ATRIAL NATRIURETIC PEPTIDE AND ITS RELATION TO CARDIAC DIMENSIONS AND FUNCTION IN PATIENTS WITH SYSTEMIC SCLEROSIS

E. Kazzam, K. Caidahl, T. Hedner, J. Hedner, R. Hällgren, A. Waldenström

LE PEPTIDE ATRIAL NATRIURÉTIQUE : SES RELATIONS AVEC LES DIMENSIONS ET LA FONCTION CARDIAQUE CHEZ DES MALADES AYANT UNE SCLÉRODERMIE

Objectifs : **Déterminer si le peptide atrial natriurétique est augmenté chez les patients ayant une sclérodermie et évaluer sa relation avec la fonction et les dimensions cardiaques.**

Méthodes : **Le taux plasmatique du peptide atrial natriurétique a été mesuré par technique radioimmunologique chez 30 malades ayant une sclérodermie et chez 48 sujets témoins comparables pour l'âge et le sexe. La structure et la fonction cardiaques ont été étudiées par échocardiographie bidimensionnelle.**

Résultats : **Le taux de peptide atrial natriurétique était nettement élevé chez les malades par rapport aux témoins (239,4 ± 59 vs 178,2 ± 36 pmpl/l, $p < 0,0005$). Le grand axe de l'oreillette gauche et sa surface étaient augmentés. La valeur du peptide atrial natriurétique était directement reliée à ces deux mesures ($r = 0,27$, $p < 0,05$ et $r = 0,40$, $p < 0,005$) respectivement ; elle était également reliée à l'augmentation du grand axe de l'oreillette droite ($r = 0,27$, $p < 0,05$). En revanche, elle n'était pas corrélée à la fonction systolique du ventricule gauche estimée par la fraction d'éjection, les modifications du rapport entre surface et fraction d'éjection, ces mesures ne différant pas entre patients et sujets témoins. Cependant, il y avait une corrélation inverse entre le taux de peptide atrial natriurétique et le volume d'éjection ($r = -0,35$, $p < 0,05$). Il y avait également une relation inverse entre le peptide atrial natriurétique et le grand axe du ventricule gauche ($r = -0,42$, $p < 0,005$) et le volume du ventricule gauche à la fin de la diastole ($r = -0,42$, $p < 0,005$). Différentes mesures indiquaient une hypertrophie ventriculaire gauche chez les patients en dépit d'une petite cavité. Le peptide atrial natriurétique était directement relié aux critères d'hypertrophie ventriculaire gauche, comme l'épaisseur du septum interventriculaire ($r = 0,44$, $p < 0,005$), ou de la paroi postérieure ($r = 0,34$, $p < 0,05$) le rapport épaisseur pariétale sur dimension de la cavité ($r = 0,36$, $p < 0,05$) et la surface myocardique ventriculaire gauche ($r = 0,36$, $p < 0,05$). Il n'y avait pas de relation entre la concentration de peptide atrial natriurétique et la fréquence cardiaque, la pression artérielle ou la résistance périphérique totale.**

Conclusion : **Ces résultats suggèrent que la production de peptide atrial natriurétique n'est pas réduite au cours de la sclérodermie. Bien plus, le taux est élevé, en relation avec le degré d'hypertrophie ventriculaire gauche. La détermination du taux de peptide atrial natriurétique peut donc être utile pour révéler une atteinte cardiaque chez les malades atteints de sclérodermie.**

Mots-clés :
peptide atrial natriurétique, sclérodermie

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Atrial natriuretic peptide (ANP) is a natriuretic, diuretic and vasodilating hormone originally found in the cardiac atria, and secreted in response to atrial stretch [1-4], possibly also influencing cardiac function by mechanisms independent of changes in total body fluid volume [5]. Recently several reports have demonstrated that the cardiac ventricles are capable of synthesizing and storing substantial amounts of ANP during cardiac hypertrophy [6] and failure [7, 8]. In animal models of severe left ventricular (LV) hypertrophy, the total ANP-mRNA content of the ventricle may even markedly exceed that of the atrium [4]. Increased amounts of circulating ANP have been found in valvular heart disease [9, 10] and acute myocardial infarction [8]. In congestive heart failure, plasma ANP is directly related to the severity of cardiac dysfunction as judged by NYHA classification [11]. Pharmacological therapy reducing atrial pressures also results in a rapid reduction of ANP release in patients with cardiac dysfunction [12, 13]. Therefore ANP determinations may be useful in the evaluation of patients with cardiac diseases. However the role of the cardiac atria and ventricles for ANP secretion in a variety of disorders has not been sufficiently studied.

Systemic sclerosis (SScl) is a multisystemic disease characterized by fibrotic, inflammatory and degenerative changes in the skin and other organs including the heart [14]. Cardiac involvement seems to be an indicator of poor prognosis [15, 16] and we have previously been able to demonstrate that cardiac dimensions as well as diastolic function are abnormal in SScl [17, 18]. As SScl primarily is an inflammatory disease with fibrosis being a major pathoanatomic finding in cardiac involvement, we were interested to determine whether the myocardium — in spite of fibrosis — is able to synthesize and secret ANP in relation to cardiac dimensions and function as in other types of heart failure. Therefore, we evaluated the relation between plasma ANP and cardiac dimensions and LV performance in a consecutive series of patients with SScl.

PATIENTS AND METHODS

Thirty consecutive patients (15 men and 15 females : age range 25-77 years, mean 54.5 years), with systemic sclerosis according to the American Rheumatism Association (ARA) criteria [19] were studied. The patients were referred from hospitals and outpatient units in the Uppsala region to Uppsala University Hospital. Their disease had been recognized for 5.6 (range 0.5-23) years. For comparative reasons 48 age and sex-matched control subjects (26 men and 22

females, age range 25-77 years, mean 54.6 years) were selected from the general population of Uppsala as previously described [20].

Echocardiographic examination

Two-dimensional echocardiography (2-D echo) was performed by means of Hewlett Packard ultrasound imaging system model 77020A, version K with a 2.5 or 3.5 MHz phased array transducer as previously described [17]. The echocardiographic recordings of routine projections, the parasternal long-axis and short-axis (aortic, mitral and papillary) planes, and the apical four-chamber, long-axis and two-chamber views, were stored on VHS 0.5 inch video tapes by means of a Panasomic video recorder NV 8100.

Echocardiographic measurements

The 2-D echo atrial and LV dimensions were measured and functional parameters including ejection fraction, fractional area change, end-systolic wall stress, and stroke volume calculated as described in detail previously [17, 18]. Because the patients were smaller than the controls and since these echocardiographic parameters are influenced by body surface area, all measurements were adjusted for body surface area. Total peripheral resistance (TPR) was calculated according to the formula TPR = mean arterial blood pressure × 1.33 (60/cardiac output).

Blood analysis

For the measurement of plasma ANP, blood was obtained from an antecubital vein at rest after overnight fasting in the recumbent position (8-10 a.m.). Blood was collected in EDTA coated tubes, immediately put on ice, centrifuged at 4°C for 10 min and aliquots of plasma were stored at − 70°C until the time for analysis. ANP was measured using a specific radioimmunoassay technique, as previously described.

Statistical analysis

Data are presented as mean ± standard deviation (SD) of the mean. Unpaired two-sided t-test was used to compare differences between patients and controls. Pearson's correlation coefficients were computed to illustrate certain relationships between two variables as indicated and p values < 0.05 were considered significant.

RESULTS

In spite of similar heights, patients weighed less than controls and they had smaller body surface area (1.7 ± 0.04 *vs* 1.9 ± 0.03 m², $p < 0.05$). Blood pressure and total peripheral resistance were similar in the two groups.

Plasma ANP concentration

The mean venous ANP concentration was significantly increased among patients as compared to controls (239.4 ± 59 *vs* 178.2 ± 36 pmol/l, $p < 0.0005$). There was no relation between ANP and systolic or diastolic blood pressure, mean arterial blood pressure, total peripheral resistance, duration of the disease or scleroderma scoring.

Relationships between plasma ANP and cardiac dimensions

Stop frames from the 2-D echo investigations were interpretable in the long-axis view in 28/30 patients and 44/48 controls, while in the apical four-chamber view corresponding numbers were 23/30 and 46/48.

Left atrial dimensions

Apical four chamber view: the left atrial systolic long-axis (30 ± 4.9 *vs* 27 ± 4.2 mm/m², $p < 0.005$) and area (748 ± 167 *vs* 613 ± 214 mm²/m², $p < 0.005$) were increased among the patients. ANP was related to both measurements ($r = 0.27$, $p < 0.05$ and $r = 0.40$, $p < 0.005$; *Fig. 1*).

Right atrial dimensions

Apical four chamber view: the right atrial systolic long axis was increased among patients (30 ± 4.7 *vs* 27 ± 3.4 mm/m², $p < 0.05$) and correlated to plasma ANP ($r = 0.27$, $p < 0.05$) (*Fig. 2*). There was no relation between plasma ANP and right atrial area, which did not differ between patients and controls even when body surface area was taken into account.

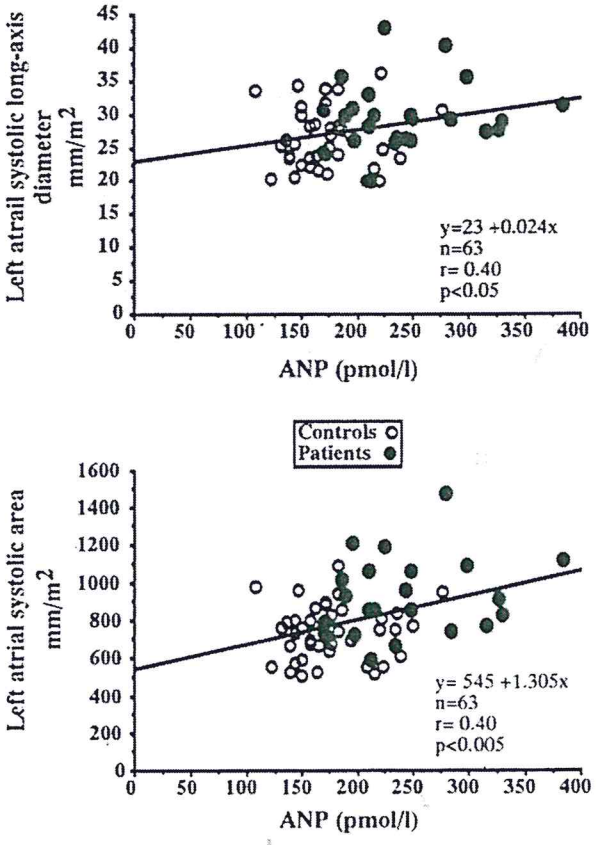

FIG. 1. The relation between plasma ANP and left atrial dimensions.

FIG. 1. Rapport entre le taux plasmatique du peptide natriurétique auriculaire (ANP) et les dimensions auriculaires gauches.

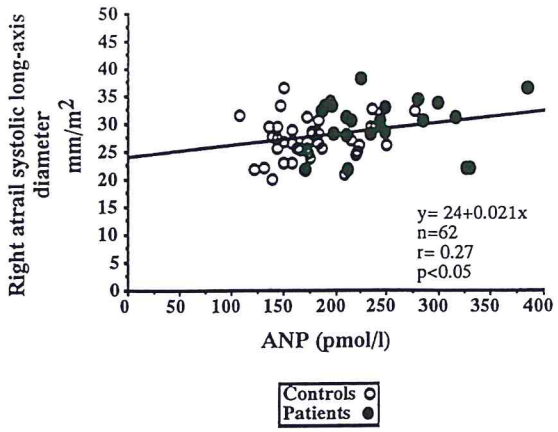

FIG. 2. The relation between plasma ANP and right atrial long-axis diameter.

FIG. 2. Rapport entre le taux plasmatique du peptide natriurétique auriculaire (ANP) et le plus grand diamètre de l'oreillette droite.

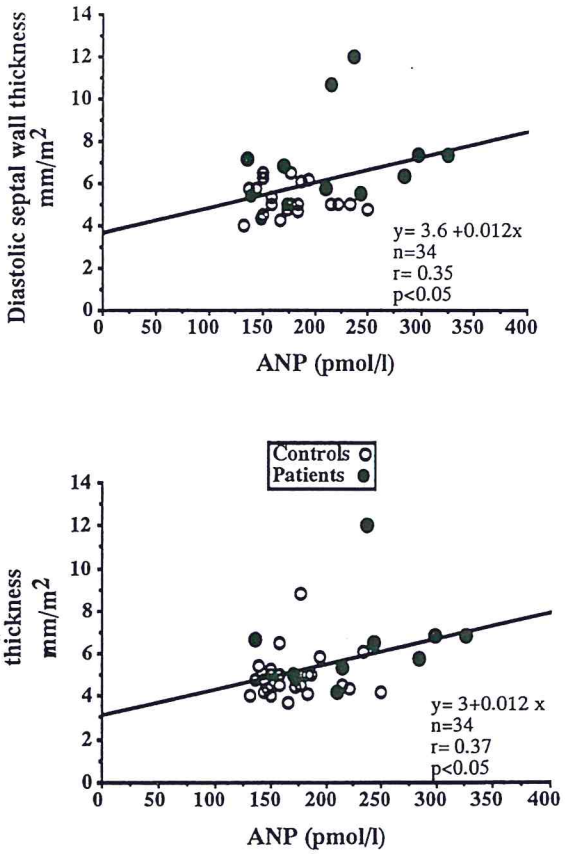

FIG. 3. The relation between plasma ANP and LV wall thickness.

FIG. 3. Rapport entre le taux plasmatique du peptide natriurétique auriculaire (ANP) et l'épaisseur de la paroi du ventricule gauche.

Left ventricular dimensions

Parasternal short-axis view at the papillary muscle level: the LV diastolic septal (7.4 ± 2.1 *vs* 5.2 ± 0.7 mm/m^2, $p < 0.0005$) and posterior wall (6.2 ± 2.2 *vs* 5.0 ± 1.0 mm/m^2, $p < 0.0005$) thicknesses were increased in the patients group. The ANP level was related to both measurements ($r = 0.35$, $p < 0.05$ and $r = 0.37$, $p < 0.05$) respectively (*Fig. 3*). ANP was significantly correlated ($r = 0.42$, $p < 0.05$) with the diastolic LV myocardial area, which was increased among the patients (1.325 ± 338 *vs* 998 ± 145 mm^2/m^2, $p < 0.0005$). From the apical two-chamber view: plasma ANP was related to the LV end-diastolic long axis diameter ($r = -0.37$, $p < 0.005$), which was shorter among patients (71 ± 8.9 *vs* 77 ± 8.3 mm, $p < 0.05$) (*Fig. 4*). The plasma ANP level was also related to the LV diastolic ($r = -0.40$, $p < 0.005$) and systolic ($r = -0.42$, $p < 0.005$) areas (*Fig. 5*), which were smaller among patients ($p < 0.005$ and $p < 0.05$, respectively).

Left ventricular systolic function

The ANP concentration was not related to LV systolic function as estimated by ejection fraction, fractional area change, or end-systolic wall stress. However, ANP was inversely related to stroke volume ($r = -0.35$, $p < 0.05$), which was lower among patients (68 ± 25 *vs* 91 ± 30 ml, $p < 0.005$).

Diastolic measurements of LV hypertrophy

The plasma ANP level was significantly related to various measures of LV hypertrophy, which were all increased (p values after semicolon), as the interventricular septal thickness ($r = 0.44$, $p < 0.005$; $p < 0.0005$), LV posterior wall thickness ($r = 0.34$, $p < 0.05$; $p < 0.05$), the wall thickness (septum + posterior wall) ($r = 0.40$, $p < 0.05$; $p < 0.0005$), the wall thickness to cavity dimension ratio ($r = 0.36$, $p < 0.05$; $p < 0.005$) and the LV myocardial index area ($r = 0.42$, $p < 0.05$) ; $p < 0.0005$). The plasma ANP level was inversely related to the end-diastolic volume of the left ventricle ($r = 0.42$, $p < 0.005$), which was found to be decreased ($p < 0.05$).

DISCUSSION

The main finding in this study, was a 30% increase in circulating ANP in patients with SScl as compared with controls. Furthermore, a significant correlation was found between ANP and indices of cardiac dimensions and LV hypertrophy.

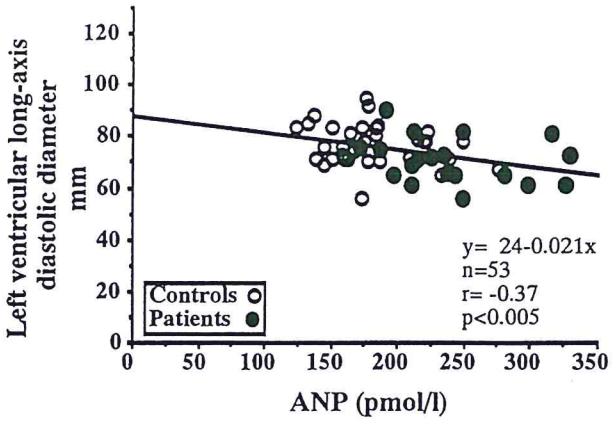

FIG. 4. The relation between plasma ANP and LV long-axis diameter.

FIG. 4. Rapport entre le taux plasmatique du peptide natriurétique auriculaire (ANP) et le plus grand diamètre du ventricule gauche.

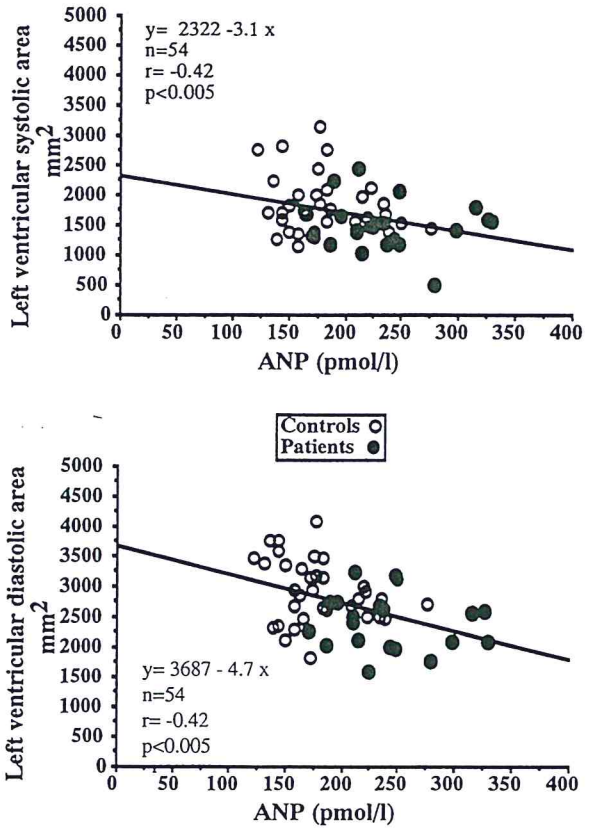

FIG. 5. The relation between plasma ANP and LV area.

FIG. 5. Rapport entre le taux plasmatique du peptide natriurétique auriculaire (ANP) et la surface du ventricule gauche.

Systemic sclerosis is primarily an inflammatory disease. It is well documented in the literature that the main cardiac involvements in SScl is myocardial fibrosis [21] and we were recently able to show that cardiac function [22] as well as myocardial perfusion are abnormal in SScl [23]. Therefore, it was considered to be of interest to determine whether the fibrosed myocardium in SScl is able to synthesize and secrete ANP in relation to altered cardiac dimensions and function as in other types of heart failure.

Several studies in children and adults indicate that ANP release is mediated by cardiac atrial distension [24]. In our patients the ANP level was related to both right and left atrial dimensions. Therefore, atrial distension is a possible mechanism behind the increased level of plasma ANP in SScl as has been reported in other types of cardiac diseases [1, 2].

There is increasing evidence in the literature that ANP is also synthesized and secreted by the ventricles and the ANP concentration might depend on factors within the LV myocardium. An underlying disease causing LV hypertrophy might lead to increased plasma ANP concentration [6, 7, 25]. It has been reported [26] that, whereas atrial stretch or dilatation may be an important stimulus for atrial ANP, ventricular ANP is increased independently of LV dilatation in patients with systolic and/or diastolic dysfunction. In a previous population study, we have reported correlations between venous plasma ANP and indices of LV function in patients with coronary heart disease [27].

Recently we reported LV hypertrophy and diastolic dysfunction [17, 18] as well as LV systolic abnormalities [20] to be common in SScl. In the present study we have found a significant increase in circulating ANP during resting conditions in the same patients with SScl. Interestingly enough, we found ANP to be more closely related to echocardiographic measurements of LV hypertrophy than to LV systolic function. This is reasonable, since we found diastolic dysfunction to be a more important abnormality than systolic dysfunction in SScl [18, 20, 22]. The correlations between the plasma ANP and the echocardiographic measurements of LV hypertrophy might suggest that ANP is also released from the left ventricle. Therefore in SScl, we cannot exclude ventricular ANP to contribute to the increased level of plasma ANP in addition to ANP released by atrial distension. However, since LV hypertrophy with increased LV filling pressure resulted in increased atrial pressure and stretch, it is not possible from the present investigation to determine the relative contribution by the atria and ventricles to ANP release.

Myocardial fibrosis, which is the main cardiac involvement in SScl [21], seems not to severely interfere with ANP production. There are two possibilities. Either, the myocardial disease is a trigger for ANP production/release, and the fibrotic process does not hamper but may promote ANP production. Or the haemodynamic consequences with LV hypertrophy and left atrial distension is the important factor, and the stimulus is so strong that despite low production in fibrotic myocardium the nonfibrotic parts produce an excess of ANP. In the latter case, the ANP secretion takes most

likely place in the atria, and LV hypertrophy causes increased ANP levels only through the mechanism of increased LV filling pressures.

Limitation of the study

Reports from pathoanatomical studies have shown myocardial fibrosis to be prevalent among SScl patients, but we have no biopsy data to support this in our study. The base for aetiological discussion is therefore hypothetical. A stronger evidence for LV secretion of ANP in SScl and its relation to LV function and hypertrophy can only be achieved by ANP and AMP-mRNA analysis in LV biopsies.

CONCLUSION

Circulating ANP is elevated in patients with SScl, in relation to LV hypertrophy but not to LV systolic function. ANP may be useful as a marker of cardiac involvement in patients with SScl. Whether it is the hypertrophied ventricular tissue or distended atrial walls that are mainly responsible for the increased ANP levels remains to be elucidated.

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SUMMARY

Objectives: Were to determine whether plasma atrial natriuretic peptide (ANP) is increased in patients with systemic sclerosis (SScl) and to evaluate its relation to cardiac dimensions and function.
Methods: Using radio-immunoassay, plasma ANP was determined in 30 patients with SScl and 48 age and sex matched controls. The plasma ANP level was related to cardiac structure and function as determined by two-dimensional echocardiography (2-D echo).
Results: Plasma ANP was markedly elevated among patients as compared to controls (239,4 ± 59 *vs* 178.2 ± 36 pmpl/l, $p < 0.0005$). The left atrial long-axis and area were increased, and ANP was directly related to both measurements ($r = 0.27$, $p < 0.05$ and $r = 0.40$, $p < 0.005$, respectively). Plasma ANP was also related to the increased right atrial long-axis ($r = 0.27$, $p < 0.05$). The ANP level was not related to LV systolic function as estimated by ejection fraction, fractional area change and end-systolic wall stress, neither did these measures differ between patients and controls. However, there was an inverse correlation between ANP level and stroke volume ($r = -0.35$, $p < 0.05$), which was lower among the patients ($p < 0.005$). ANP displayed also an inverse relation to LV long axis diameter ($r = -0.37$, $p < 0.005$) and area ($r = -0.42$, $p < 0.005$) as well as to LV end-diastolic volume ($r = -0.42$, $p < 0.005$). Various measurements indicated LV hypertrophy among the SScl patients in spite of a small LV cavity. ANP was directly related to measures of LV hypertrophy, as interventricular septum thickness ($r = 0.44$, $p < 0.005$), LV posterior wall thickness ($r = 0.34$, $p < 0.05$), the wall thickness to cavity dimension ratio ($r = 0.36$, $p < 0.05$), and LV myocardial area ($r = 0.36$, $p < 0.05$). There was no relationship between ANP concentration and heart rate, blood pressure or total peripheral resistance.
Conclusion: These results suggest that the ANP production is not reduced in SScl. Rather, circulating ANP is elevated in relation to the degree of LV hypertrophy. This implies that ANP may be useful for the identification of cardiac involvement in patients with SScl.

Key words :
atrial natriuretic peptide, cardiac dimensions, systemic sclerosis

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Méthodes : Le taux plasmatique du peptide atrial natriurétique a été mesuré par technique radioimmunologique chez 30 malades ayant une sclérodermie et chez 48 sujets témoins comparables pour l'âge et le sexe. La structure et la fonction cardiaques ont été étudiées par échocardiographie bidimensionnelle.
Résultats : Le taux de peptide atrial natriurétique était nettement élevé chez les malades par rapport aux témoins ($239,4 \pm 59$ vs $178,2 \pm 36$ pmpl/l, $p < 0,0005$). Le grand axe de l'oreillette gauche et sa surface étaient augmentés. La valeur du peptide atrial natriurétique était directement reliée à ces deux mesures ($r = 0,27$, $p < 0,05$ et $r = 0,40$, $p < 0,005$) respectivement ; elle était également reliée à l'augmentation du grand axe de l'oreillette droite ($r = 0,27$, $p < 0,05$). En revanche, elle n'était pas corrélée à la fonction systolique du ventricule gauche estimée par la fraction d'éjection, les modifications du rapport entre surface et fraction d'éjection, ces mesures ne différant pas entre patients et sujets témoins. Cependant, il y avait une corrélation inverse entre le taux de peptide atrial natriurétique et le volume d'éjection ($r = -0,35$, $p < 0,05$). Il y avait également une relation inverse entre le peptide atrial natriurétique et le grand axe du ventricule gauche ($r = -0,42$, $p < 0,005$) et le volume du ventricule gauche à la fin de la diastole ($r = -0,42$, $p < 0,005$). Différentes mesures indiquaient une hypertrophie ventriculaire gauche chez les patients en dépit d'une petite cavité. Le peptide atrial natriurétique était directement relié aux critères d'hypertrophie ventriculaire gauche, comme l'épaisseur du septum interventriculaire ($r = 0,44$, $p < 0,005$), ou de la paroi postérieure ($r = 0,34$, $p < 0,05$) le rapport épaisseur pariétale sur dimension de la cavité ($r = 0,36$, $p < 0,05$) et la surface myocardique ventriculaire gauche ($r = 0,36$, $p < 0,05$). Il n'y avait pas de relation entre la concentration de peptide atrial natriurétique et la fréquence cardiaque, la pression artérielle ou la résistance périphérique totale.
Conclusion : Ces résultats suggèrent que la production de peptide atrial natriurétique n'est pas réduite au cours de la sclérodermie. Bien plus, le taux est élevé, en relation avec le degré d'hypertrophie ventriculaire gauche. La détermination du taux de peptide atrial natriurétique peut donc être utile pour révéler une atteinte cardiaque chez les malades atteints de sclérodermie.

Mots-clés :
peptide atrial natriurétique, sclérodermie

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Atrial natriuretic peptide (ANP) is a natriuretic, diuretic and vasodilating hormone originally found in the cardiac atria, and secreted in response to atrial stretch [1-4], possibly also influencing cardiac function by mechanisms independent of changes in total body fluid volume [5]. Recently several reports have demonstrated that the cardiac ventricles are capable of synthesizing and storing substantial amounts of ANP during cardiac hypertrophy [6] and failure [7, 8]. In animal models of severe left ventricular (LV) hypertrophy, the total ANP-mRNA content of the ventricle may even markedly exceed that of the atrium [4]. Increased amounts of circulating ANP have been found in valvular heart disease [9, 10] and acute myocardial infarction [8]. In congestive heart failure, plasma ANP is directly related to the severity of cardiac dysfunction as judged by NYHA classification [11]. Pharmacological therapy reducing atrial pressures also results in a rapid reduction of ANP release in patients with cardiac dysfunction [12, 13]. Therefore ANP determinations may be useful in the evaluation of patients with cardiac diseases. However the role of the cardiac atria and ventricles for ANP secretion in a variety of disorders has not been sufficiently studied.

Systemic sclerosis (SScl) is a multisystemic disease characterized by fibrotic, inflammatory and degenerative changes in the skin and other organs including the heart [14]. Cardiac involvement seems to be an indicator of poor prognosis [15, 16] and we have previously been able to demonstrate that cardiac dimensions as well as diastolic function are abnormal in SScl [17, 18]. As SScl primarily is an inflammatory disease with fibrosis being a major pathoanatomic finding in cardiac involvement, we were interested to determine whether the myocardium — in spite of fibrosis — is able to synthesize and secret ANP in relation to cardiac dimensions and function as in other types of heart failure. Therefore, we evaluated the relation between plasma ANP and cardiac dimensions and LV performance in a consecutive series of patients with SScl.

PATIENTS AND METHODS

Thirty consecutive patients (15 men and 15 females : age range 25-77 years, mean 54.5 years), with systemic sclerosis according to the American Rheumatism Association (ARA) criteria [19] were studied. The patients were referred from hospitals and outpatient units in the Uppsala region to Uppsala University Hospital. Their disease had been recognized for 5.6 (range 0.5-23) years. For comparative reasons 48 age and sex-matched control subjects (26 men and 22

females, age range 25-77 years, mean 54.6 years) were selected from the general population of Uppsala as previously described [20].

Echocardiographic examination

Two-dimensional echocardiography (2-D echo) was performed by means of Hewlett Packard ultrasound imaging system model 77020A, version K with a 2.5 or 3.5 MHz phased array transducer as previously described [17]. The echocardiographic recordings of routine projections, the parasternal long-axis and short-axis (aortic, mitral and papillary) planes, and the apical four-chamber, long-axis and two-chamber views, were stored on VHS 0.5 inch video tapes by means of a Panasomic video recorder NV 8100.

Echocardiographic measurements

The 2-D echo atrial and LV dimensions were measured and functional parameters including ejection fraction, fractional area change, end-systolic wall stress, and stroke volume calculated as described in detail previously [17, 18]. Because the patients were smaller than the controls and since these echocardiographic parameters are influenced by body surface area, all measurements were adjusted for body surface area. Total peripheral resistance (TPR) was calculated according to the formula TPR = mean arterial blood pressure × 1.33 (60/cardiac output).

Blood analysis

For the measurement of plasma ANP, blood was obtained from an antecubital vein at rest after overnight fasting in the recumbent position (8-10 a.m.). Blood was collected in EDTA coated tubes, immediately put on ice, centrifuged at 4°C for 10 min and aliquots of plasma were stored at − 70°C until the time for analysis. ANP was measured using a specific radioimmunoassay technique, as previously described.

Statistical analysis

Data are presented as mean ± standard deviation (SD) of the mean. Unpaired two-sided t-test was used to compare differences between patients and controls. Pearson's correlation coefficients were computed to illustrate certain relationships between two variables as indicated and p values < 0.05 were considered significant.

RESULTS

In spite of similar heights, patients weighed less than controls and they had smaller body surface area (1.7 ± 0.04 *vs* 1.9 ± 0.03 m², $p < 0.05$). Blood pressure and total peripheral resistance were similar in the two groups.

Plasma ANP concentration

The mean venous ANP concentration was significantly increased among patients as compared to controls (239.4 ± 59 *vs* 178.2 ± 36 pmol/l, $p < 0.0005$). There was no relation between ANP and systolic or diastolic blood pressure, mean arterial blood pressure, total peripheral resistance, duration of the disease or scleroderma scoring.

Relationships between plasma ANP and cardiac dimensions

Stop frames from the 2-D echo investigations were interpretable in the long-axis view in 28/30 patients and 44/48 controls, while in the apical four-chamber view corresponding numbers were 23/30 and 46/48.

Left atrial dimensions

Apical four chamber view: the left atrial systolic long-axis (30 ± 4.9 *vs* 27 ± 4.2 mm/m², $p < 0.005$) and area (748 ± 167 *vs* 613 ± 214 mm²/m², $p < 0.005$) were increased among the patients. ANP was related to both measurements ($r = 0.27$, $p < 0.05$ and $r = 0.40$, $p < 0.005$; *Fig. 1*).

Right atrial dimensions

Apical four chamber view: the right atrial systolic long axis was increased among patients (30 ± 4.7 *vs* 27 ± 3.4 mm/m², $p < 0.05$) and correlated to plasma ANP ($r = 0.27$, $p < 0.05$) (*Fig. 2*). There was no relation between plasma ANP and right atrial area, which did not differ between patients and controls even when body surface area was taken into account.

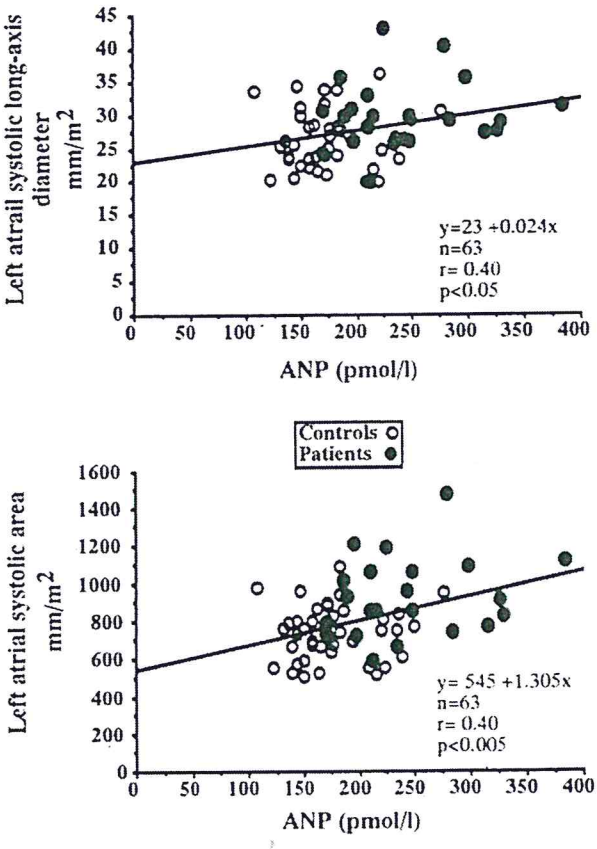

FIG. 1. The relation between plasma ANP and left atrial dimensions.

FIG. 1. Rapport entre le taux plasmatique du peptide natriurétique auriculaire (ANP) et les dimensions auriculaires gauches.

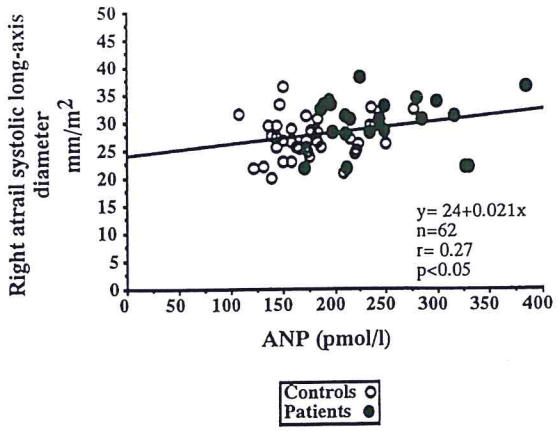

FIG. 2. The relation between plasma ANP and right atrial long-axis diameter.

FIG. 2. Rapport entre le taux plasmatique du peptide natriurétique auriculaire (ANP) et le plus grand diamètre de l'oreillette droite.

Left ventricular dimensions

Parasternal short-axis view at the papillary muscle level: the LV diastolic septal (7.4 ± 2.1 *vs* 5.2 ± 0.7 mm/m^2, $p < 0.0005$) and posterior wall (6.2 ± 2.2 *vs* 5.0 ± 1.0 mm/m^2, $p < 0.0005$) thicknesses were increased in the patients group. The ANP level was related to both measurements ($r = 0.35$, $p < 0.05$ and $r = 0.37$, $p < 0.05$) respectively (*Fig. 3*). ANP was significantly correlated ($r = 0.42$, $p < 0.05$) with the diastolic LV myocardial area, which was increased among the patients (1.325 ± 338 *vs* 998 ± 145 mm^2/m^2, $p < 0.0005$). From the apical two-chamber view: plasma ANP was related to the LV end-diastolic long axis diameter ($r = -0.37$, $p < 0.005$), which was shorter among patients (71 ± 8.9 *vs* 77 ± 8.3 mm, $p < 0.05$) (*Fig. 4*). The plasma ANP level was also related to the LV diastolic ($r = -0.40$, $p < 0.005$) and systolic ($r = -0.42$, $p < 0.005$) areas (*Fig. 5*), which were smaller among patients ($p < 0.005$ and $p < 0.05$, respectively).

Left ventricular systolic function

The ANP concentration was not related to LV systolic function as estimated by ejection fraction, fractional area change, or end-systolic wall stress. However, ANP was inversely related to stroke volume ($r = -0.35$, $p < 0.05$), which was lower among patients (68 ± 25 *vs* 91 ± 30 ml, $p < 0.005$).

Diastolic measurements of LV hypertrophy

The plasma ANP level was significantly related to various measures of LV hypertrophy, which were all increased (p values after semicolon), as the interventricular septal thickness ($r = 0.44$, $p < 0.005$; $p < 0.0005$), LV posterior wall thickness ($r = 0.34$, $p < 0.05$; $p < 0.05$), the wall thickness (septum + posterior wall) ($r = 0.40$, $p < 0.05$; $p < 0.0005$), the wall thickness to cavity dimension ratio ($r = 0.36$, $p < 0.05$; $p < 0.005$) and the LV myocardial index area ($r = 0.42$, $p < 0.05$) ; $p < 0.0005$). The plasma ANP level was inversely related to the end-diastolic volume of the left ventricle ($r = 0.42$, $p < 0.005$), which was found to be decreased ($p < 0.05$).

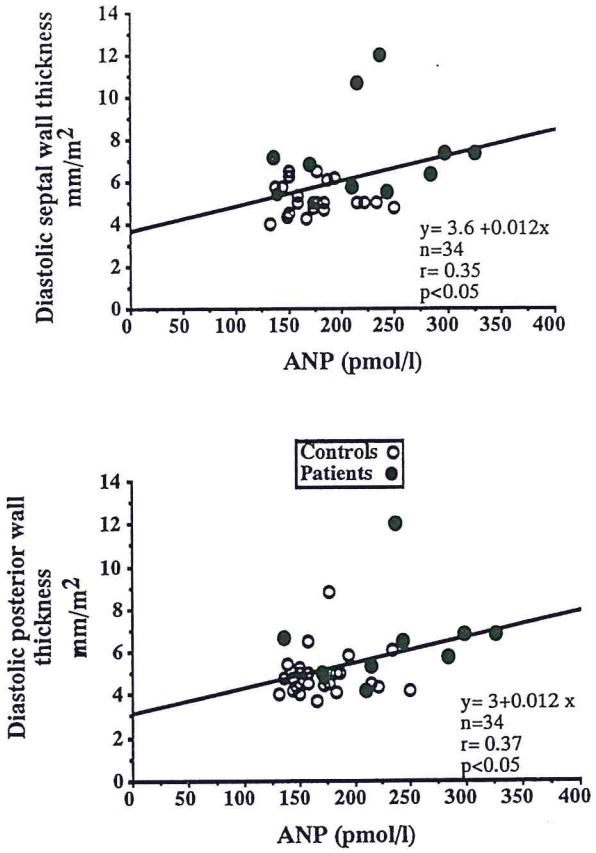

FIG. 3. The relation between plasma ANP and LV wall thickness.

FIG. 3. Rapport entre le taux plasmatique du peptide natriurétique auriculaire (ANP) et l'épaisseur de la paroi du ventricule gauche.

DISCUSSION

The main finding in this study, was a 30% increase in circulating ANP in patients with SScl as compared with controls. Furthermore, a significant correlation was found between ANP and indices of cardiac dimensions and LV hypertrophy.

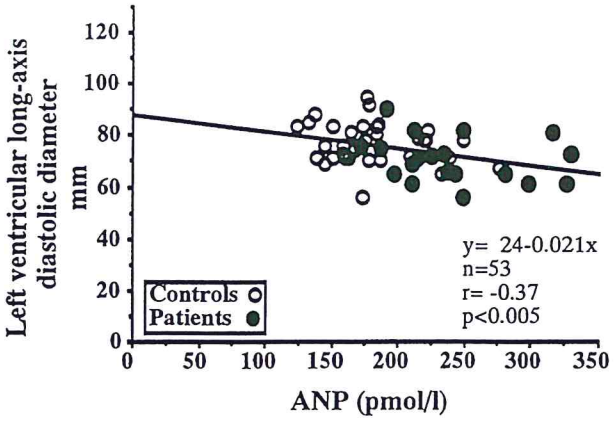

FIG. 4. The relation between plasma ANP and LV long-axis diameter.

FIG. 4. Rapport entre le taux plasmatique du peptide natriurétique auriculaire (ANP) et le plus grand diamètre du ventricule gauche.

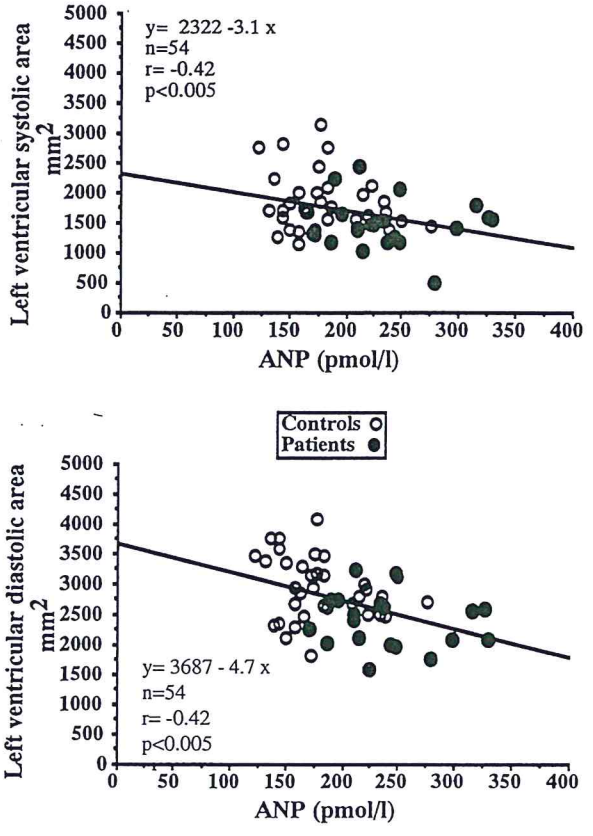

FIG. 5. The relation between plasma ANP and LV area.

FIG. 5. Rapport entre le taux plasmatique du peptide natriurétique auriculaire (ANP) et la surface du ventricule gauche.

Systemic sclerosis is primarily an inflammatory disease. It is well documented in the literature that the main cardiac involvements in SScl is myocardial fibrosis [21] and we were recently able to show that cardiac function [22] as well as myocardial perfusion are abnormal in SScl [23]. Therefore, it was considered to be of interest to determine whether the fibrosed myocardium in SScl is able to synthesize and secrete ANP in relation to altered cardiac dimensions and function as in other types of heart failure.

Several studies in children and adults indicate that ANP release is mediated by cardiac atrial distension [24]. In our patients the ANP level was related to both right and left atrial dimensions. Therefore, atrial distension is a possible mechanism behind the increased level of plasma ANP in SScl as has been reported in other types of cardiac diseases [1, 2].

There is increasing evidence in the literature that ANP is also synthesized and secreted by the ventricles and the ANP concentration might depend on factors within the LV myocardium. An underlying disease causing LV hypertrophy might lead to increased plasma ANP concentration [6, 7, 25]. It has been reported [26] that, whereas atrial stretch or dilatation may be an important stimulus for atrial ANP, ventricular ANP is increased independently of LV dilatation in patients with systolic and/or diastolic dysfunction. In a previous population study, we have reported correlations between venous plasma ANP and indices of LV function in patients with coronary heart disease [27].

Recently we reported LV hypertrophy and diastolic dysfunction [17, 18] as well as LV systolic abnormalities [20] to be common in SScl. In the present study we have found a significant increase in circulating ANP during resting conditions in the same patients with SScl. Interestingly enough, we found ANP to be more closely related to echocardiographic measurements of LV hypertrophy than to LV systolic function. This is reasonable, since we found diastolic dysfunction to be a more important abnormality than systolic dysfunction in SScl [18, 20, 22]. The correlations between the plasma ANP and the echocardiographic measurements of LV hypertrophy might suggest that ANP is also released from the left ventricle. Therefore in SScl, we cannot exclude ventricular ANP to contribute to the increased level of plasma ANP in addition to ANP released by atrial distension. However, since LV hypertrophy with increased LV filling pressure resulted in increased atrial pressure and stretch, it is not possible from the present investigation to determine the relative contribution by the atria and ventricles to ANP release.

Myocardial fibrosis, which is the main cardiac involvement in SScl [21], seems not to severely interfere with ANP production. There are two possibilities. Either, the myocardial disease is a trigger for ANP production/release, and the fibrotic process does not hamper but may promote ANP production. Or the haemodynamic consequences with LV hypertrophy and left atrial distension is the important factor, and the stimulus is so strong that despite low production in fibrotic myocardium the nonfibrotic parts produce an excess of ANP. In the latter case, the ANP secretion takes most

likely place in the atria, and LV hypertrophy causes increased ANP levels only through the mechanism of increased LV filling pressures.

Limitation of the study

Reports from pathoanatomical studies have shown myocardial fibrosis to be prevalent among SScl patients, but we have no biopsy data to support this in our study. The base for aetiological discussion is therefore hypothetical. A stronger evidence for LV secretion of ANP in SScl and its relation to LV function and hypertrophy can only be achieved by ANP and AMP-mRNA analysis in LV biopsies.

CONCLUSION

Circulating ANP is elevated in patients with SScl, in relation to LV hypertrophy but not to LV systolic function. ANP may be useful as a marker of cardiac involvement in patients with SScl. Whether it is the hypertrophied ventricular tissue or distended atrial walls that are mainly responsible for the increased ANP levels remains to be elucidated.

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SUMMARY

Objectives: Were to determine whether plasma atrial natriuretic peptide (ANP) is increased in patients with systemic sclerosis (SScl) and to evaluate its relation to cardiac dimensions and function.

Methods: Using radio-immunoassay, plasma ANP was determined in 30 patients with SScl and 48 age and sex matched controls. The plasma ANP level was related to cardiac structure and function as determined by two-dimensional echocardiography (2-D echo).

Results: Plasma ANP was markedly elevated among patients as compared to controls (239,4 ± 59 *vs* 178.2 ± 36 pmpl/l, $p < 0.0005$). The left atrial long-axis and area were increased, and ANP was directly related to both measurements ($r = 0.27$, $p < 0.05$ and $r = 0.40$, $p < 0.005$, respectively). Plasma ANP was also related to the increased right atrial long-axis ($r = 0.27$, $p < 0.05$). The ANP level was not related to LV systolic function as estimated by ejection fraction, fractional area change and end-systolic wall stress, neither did these measures differ between patients and controls. However, there was an inverse correlation between ANP level and stroke volume ($r = -0.35$, $p < 0.05$), which was lower among the patients ($p < 0.005$). ANP displayed also an inverse relation to LV long axis diameter ($r = -0.37$, $p < 0.005$) and area ($r = -0.42$, $p < 0.005$) as well as to LV end-diastolic volume ($r = -0.42$, $p < 0.005$). Various measurements indicated LV hypertrophy among the SScl patients in spite of a small LV cavity. ANP was directly related to measures of LV hypertrophy, as interventricular septum thickness ($r = 0.44$, $p < 0.005$), LV posterior wall thickness ($r = 0.34$, $p < 0.05$), the wall thickness to cavity dimension ratio ($r = 0.36$, $p < 0.05$), and LV myocardial area ($r = 0.36$, $p < 0.05$). There was no relationship between ANP concentration and heart rate, blood pressure or total peripheral resistance.

Conclusion: These results suggest that the ANP production is not reduced in SScl. Rather, circulating ANP is elevated in relation to the degree of LV hypertrophy. This implies that ANP may be useful for the identification of cardiac involvement in patients with SScl.

Key words :
atrial natriuretic peptide, cardiac dimensions, systemic sclerosis

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