm conventional one) (Schneider Medintag, Zurich, Switzerland) were introduced through the same femoral vein with a single septal puncture. When positioned across the mitral valve, the balloons were inflated by hand with diluted contrast medium up to four atmospheres (400 kPa) for a period of 10–20 seconds. Inflations were repeated until the result appeared to be satisfactory. The loss of blood during the procedure was compensated by an intravenous infusion of saline and red cell concentrate. The total volume infused did not exceed 500 ml. A peripheral venous blood sample was collected in the supine position 48 hours after balloon dilatation for the same determinations as those performed initially.

**Hemodynamic Determinations**

Right atrium (RA), PA, and LA mean pressures and aortic (AO) systolic pressure were simultaneously recorded approximately 30 minutes before the first balloon inflation and strictly 20 minutes after the last one. Cardiac output was also measured by a thermodilution technique before and after valvulotomy. Mean mitral gradient was planimetered from simultaneous left ventricular and atrial pressures (mean of five consecutive cycles in sinus rhythm or of 10 in atrial fibrillation), and mitral valve area was calculated according to the Gorlin formula (K = 38) using systemic blood flow as cardiac output when appropriate. Repeated right heart oxymetry measurements were also carried out to provide evidence of any new left-to-right shunt.

**Analytical Methods**

Blood samples were collected simultaneously from RA, LA, PA, and AO 30 minutes before and 20 minutes after balloon dilatation into cold tubes containing dipotassium ethylenediaminetetraacetic acid. Supplementary blood samples were also obtained from PA and AO in 13 of 24 patients 1 minute after mitral orifice occlusion. Blood was centrifuged at 4,000 rpm for 20 minutes at 4°C. Plasma was stored at −20° C and used within 1 week for ANF and cGMP determinations. Plasma ANF was extracted from a 2-ml plasma aliquot on a C-18 octadecylsilane cartridge (Sep-Pak, Waters Associates, Milford, Massachusetts) and measured by a specific radioimmunoassay as reported.
TABLE 1. Clinical Data

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<th>Sex (M/F)</th>
<th>BSA (m²)</th>
<th>Treatment</th>
<th>Plasma creatinine (μmol/l)</th>
<th>HR (beats/min) Before</th>
<th>HR (beats/min) After</th>
<th>CI (l/min/m²) Before</th>
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Group 1 includes patients with sinus rhythm, and group 2 includes those with atrial fibrillation. HR, heart rate; CI, cardiac index; BSA, body surface area; MV, mitral valve; Before, After, results collected 30 minutes before and 20 minutes after balloon valvulotomy, respectively. Antiarrhythmic drugs used were amiodarone (200 mg/day) and/or flecainide (100 mg/day). Means obtained in both groups were compared using Student's t test for unpaired values.

Intraassay and interassay variations were 4.5% and 10%, respectively. Plasma aldosterone and PRA were measured only in the initial and final venous blood collections according to Pham Huu Trung and Corvol and Menard and Catt, respectively. Plasma creatinine was assayed using the usual technique adapted to a Technicon autoanalyzer.

Statistical Analysis

Data are given as mean ± SEM. Comparisons within the same group were performed using three-factor (patients, time, and site of blood collection) analysis of variance or Student’s t test for paired values. Regression analysis was also used when-
ever necessary. Comparisons between the two groups were performed using Student’s t test for unpaired values.

Results

Plasma Levels of ANF in Venous Peripheral Blood and Heart Cavities and Vessels in Patients With Mitral Stenosis

Peripheral ANF levels measured 24 hours before catheterization were 187 ± 31 and 274 ± 43 pg/ml in patients of groups 1 and 2, respectively. These values were greater (p < 0.01) than those measured under the same conditions (supine position) in a group of 10 healthy control subjects selected from the medical staff (27.7 ± 4.2 pg/ml). Plasma ANF levels were not significantly different in both groups of patients.

Plasma ANF was measured during catheterization of the right and left hearts 30 minutes before and 20 minutes after mitral valvulotomy (Figure 1). In group 1 as well as in group 2, three-factor (patients, sites of blood collection, valvulotomy) analysis of variance showed a marked variation (p < 0.001) between ANF levels in samples from different origins. Before valvulotomy, plasma ANF in AO (441 ± 92 and 643 ± 70 pg/ml in groups 1 and 2, respectively) was significantly greater (p < 0.001) than plasma ANF in RA measured simultaneously (240 ± 43 and 266 ± 35 pg/ml in groups 1 and 2, respectively). A similar significant (p < 0.001) difference was observed after valvulotomy (421 ± 49 and 707 ± 144 pg/ml for plasma ANF in AO vs. 206 ± 36 and 372 ± 90 pg/ml for plasma ANF in RA in groups 1 and 2, respectively). It was possible from these data to calculate the extraction coefficients of ANF in the systemic circulation (45.6% and 51.1% in group 1, 58.6% and 47.3% in group 2 before and after valvulotomy, respectively). The highest levels of ANF were observed in PA. Plasma ANF in LA (428 ± 88 and 682 ± 84 pg/ml in groups 1 and 2, respectively) were significantly lower (p < 0.01) than those in PA (488 ± 93 and 759 ± 92 pg/ml in groups 1 and 2, respectively) before valvulotomy. In contrast, no significant difference was observed between both parameters after valvulotomy. The extraction coefficients of ANF in the pulmonary circulation were low (12.1% and 10.0% in group 1, 10.1% and 6.2% in group 2 before and after valvulotomy, respectively) compared with those in the systemic circulation. No statistically significant difference was observed between plasma ANF levels of both groups 30 minutes before balloon valvulotomy regardless of the site (RA, PA, LA, or AO) of blood collection. However, it must be noted that differences for PA and LA almost met the admitted level of significance (p = 0.057 and 0.059, respectively), which suggests that plasma ANF concentration at these two sites tended to be greater in group 2 than in group 1 under basal conditions. Twenty minutes after balloon valvulotomy, differences between both groups became more marked because plasma ANF levels were significantly higher (p < 0.05) in group 2 (372 ± 90, 755 ± 1,52, 805 ± 134, and 707 ± 144 pg/ml) than in group 1 (206 ± 36, 386 ± 47, 429 ± 66, and 421 ± 49 pg/ml) regardless of the site of blood collection (RA, LA, PA, and AO, respectively).

Hemodynamic Data

Mean pressures in RA, PA, and LA and systolic pressure in AO measured in both groups of patients

Figure 2. Bar charts of mean blood pressure (M) in right atrium (RA), pulmonary artery (PA), and left atrium (LA) and systolic blood pressure (S) in aorta (AO) 30 minutes before (left) and 20 minutes after (right) balloon valvulotomy in two groups of patients with mitral stenosis. Group 1 (I) (n=15) includes patients with sinus rhythm, and group 2 (II) (n=9) includes those with atrial fibrillation. Data are mean±SEM.
and after valvulotomy are shown in Figure 2. There was no significant difference between groups for basal mean pressures in RA (1.4 ± 0.6 vs. 1.8 ± 0.4 mm Hg), LA (21.1 ± 1.8 vs. 18.4 ± 2.5 mm Hg), and PA (30.3 ± 3.5 vs. 26.0 ± 3.4 mm Hg) and systolic pressures in AO (118 ± 4.5 vs. 117.2 ± 4.6 for groups 1 and 2, respectively). Valvulotomy resulted in both groups in a fall (p<0.001) of mean pressure in LA (9.9 ± 1.7 and 10.3 ± 1.0 mm Hg) and PA (17.1 ± 2.1 and 20.1 ± 2.3 mm Hg for groups 1 and 2, respectively). In contrast, RA and AO pressures did not change. Cardiac index tended to be lower under basal conditions in group 2 than in group 1 (p=0.081). It was not significantly modified by balloon valvulotomy in either group. Similarly, heart rate remained unchanged. In contrast, mitral valve area increased (p<0.01) in both groups (Table 1). Oxygen saturation of hemoglobin was measured 20 minutes after balloon valvulotomy to detect a permanent shunt from the left to the right heart following the transseptal passage of the catheter. Such a shunt was not found as shown by the low oxygen saturation of hemoglobin observed in RA (73.3 ± 1.9% and 75.2 ± 2.0% in groups 1 and 2, respectively) and PA (75.4 ± 1.2% and 75.8 ± 2.4% in groups 1 and 2, respectively). These values were very close to those measured in samples from the same origin 30 minutes before valvulotomy (75.2 ± 1.5% and 75.0 ± 1.1% in RA and PA, respectively, in group 1; 73.3 ± 1.9% and 75.4 ± 1.2% in RA and PA, respectively, in group 2). Oxygen saturation of hemoglobin in AO was normal in both groups (95.9 ± 0.5% and 95.4 ± 0.7% in groups 1 and 2, respectively) and did not change after valvulotomy (97.1 ± 0.3% and 95.6 ± 1.0% in groups 1 and 2, respectively).

Correlation Between ANF Plasma Levels and Hemodynamic Data

Essentially, we studied the correlation between plasma ANF in PA (y axis; pg/ml), which seems, in the present study, the best index of locally secreted ANF and LA pressure (x axis; mm Hg). Both parameters were significantly correlated before (y = 30.6x - 159; r = 0.61, p<0.05) and after (y = 22.4x + 208; r = 0.58, p<0.05) valvulotomy in group 1. On the contrary, no correlation was observed in group 2 either before or after valvulotomy (Figure 3). The effect of valvulotomy on plasma ANF was evaluated with three-factor (patients,
sites of blood collection, valvulotomy) analysis of variance. ANF plasma levels, as a whole, fell significantly (p<0.001) after valvulotomy in group 1, whereas they increased in group 2 (p<0.05). We studied, in some patients (seven in group 1 and six in group 2), the effect of balloon occlusion of the mitral valve on plasma ANF in PA (Figure 4). Plasma ANF increased significantly 1 minute after balloon occlusion in group 1 (p<0.01). There was also an increase in group 2, but it did not reach the level of significance.

We could also measure plasma ANF in the peripheral venous blood 48 hours after mitral valvulotomy (Table 2). In group 1, ANF levels at this time (97±22 pg/ml) were significantly (p<0.05) lower than 24 hours before valvulotomy (187±31 pg/ml). In contrast, no difference was observed in patients of group 2 (241±38 and 275±43 pg/ml 48 hours after and 24 hours before valvulotomy, respectively). Therefore, plasma ANF concentration 48 hours after valvulotomy was greater (p<0.05) in group 2 than in group 1.

**Correlation Between ANF Plasma Levels and cGMP Plasma Levels**

Twenty-four hours before catheterization, cGMP levels in the peripheral venous blood were not significantly different in groups 1 (7.50±1.26 pmol/ml) and 2 (7.86±1.5 pmol/ml). These values were greater (p<0.05) than those measured under the same conditions (supine position) in a group of 11 healthy control subjects selected from the medical staff (4.31±0.37 pmol/ml). During catheterization, plasma cGMP levels varied with the site of blood collection in both groups of patients (Figure 5). Before valvulotomy, plasma cGMP was significantly (p<0.05) greater in LA (10.03±1.21 and 9.09±1.78 pmol/ml in groups 1 and 2, respectively) than in PA (9.08±1.01 and 8.01±1.55 pmol/ml, respectively). Therefore, it was possible to calculate a net addition of cGMP to the pulmonary circulation that was 10.5% and 13.5% in groups 1 and 2, respectively. Net addition (9.3%) was also found after valvulotomy in group 1 (10.14±1.21 and 9.28±0.91 pmol/ml in LA and PA, respectively; p<0.05) but not in group 2. Plasma cGMP in AO (10.55±1.41 and 8.92±1.73 pmol/ml in groups 1 and 2, respectively) was higher than in RA (8.63±0.79 and 6.51±1.33 pmol/ml in groups 1 and 2, respectively) before mitral valvulotomy. This indicates that cGMP was cleared from the systemic circulation with extraction coefficients of 18.2% and 27.0% in groups 1 and 2, respectively. These differences between cGMP concentrations in AO and RA were not observed 30 minutes after mitral valvulotomy. There was no difference between cGMP plasma levels of either group regardless of the site (RA, PA, LA, or AO) or the time (20 minutes before or 30 minutes after valvulotomy) of blood collection.

Plasma cGMP in AO was also measured simultaneously with PA plasma ANF in a limited number of patients 1 minute after balloon occlusion (Figure 4). Plasma cGMP increased significantly in both groups 1 (p<0.05) and 2 (p<0.01). Then, 20 minutes after valvulotomy, it fell rapidly to reach levels

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**Table 2. Plasma and Urinary Parameters 24 Hours Before and 48 Hours After Balloon Valvulotomy in Patients With Mitral Stenosis**

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<td>ANF (pg/ml)</td>
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<td>Aldosterone (pg/ml)</td>
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</table>

Statistical analysis:

Group 1 vs. group 2

**Before vs. after (group 1)** NS * NS NS NS NS

**Before vs. after (group 2)** NS * NS NS NS

Values are mean±SEM. Student’s t test for unpaired values was used for comparisons between groups, and Student’s t test for paired values was used for comparisons within the same group between data before and after valvulotomy.

*p<0.05.

ANF, atrial natriuretic factor; cGMP, cyclic GMP; PRA, plasma renin activity; AI, angiotensin I.

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**Figure 5. Bar charts of plasma cyclic GMP (cGMP) in right atrium (RA), pulmonary artery (PA), left atrium (LA), and aorta (AO) 30 minutes before (left) and 20 minutes after (right) balloon valvulotomy in two groups of patients with mitral stenosis. Group 1 (I) (n=14) includes patients with sinus rhythm and group 2 (II) (n=9) includes those with atrial fibrillation. Data are mean±SEM.**
close to (group 1) or slightly higher than (group 2) those measured 30 minutes before this maneuver.

We also compared plasma cGMP levels in the peripheral venous blood measured 24 hours before and 48 hours after balloon valvulotomy (Table 2). Plasma cGMP fell significantly (p<0.05) in both groups (7.50 ± 1.26 vs. 4.21 ± 0.48 pmol/ml in group 1 and 7.86 ± 1.50 vs. 5.69 ± 0.77 pmol/ml in group 2).

Plasma cGMP in LA (y axis; pmol/ml) was significantly correlated with plasma ANF in PA (x axis; pg/ml) before balloon valvulotomy in group 1 (y = 0.0109x + 4.65; r = 0.89, p<0.01) (Figure 6). No significant correlation was observed in group 2 20 minutes before balloon valvulotomy and in either group 30 minutes after balloon valvulotomy. Plasma cGMP (y) and plasma ANF (x) measured in the peripheral venous blood 24 hours before and 48 hours after valvulotomy were also significantly correlated (y = 0.0276x + 2.33; r = 0.61, p<0.01) in group 1.

**Renin and Aldosterone**

PRA and plasma aldosterone were measured 24 hours before and 48 hours after balloon valvulotomy (Table 2). Neither parameter changed significantly in either group. Plasma aldosterone was higher (p<0.05) in group 1 than in group 2 48 hours after balloon valvulotomy.

**Discussion**

The present study provides information on central plasma ANF levels in mitral stenosis before and after balloon valvulotomy. Preliminary results in abstract form have been reported by Waldman et al., who observed that plasma ANF in PA increased some minutes after valvulotomy and then decreased to levels lower than initial levels. Our present study first indicates that plasma ANF measured in the peripheral venous blood is seven to ten times greater in patients with severe mitral stenosis but without physical sign of congestive heart failure than in healthy control subjects. Plasma ANF levels were not significantly different in RA and the peripheral venous blood. The highest values were found in PA (488 ± 93 and 759 ± 92 pg/ml in groups 1 and 2, respectively). High values of ANF in PA of patients with mitral stenosis have been also observed by Waldman et al and Yoshimi et al but with a greater dispersion (228 ± 124 and 357 ± 381 pg/ml, respectively) than in our present study. The high gradient of ANF concentrations between RA and PA indicates a net addition of ANF in the right heart. This confirms that ANF is not secreted directly from the atrial wall but through the coronary sinus. Plasma ANF in AO was significantly greater than that in RA regardless of the time of blood collection and the group of patients. The coefficient of extraction of ANF in the systemic circulation calculated from these data was 45–60%. This confirms that ANF is catabolized in the tissues, probably for the most part in the kidney. Plasma ANF in LA was also lower than that in PA. But the coefficient of extraction of ANF in the pulmonary circulation only reached 6–12%. This indicates that plasma ANF is little destroyed during its passage through the lungs. An alternative possibility suggested by the finding of ANF in the walls of the pulmonary vessels is that ANF is both destroyed and produced in the pulmonary circulation.

It was possible in the present study to measure simultaneously plasma ANF and blood pressures in the different heart cavities and vessels. Essentially, we studied ANF concentration in PA because this parameter was considered to be the best index of ANF secretion. Moreover, we verified that plasma ANF in LA was highly correlated with ANF in PA regardless of the group of patients and the time of blood collection (r = 0.93–0.99; p<0.001). This indicates that variations of each value obey the same regulation. Plasma ANF in PA was correlated with mean blood pressure in LA in group 1 both before and after valvulotomy. The range of pressures studied was between 10 and 35 mm Hg (1.33 and 4.66 kPa). In contrast, no correlation was observed between plasma ANF in PA and RA pressure. Correlations between central plasma levels of ANF and hemodynamic data have previously been studied in humans. Bates et al found that RA pressure in patients with various cardiac diseases was the
hemodynamic variable that best correlated with plasma ANF in the right ventricle (RV). Correlation of pulmonary arterial wedge pressure with RV plasma ANF was also significant in their study. Sato et al.\textsuperscript{13} also observed in a series of 17 patients that plasma ANF in PA was significantly correlated with mean pulmonary arterial wedge pressure but, in contrast with Bates et al, they found no correlation of plasma ANF with mean RA pressure under control conditions—only after injection of contrast medium. Our study provides, for the first time, direct information on the relation between ANF secretion and pressure in LA in a homogeneous series of 15 patients in sinus rhythm with the same cardiac disease (group 1). Mitral stenosis represents a particularly valuable model because it is associated with an increase in LA pressure. The hypothesis of a predominant role of LA pressure (also reflected by pulmonary arterial wedge pressure) in ANF secretion is in accordance with the findings of Reinhardt et al.\textsuperscript{17} who reported an increase of natriuresis in dogs after elevation of LA pressure. In contrast, Garcia et al.\textsuperscript{18} concluded from the effects of removal of right or left atrial appendages in the rat that the right atrium played the major role in ANF-mediated volume homeostasis. Also in favor of the role of LA pressure in ANF secretion is the fact that ANF in PA was the highest 1 minute after balloon occlusion, a time at which LA pressure was also the highest. Finally, it must be noted that in patients in group 1, there were parallel decreases in plasma ANF and in PA or LA pressures after valvulotomy, whereas RA and AO pressures did not change.

Our present study also demonstrates that secretion of plasma ANF remains elevated and, therefore, is inappropriate in response to the fall of LA and PA pressures in patients with atrial fibrillation (group 2). Under basal conditions, there was no difference between either group in plasma ANF concentration in peripheral blood, RA, and AO. However, plasma ANF in LA and PA tended to be higher in group 2. In addition, while plasma ANF in PA was correlated with LA pressure in patients of group 1, no such correlation was observed in patients of group 2. It was also found that while LA and PA pressures decreased similarly in patients of both groups after mitral valvulotomy, plasma ANF levels fell only in group 1. In patients of group 2, ANF plasma levels did not decrease after mitral valvulotomy but, on the contrary, increased slightly, although significantly ($p<0.01$). This opposite effect of valvulotomy on plasma ANF in both groups is the reason why plasma ANF levels in PA were greater ($p<0.05$) in group 2 than in group 1 20 minutes after valvulotomy. Similarly, plasma ANF concentration in the peripheral blood fell after balloon valvulotomy in patients of group 1, whereas it remained unchanged in those of group 2 (24 hours before vs. 48 hours after mitral valvulotomy). The persistent elevation of plasma ANF in these patients may explain the lower concentration of plasma aldosterone observed 48 hours after balloon valvulotomy in group 2. The only apparent relation between plasma ANF in PA and LA pressure in patients of group 2 is the increase of plasma ANF 1 minute after balloon occlusion of the mitral valve. The reason atrial fibrillation modified ANF response to LA pressure remains unknown. High plasma ANF levels have been observed in cardiac failure.\textsuperscript{4,5} Although all patients of the group with atrial fibrillation were without physical signs of cardiac failure, mean cardiac index tended to be lower in this group. However, cardiac index does not seem to play an essential role in the results because it was not significantly correlated with the change in PA plasma ANF after balloon valvulotomy. In addition, PA plasma ANF was not significantly different in the 12 patients with the lowest cardiac indexes and in the 12 others with the highest cardiac indexes both before ($p=0.11$) and after ($p=0.13$) valvulotomy. Patients of group 2 were older than those of group 1. This may have played a role because plasma ANF increases progressively with age.\textsuperscript{19} In fact, plasma ANF in PA was not significantly different when the population studied was separated into two groups including the 12 oldest and the 12 youngest patients, respectively, before ($p=0.52$) as well as after ($p=0.14$) balloon valvulotomy. Moreover, PA plasma ANF was not significantly correlated with age either 30 minutes before or 20 minutes after valvulotomy in group 1 as well as in group 2.

Supraventricular tachycardia has also been shown to stimulate ANF secretion.\textsuperscript{2,3,20} Microelectrode studies indicate that cells in the fibrillating atrium may fire 500 times per minute.\textsuperscript{21} This very high rate could participate in the pathophysiological mechanism. A similar influence of atrial fibrillation on plasma ANF has been reported by Roy et al.\textsuperscript{2} Plasma ANF was high in patients with atrial fibrillation and decreased 1 hour after cardioversion to sinus rhythm. The authors suggested that high atrial pressure and chronic atrial stretch contributed to the high plasma ANF during atrial fibrillation, although they did not measure atrial pressure under this condition. This hypothesis is not verified in our present study because LA pressure fell in both groups after valvulotomy, whereas plasma ANF in PA declined only in group 1. Because atrial stretch or wall tension is influenced by chamber radius as well as pressure, we tried to estimate the effect of LA dimension on plasma ANF release. LA diameter tended to be greater in patients of group 2 than in those of group 1 ($p=0.066$). However, there was no difference in PA plasma ANF when the 12 patients with the highest LA diameters were compared with the 12 others with the lowest LA diameters before ($p=0.57$) as well as after ($p=0.65$) valvulotomy. Furthermore, PA plasma ANF was not significantly correlated with LA diameter either 30 minutes before or 20 minutes after valvulotomy in group 1 as well as in group 2. In conclusion, it is
likely that the high PA and LA plasma ANF and the inappropriate response of PA plasma ANF to the decrease in LA pressure that are observed in patients with atrial fibrillation are due to several related factors such as high rate of firing of the atrium, abnormal stretch of the atrial wall, and larger atrial volume. None of them plays an exclusive role, and their respective parts are still to be defined. In this regard, it is noteworthy to indicate that the six patients who had been excluded from the principal analyses for previous atrial fibrillation responded like the patients of group 2. Indeed, plasma ANF in PA did not decrease but, on the contrary, increased after valvulotomy (481.2 ± 255.6 vs. 768.2 ± 306.3 pg/ml 30 minutes before and 20 minutes after valvulotomy, respectively; p<0.05), whereas LA pressure diminished (16.5 ± 3.4 vs. 8.0 ± 1.4 mm Hg 30 minutes before and 20 minutes after valvulotomy, respectively). This result suggests that the inappropriate response of PA plasma ANF to the decrease in LA pressure was the consequence of a persistent anatomic disease of the atrium rather than that of atrial arrhythmia by itself that had been treated in these patients.

cGMP, which is the second messenger of ANF, was measured simultaneously with ANF in all the plasma samples because it has already been shown that changes in plasma cGMP concentration depend to some extent on the plasma concentration of ANF.22,23 Plasma cGMP concentrations in the peripheral venous blood measured under basal conditions were not different in groups 1 and 2 and were slightly higher than those of healthy subjects. Plasma cGMP in AO was higher than that in RA in both groups before mitral valvulotomy, which allowed a coefficient of extraction of cGMP of 18–27% to be calculated. This confirms that cGMP is cleared from blood in the systemic circulation. In contrast, plasma cGMP was higher in LA than in PA in both groups before as well as after balloon valvulotomy. Therefore, there was a net production of cGMP in the pulmonary circulation that corresponded to 9–14% of the amount of this nucleotide present in PA. This suggests that the presence of ANF receptors in the lungs is linked to guanylate cyclase. In group 1, plasma cGMP in LA was significantly correlated to ANF in PA before valvulotomy, which is also in favor of this hypothesis. No such correlation was observed in patients of group 2. Therefore, cGMP production in the lungs of patients with atrial fibrillation appears not to be directly related to ANF present in the afferent blood. Moreover, there was also a significant correlation between plasma ANF and plasma cGMP in the peripheral venous blood of patients of group 1 when the results 24 hours before and 48 hours after balloon valvulotomy were pooled. In contrast, neither parameter was significantly correlated in group 2. Parallel changes of ANF and cGMP in group 2 were only observed 1 minute after balloon valvulotomy. Both parameters increased from their basal concentrations (30 minutes before valvulotomy). Then, they decreased again when balloon occlusion of the mitral valve was stopped. The reason for this inappropriate secretion of cGMP in response to ANF in group 2 remains unknown. It has been shown that immunoreactive ANF in human plasma exhibits a great diversity of molecular forms.24 This study provides no information on the molecular distribution of ANF in either patient group. It can be hypothesized that in patients with atrial fibrillation, high ANF levels correspond in part to ANF molecular forms devoid of biological activity. Alternatively, higher plasma ANF levels in patients with atrial fibrillation could downregulate the specific ANF receptors and thus modify the relation between the plasma concentration of this peptide and that of cGMP. Such a downregulation has been observed for ANF receptors in the platelets of patients with cardiac failure.25

Plasma ANF may play a role in the pathophysiology of mitral stenosis. In response to elevated pressure in LA, ANF secretion is increased, which in turn results in an increased plasma cGMP in the pulmonary circulation. ANF, through cGMP, would diminish the vascular resistances in the lung capillaries and thus counteract the effect of the mitral stenosis on PA pressure. Such a hypothesis is in agreement with the beneficial effect of the infusion of ANF in patients with cardiac failure associated with the decrease of pulmonary capillary wedge pressure.4,26

References

**Key Words** • mitral stenosis • atrial fibrillation • atrial natriuretic factor • 3',5' cyclic guanosine monophosphate
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