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Functional Explanation for Increased Atrial Natriuretic Peptide in Systemic Sclerosis

ELSADIG KAZZAM, M.D., PH.D., KENNETH CAIDAHL, M.D., PH.D.,* THOMAS HEDNER, M.D., PH.D.† ANDERS WALDENSTRÖM, M.D., PH.D.

Departments of Internal Medicine, Umeå and Uppsala University Hospitals, Umeå and Uppsala, and Departments of *Clinical Physiology and †Clinical Pharmacology, Sahlgren's University Hospital, Gothenburg, Sweden

Summary: We related atrial natriuretic peptide (ANP) among 30 consecutive patients with systemic sclerosis (SScl) and 48 gender- and age-matched controls to the measurements of left ventricular (LV) function as evaluated by echocardiography and external pulse curves to determine possible causative factors for an increased level of plasma ANP. The patients had a markedly elevated plasma ANP level (239.4 ± 59 vs. 178.2 ± 36 pmol/l, $p < 0.0005$), which was not related to LV systolic function, heart rate, or blood pressure. Patients had LV hypertrophy and plasma ANP correlated directly to interventricular septal thickness ($r = 0.41$, $p < 0.005$), LV posterior wall thickness ($r = 0.32$, $p < 0.01$), and wall thickness to cavity dimension ($r = 0.44$, $p < 0.0005$), LV mass index ($r = 0.40$, $p < 0.005$). LV early filling properties were impaired, with reduction of atrial emptying index ($p < 0.0005$) and increased contribution of atrial contraction to LV filling. Plasma ANP correlated to atrial emptying index ($r = 0.41$, $p < 0.0005$) and to apex-cardiographic a wave ($r = 0.28$, $p < 0.05$). Plasma ANP was also related to left atrial dimension index ($r = 0.27$, $p < 0.05$), and was still related to atrial emptying index, but not to left atrial dimension, when considering the degree of LV hypertrophy in multivariate analysis. We conclude that ANP is elevated in patients with SScl. Reduced LV compliance, probably due to increased fibrosis, may cause changes in atrial pressure sufficient to stimulate ANP production without systolic dysfunction as a prerequisite.

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Address for reprints:

Dr. Elsadig Kazzam, M.D., Ph.D.
Department of Internal Medicine
Umeå University Hospital
S-901 85 Umeå, Sweden.

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Introduction

Atrial natriuretic peptide (ANP) is a natriuretic, diuretic, and vasodilating hormone originally found in the atria and secreted in response to atrial stretch in direct relation to atrial pressure.[1–3] ANP influences cardiac function by mechanisms independent of changes in total body fluid volume.[4] Recently, several reports have demonstrated that the cardiac ventricles are capable of synthesizing and storing substantial amounts of ANP in conditions with cardiac hypertrophy[5] and failure,[5–7] including acute myocardial infarction.[7] In congestive heart failure, plasma ANP is directly related to the severity of cardiac dysfunction as judged by New York Heart Association (NYHA) classification.[8] Pharmacologic therapy reducing atrial pressures also results in a rapid reduction of ANP release in patients with cardiac dysfunction.[9–11] In addition to atrial storage of ANP,[12] there is also an increased ventricular synthesis of ANP in the failing heart, leading to further increase in the circulating amount of plasma ANP.[13] In fact, in the failing human ventricle, the ANP content is comparable with that of the atrium, and in animal models of severe LV hypertrophy the total ANP-mRNA content of the ventricle may even markedly exceed that of the atrium.[12] Thus, ANP determination may be useful in the evaluation of patients with cardiac diseases. Systemic sclerosis is a multisystemic disease characterized by fibrotic, inflammatory, and degenerative changes in the skin and in other organs, including the heart.[14] We have previously been able to demonstrate that cardiac function is abnormal in a consecutive series of patients with SScl,[15,16] and such involvement seems to be associated with a poor prognosis.[17,18] As SScl is primarily an inflammatory disease, with fibrosis being a main finding in cardiac involvement, we were interested in determining whether the myocardium—in spite of fibrosis—is able to synthesize and secrete ANP in relation to cardiac dimensions and function as in other types of heart failure.

This study was performed to evaluate whether the level of plasma ANP is increased and to study the relationship between plasma ANP and left ventricular (LV) systolic and diastolic function, as assessed by M-mode echocardiography, in patients with SScl and in normal subjects drawn from the general population register.

TABLE I General characteristics of controls and patients (mean ± SE)

	Controls n = 48	Patients n = 30	p Value
Age (years)	54.9 ± 2.1	54.5 ± 2.4	NS
Sex (female/male)	26/22	15/15	
Height (cm)	172.7 ± 1.1	170.9 ± 1.9	NS
Weight (kg)	73.1 ± 1.8	65.1 ± 2.0	< 0.05
BSA (m2)	1.9 ± 0.03	1.7 ± 0.04	< 0.05
SBP (mmHg)	134.6 ± 2.6	132.9 ± 3.5	NS
DBP (mmHg)	81.6 ± 1.4	78.7 ± 2.1	NS

Abbreviations: BSA = body surface area, SBP = systolic blood pressure, DBP = diastolic blood pressure, NS = not significant.

Material and Methods

Subjects

Thirty consecutive patients (15 men and 15 women; age range 25–77, mean 54.5 years) with SScl according to the American Rheumatism Association (ARA) criteria[19] were studied. The patients were referred to Uppsala University Hospital from hospitals and outpatient units in the Uppsala region. Their disease had been recognized for 5.6 (range 0.5–23) years. For comparison, 48 (26 men and 22 women, age range 25–77, mean 54.6 years), age- and gender-matched control subjects were selected from the general population of Upssala.[15] The general characteristics of the patients and controls are shown in Table I.

Electrocardiography and Pulse Curves

A standard 12-lead resting electrocardiogram (ECG), pulse curves, and phonocardiogram were recorded using a direct writing ink-jet 7-channel Mingograph (Siemens Elema, Sweden) as previously described.[15,16]

Echocardiography

Echocardiography was performed using a Hewlett Packard ultrasound imaging system model 77020A, equipped with a 2.5 or 3.5 MHz phased-array transducer.[16] M-mode echocardiograms, guided by two-dimensional echocardiography, were recorded on strip charts (Honeywell, 8100, dry silver paper) at a speed of 50 mm/s. Investigations were performed with the subjects lying in the left lateral position.

Measurements

M-mode echocardiographic measurements were obtained from three beats, leading-edge to leading-edge method, and the mean was used for further calculations according to the recommendations of the American Society of Echocardiography. Systolic and diastolic time intervals (five beats) were measured by means of a digitizing table-minicomputer system as previously described in detail.[15,16]

LV internal diameter, interventricular septal thickness, and posterior wall thickness were measured at end-systole and end-diastole. Ejection fraction, mean velocity of circumferential fiber shortening, LV meridional end-systolic wall stress (10^3dyn/cm^2) and end-systolic volume index (calculated as end-systolic volume/body surface area) were calculated. As additional measures of contractility, we also calculated the ratio end-systolic wall stress/end-systolic volume index and systolic time intervals.[15] LV diastolic function was evaluated by the following parameters: apexcardiographic a/H ratio, the A2-O interval, the LV mass and ventricular mass index, left atrial diameter (measured at the aortic valve closure and adjusted for body surface area).[16] The left atrial emptying index was obtained from the posterior aortic wall motion as an estimate of early LV filling properties.[16] One investigator carried out all recordings, measurements, and interpretations. Measurement points were agreed upon by two observers and only beats with acceptable or good quality were used for measurements.

Blood Analysis

For the measurement of the plasma ANP, blood samples were drawn 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.[20]

Severity of Skin Lesions

The severity of skin lesions was assessed by a simple scoring system; skin thickening was estimated at 18 anatomical sites by a 4-grade scale; 0 for normal skin and grade 3 for the most severe thickening and induration of the skin. The maximum score was therefore 54.

Statistics

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

Results

General Characteristics

In spite of similar heights, patients weighed less than controls and they had smaller body surface area ($p < 0.05$). Heart rate was found to be increased among the patients (68 ± 1.7 vs. 62 ± 1.4 beats/min, $p < 0.01$). Blood pressure and total peripheral resistance were similar in the two groups.

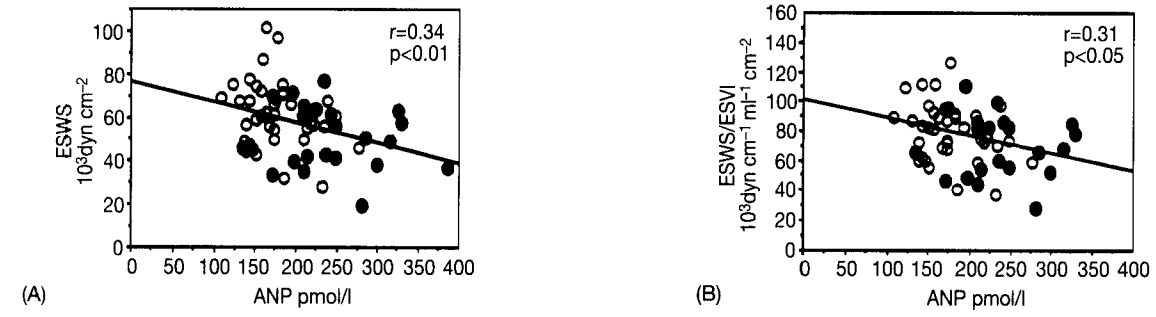

FIG. 1 The relation between atrial natriuretic peptide (ANP) and (A) end-systolic wall stress (ESWS) and (B) end-systolic wall stress to end-systolic volume index (ESVI) ratio. ○ = Controls, ● = patients.

ANP Level

The mean venous ANP concentration was significantly increased in the patient group compared with controls (239.4 ± 59 vs. 178.2 ± 36 pmol/l, $p < 0.0005$).

Relation between ANP and Hemodynamic Data

There was no relation between ANP and heart rate, systolic and diastolic pressures, mean arterial blood pressure, total peripheral resistance, duration of the disease, or scleroderma scoring.

Relation between ANP and LV Systolic Function

In the patient group, the ratio pre-ejection period/LV ejection time (PEP/LVET) was significantly higher ($p < 0.001$) than among controls. There was neither a relation between ANP and PEP/LVET, nor between ANP and indices of the LV contractility (LV end-systolic diameter, stroke volume, ejection fraction, and velocity of circumferential fiber shortening), which were similar in the two groups. However, there was a relation to wall stress: end-systolic wall stress (51 ± 2.8 vs. 63 ± 2.2 10^3dyn cm^{-2}, $p < 0.005$) and end-systolic wall stress adjusted for end-systolic volume index (2.9 ± 0.2 vs. 3.3 ± 0.1 10^3dyn $cm^{-1}ml^{-1}cm^2$, $p < 0.05$) were found to be lower in the group of patients. Plasma ANP was inversely correlated with end-systolic wall stress ($r = 0.34$, $p < 0.01$) as well as end-systolic wall stress adjusted for end-systolic volume index ($r = 0.31$, $p < 0.05$) (Fig. 1).

Relation between ANP and LV Hypertrophy

The plasma ANP correlated to various measures of LV hypertrophy, which were increased among patients compared with controls, such as interventricular septal thickness ($r = 0.41$, $p < 0.005$; 12.2 ± 0.5 vs. 9.9 ± 0.3 mm, $p < 0.0005$), LV posterior wall thickness ($r = 0.32$, $p < 0.05$; 10.1 ± 0.4 vs. 9.1 ± 0.3 mm, $p < 0.05$), LV septal + posterior wall thickness ($r = 0.43$, $p < 0.005$; 0.56 ± 0.03 vs. 0.47 ± 0.02, $p < 0.0005$), wall thickness to cavity dimension ratio, ($r = 0.44$, $p < 0.005$; 0.56 ± 0.03 vs. 0.47 ± 0.02, $p < 0.0005$), and LV mass index ($r = 0.40$, $p < 0.005$; 115.6 ± 6.5 vs. 94.8 ± 3.2 g m^{-2}, $p < 0.005$) (Fig. 2).

Relation between ANP and LV Distensibility

There was a significant correlation between ANP and measurements of LV distensibility. Thus, ANP was correlated with the apexcardiographic a/H% ($r = 0.28$, $p < 0.5$) and left atrial index ($r = 0.27$, $p < 0.05$) which were increased among the patients (11.9 ± 0.9 vs. 9.6 ± 0.6, $p < 0.05$ and 21.9 ± 1.0 vs. 19.3 ± 0.4 mm m^{-2}, $p < 0.005$, respectively) (Fig. 3).

Relation between ANP and LV Early Filling

ANP correlated significantly with left atrial emptying index ($r = 0.41$, $p < 0.001$) which was lower (0.63 ± 0.03 vs. 0.87 ± 0.01, $p < 0.0005$) in the group of patients, indicating impaired early LV filling (Fig. 4).

Relation between ANP and Measurements of LV Relaxation

ANP was not related to the isovolumic relaxation time which did not differ between patients and controls.

Significance of Left Atrial Index and LV Mass Index in ANP Secretion

Multivariate analysis was used to evaluate the role of atrial stretch, and LV hypertrophy in ANP secretion. Left atrial index was taken as a measurement of atrial stretch, and LV mass index as a measurement of LV hypertrophy. Atrial emptying index was also taken into account as a measurement of LV diastolic function. The relation between left atrial index and ANP was abolished when LV mass index and left atrial emptying index were taken into account (Table II).

Discussion

Mechanism of ANP Secretion in Different Cardiac Diseases

The origin and the mechanism of secretion of ANP in different cardiac diseases are not yet fully understood. Previous reports have shown that ANP normally is stored in the atrial myocardium and released in response to distension of the cardiac atria.[1,3,12] However, recent reports have shown that ANP is also synthesized in small amounts in extra-atrial sites, in-

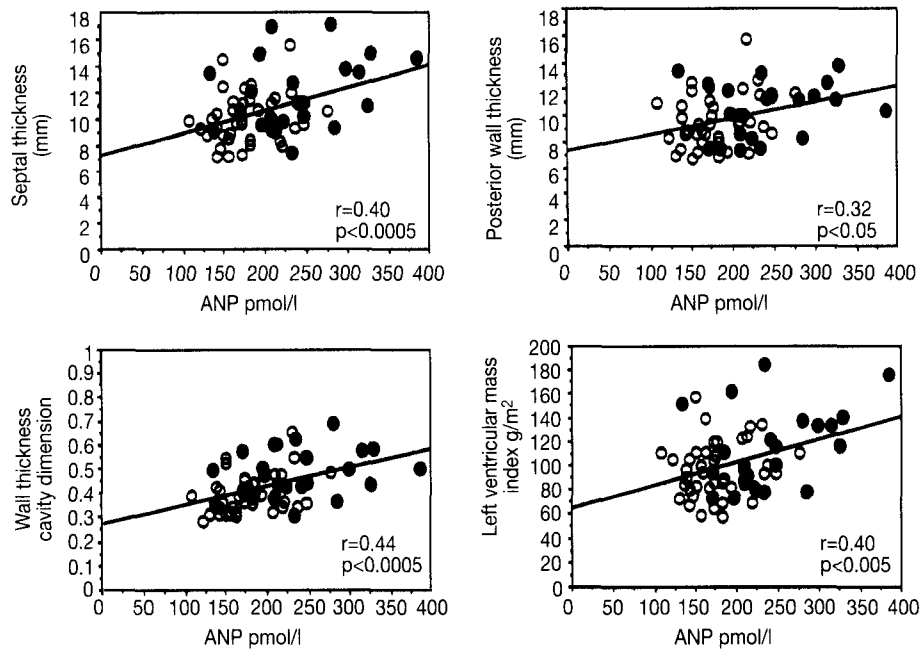

FIG. 2 The relation between atrial natriuretic peptide (ANP) and left ventricular hypertrophy. ○ = Controls, ● = patients.

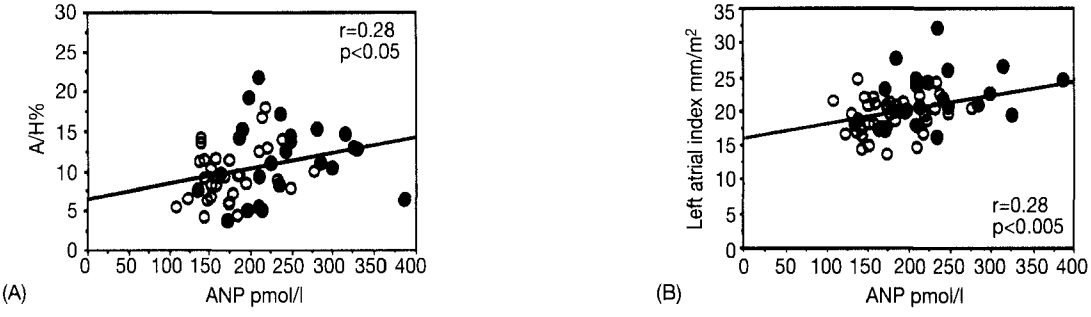

FIG. 3 The relation between atrial natriuretic peptide (ANP) and left ventricular distensibility. ○ = Controls, ● = patients.

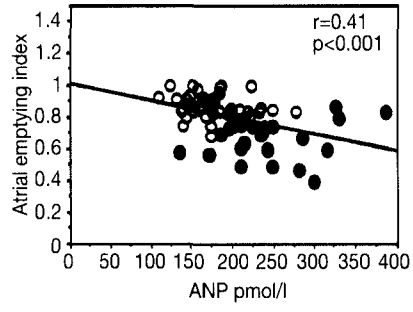

FIG. 4 The relation between atrial natriuretic peptide (ANP) and left ventricular early filling. ○ = Controls, ● = patients.

TABLE II Multivariate analysis of LV mass, diastolic function (atrial emptying index), and LV atrial dimension as predictors of plasma ANP concentration

	Beta coefficient	*t* Value	p Value
Left ventricular mass index	0.552	7.05	0.0201
Atrial emptying index	−127.6	2.55	0.0105
Left atrial index	1.179	1.67	0.4779

cluding the ventricles,[21–23] and in substantial amounts in ventricles with hypertrophy or heart failure in animals.[6, 24–26] The total ANP-mRNA content of the ventricle in animal models of severe LV hypertrophy may even markedly exceed that of the atrium.[12] Edwards *et al.* reported the presence of ANP in the ventricles of autopsied and biopsied humans with heart failure, but not in control autopsied human hearts.[27] Furthermore, Yase[28] and co-workers have also shown that ANP is released in increased amounts into the circulation from the left ventricle in patients with dilated cardiomyopathy compared with con-

trol subjects, and this increased secretion of ANP may represent an important compensatory mechanism in heart failure.[28] Infusion of ANP in patients with congestive heart failure, including those with dilated cardiomyopathy, was found to improve LV function by reducing both the increased preload and afterload.[4, 29, 30] Recently reported data indicate that ANP may be released by different mechanisms in atrial and ventricular myocardial tissue. In atrial myocytes, ANP is released by a regulated granular pathway, while in ventricular tissue there seems to be a direct nongranular release through a constitutive pathway.[5, 13] Thus, plasma ANP may originate from both atrial and ventricular stores in different cardiac diseases.

Possible Factors behind the Increased ANP Level in SScl

In the present study, we were able to demonstrate that the plasma ANP level is increased in SScl by 30% compared with controls. Therefore, it would be interesting to determine the importance of the main factors which could be responsible for the increased production of ANP, that is, atrial distension and LV hypertrophy and/or dysfunction.

Role of Atrial Distension for Increased ANP Level in SScl

The significant correlation between ANP and left atrial index suggests that atrial stretch is a possible mechanism for the release of ANP in SScl from atrial sources, as was previously reported in other cardiac diseases.[1] We also found a weaker but significant correlation between ANP and the apexcardiographic a wave. This was increased among patients, indicating a reduction of LV compliance and consequently a possible increase in atrial pressure. Therefore, both increased atrial pressure and stretch may be stimuli for the increased level of ANP.

Role of LV Systolic Function for Increased ANP in SScl

It was interesting that we did not find any relation between ANP and LV systolic function, which was found to be slightly abnormal in the present study population.[15] Therefore, it is unlikely that plasma ANP level is dependent on LV systolic function in patients with SScl.

Possible Role of LV Hypertrophy and Diastolic Function for Increased ANP Level in SScl

Left ventricular hypertrophy and diastolic dysfunction have been found to be prevalent in patients with SScl.[16] We found a significant correlation between plasma ANP and the measurements of LV hypertrophy, as well as the measurements of LV diastolic dysfunction. However, no relation between ANP and LV end-diastolic diameter was found in either group. The inverse correlation between ANP and atrial emptying index in the present study is in agreement with earlier published findings in patients with heart failure.[31] The significant correlation between ANP and the measurements of LV hypertrophy and diastolic dysfunction does not exclude ventricular contribution to the increased ANP in SScl independent of LV dilation. Edwards *et al.*,[32] by using endomyocardial biopsy, were also able to demonstrate a high prevalence of ventricular ANP in patients with either systolic or diastolic dysfunction independent of chamber dilation.

Possible Explanation for Increased ANP Level in SScl

We found somewhat better correlations between the plasma ANP and the echocardiographic measurements of LV hypertrophy, for example, septal thickness ($r = 0.41$, $p < 0.005$) and LV mass ($r = 0.40$, $p < 0.005$), than between ANP and left atrial size ($r = 0.28$, $p < 0.05$). A somewhat higher correlation than the latter was found between ANP and LV diastolic function as estimated by left atrial emptying index ($r = -0.41$, $p < 0.001$). Furthermore, in a multivariate analysis applied to determine the independent factors for the release of ANP, the relation between ANP and left atrial index was abolished when LV mass index and left atrial emptying index were taken into account. Thus, LV hypertrophy and impaired diastolic function may also be directly responsible for the increased level of plasma ANP in the SScl patients. The lack of correlation between ANP and systolic as well as diastolic blood pressure, mean atrial blood pressure and total peripheral resistance supports this conclusion. Thus, in the present study, the significant correlation between plasma ANP and the measurement of left atrial distension, LV hypertrophy, and diastolic dysfunction suggest that ANP in SScl originates from both atrial and ventricular sources.

Left ventricular hypertrophy usually is a consequence of chronic volume and/or pressure overload of the heart.[33] The mechanism behind LV hypertrophy in these patients is not, primarily, altered loading conditions, but rather myocardial fibrosis, which has been found to be the main component of cardiac involvement in SScl.[34, 35] Thus, myocardial fibrosis per se seems not to interfere with ANP production.

It is important to mention that LV mass index will include both hypertrophy and fibrosis, and the fact that the mass index is increased in SScl could mean that there is an increased fibrosis without an increase in the number of functioning cardiac cells. Pathoanatomical studies have shown myocardial fibrosis to be prevalent among SScl patients, but ethical considerations prevented us from taking myocardial biopsies in this noninvasive study. The basis for etiologic discussion is therefore hypothetical. Stronger evidence for LV secretion of ANP in SScl and its relation to LV function and hypertrophy can only be achieved by ANP and ANP-mRNA analysis in LV biopsies.

Conclusion

We conclude that, in patients with SScl, plasma ANP level is increased without systolic dysfunction as a prerequisite. Early detection, follow-up, and treatment of diastolic dysfunction in SScl are important to avoid the development of clinical heart failure,[36] and perhaps ANP can be used as an index for cardiac involvement in patients with SScl. Further studies are, however, required to confirm this hypothesis.

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