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Atrial natriuretic peptide: relation to left ventricular filling properties in patients with systemic sclerosis ☆

Elsadig Kazzam*[a], Kenneth Caidahl[b], Thomas Hedner[c], Jan Hedner[c], Anders Waldenström[d]

[a]*Department of Internal Medicine, Uppsala University Hospital, S-751 85 Uppsala, Sweden*
[b]*Department of Clinical Physiology,* [c]*Department of Clinical Pharmacology, Sahlgren's University Hospital, Gothenburg, Sweden,*
[d]*Department of Internal Medicine, Umeå University Hospital, Sweden*

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Abstract

To determine the relation between left ventricular filling properties and plasma atrial natriuretic peptide in systemic sclerosis, we evaluated 30 consecutive patients and 48 age- and sex-matched controls. The venous plasma atrial natriuretic peptide was measured by radio-immunoassay. Left ventricular involvement was evaluated by echocardiography and mitral regurgitation was evaluated by Doppler. The patient group had markedly elevated plasma atrial natriuretic peptide as compared to the matched controls (239.4 ± 59 vs. 178.2 ± 36 pmol/l, $P < 0.0005$). We found signs of impaired left ventricular filling properties among the patients, with an increase of the Doppler A-wave velocity and A/E ratio. A relative reduction of early filling was found in spite of some degree of mitral regurgitation in two-thirds of the patients. The plasma atrial natriuretic peptide concentration was related to the A-wave velocity ($r = 0.44$, $P < 0.0005$), the A/E ratio ($r = 0.40$, $P < 0.005$), and also to the degree of mitral regurgitation ($r = 0.43$, $P < 0.005$). The relationship to the A-wave velocity remained when considering possible confounding factors. We conclude that the previously observed fibrotic process in systemic sclerosis does not prevent production and liberation of plasma atrial natriuretic peptide in relation to factors distending the left atrium, such as altered left ventricular filling properties and the presence of mitral regurgitation. However, the moderate relationships between atrial natriuretic peptide and haemodynamic variables indicate that the peptide might also be an independent indicator of cardiac involvement in systemic sclerosis.

Keywords: Atrial natriuretic peptide; Diastolic function; Echocardiography; Left ventricle; Mitral regurgitation; Systemic sclerosis

1. Introduction

Atrial natriuretic peptide is a natriuretic, diuretic and vasodilating hormone originally

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* Corresponding author.

found in the atria and secreted in response to atrial distension [1]. Recently, several reports have demonstrated that the cardiac ventricles are capable of synthesizing and storing substantial amounts of the plasma atrial natriuretic peptide during cardiac hypertrophy [2] and failure [3]. The circulating plasma atrial natriuretic peptide is, in congestive heart failure, directly related to the severity of the cardiac dysfunction, as judged by NYHA classification [4].

The characteristic manifestation of cardiac involvement in systemic sclerosis is myocardial fibrosis, and we were recently able to demonstrate that cold could induce coronary vasospasm causing reversible myocardial perfusion defects in this disease [5]. Autopsy studies [6], and in the present study population echocardiography [7], have shown left ventricular hypertrophy to be prevalent. Using Doppler echocardiography we found that left ventricular filling is impaired and that mitral regurgitation is more common among patients with systemic sclerosis than previously thought [8]. Therefore, myocardial fibrosis, ischemia, and hypertrophy may well explain isolated diastolic dysfunction in systemic sclerosis, described in early reports [9,10]. Interestingly, atrial natriuretic peptide has been shown to influence cardiac function also by mechanisms independent of changes in total body fluid volume [11]. A large number of studies have confirmed a good correlation between the plasma atrial natriuretic peptide level and left atrial pressure and distension [12]. Its relation to left ventricular function is less well described, and particularly it has not been studied in patients with systemic sclerosis. This is of particular interest as collagen infiltration might interfere with myocardial atrial natriuretic peptide synthesis and secretion. This study was performed to evaluate the relationship between plasma atrial natriuretic peptide and cardiac filling properties in patients with systemic sclerosis and normal subjects drawn from the general population register.

2. Material and methods

2.1. Subjects

Thirty consecutive patients (15 men and 15 women; age range, 25–77 years; mean age 54.5 years), with systemic sclerosis according to the American Rheumatism Association (ARA) criteria [13] 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 a mean of 5.6 years (range, 0.5–23 years). The clinical characteristics of the patients are summarized in Table 1. For comparative purposes, 48 age- and sex-matched control subjects (26 men and 22 women; age range, 25–77 years; mean age 54.6 years), were randomly selected from the general population register of Uppsala city. All patients and controls gave their informed consent to parti-

Table 1
The relationship of atrial natriuretic peptide to indexes of left ventricular hypertrophy and filling as well as to mitral regurgitation

	Controls	*P*-value	Patients	Correlation to atrial natriuretic peptide	
				r-value	*P*-value
Septal thickness (mm)	12.2 ± 0.5	<0.0005	9.9 ± 0.3	0.41	<0.0005
Posterior wall (mm)	10.1 ± 0.4	<0.05	9.1 ± 0.3	0.32	<0.01
Left ventricular mass index (g/m^2)	116 ± 7	<0.005	95 ± 3	0.40	<0.005
Left atrial index (mm/m^2)	22 ± 1.0	<0.005	19 ± 0.4	0.28	<0.05
A-wave velocity (m/s)	0.54 ± 0.02	<0.002	0.74 ± 0.07	0.44	<0.0005
E-wave velocity (m/s)	0.69 ± 0.03	NS	0.72 ± 0.07	0.26	<0.05
A/E ratio	0.80 ± 0.04	<0.0005	1.09 ± 0.08	0.40	<0.005
Mitral regurgitation					
Presence (%)	15	<0.001	67	0.32	<0.01
Degree (grade 0–4)	0.1 ± 0.4	<0.0005	1.3 ± 0.3	0.43	<0.005

cipate in this study and the ethical committee has approved the study protocol.

2.2. Blood analysis

For the measurement of the plasma atrial natriuretic peptide, blood was obtained from an antecubital vein at rest, after overnight fasting in the recumbent position (20:00–10:00 h). 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. Atrial natriuretic peptide was measured using a specific radioimmunoassay technique, as previously reported [14].

2.3. Doppler and M-mode echocardiographic recording

A Doppler system (Alfred®, Vingmed A/S) equipped with a 2.0 MHz pulsed and continuous wave Doppler transducer (diameter 13.7 mm) was used to record the mitral flow spectrum and to grade mitral regurgitation semi-quantitatively (grades 0.5, 1, 2, 3 or 4), where grade 1 was assigned to those with a holosystolic but weak regurgitant spectrum [15]. M-mode echocardiographic recordings were obtained by means of a Hewlett Packard ultrasound imaging system, model 77020A, version K with a 2.5 or 3.5 MHz phased array transducer as previously described [7].

2.4. Measurements

From the Doppler spectral recording of the mitral flow profile, we measured the peak velocity of atrial (A) contribution to the left ventricular filling and its relationship to early (E) peak velocity, by means of a computer technique [12]. We measured also the time velocity integrals (area) of the first third of diastole and of the E- and A-waves. From M-mode recordings, wall thickness, left atrial size and left ventricular mass were measured, according to the recommendations of the American Society of Echocardiography as previously described [11].

2.5. Statistical analysis

Data are presented as mean ± S.D. of the mean. The 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.

3. Results

Apart from the lower weight of the patients (65.1 ± 11.0 vs. 73.4 ± 12.6 kg, $P < 0.01$), the general characteristics were similar in both groups. Thus, neither systolic (134.9 ± 2.6 vs. 132.9 ± 3.5 mmHg), nor diastolic (81.4 ± 1.4 vs. 78.7 ± 2.1 mmHg) blood pressure differed between the two groups.

The mean venous atrial natriuretic peptide concentration was significantly higher among the patients as compared to the controls (239.4 ± 59 vs. 178.2 ± 36 pmol/l, $P < 0.0005$). There was no significant relationship between the plasma atrial natriuretic peptide and age, heart rate, blood pressures, total peripheral resistance, duration of the disease or scleroderma scoring.

The patients had left ventricular hypertrophy in comparison with the controls, according to various measures, Table 1. Thus, the left ventricular wall thicknesses, as well as mass, were increased. We found a somewhat closer relationship between atrial natriuretic peptide and the measures of left ventricular hypertrophy, than between the hormone and atrial dimension, Table 1.

Furthermore, the atrial natriuretic peptide concentrations were related to the area of the A-wave ($P < 0.0005$), and also to its height, (Table 1 and Fig. 1) as well as to the area of the E-wave ($P < 0.01$). In spite of the weak positive relationship between the peptide and the early filling velocity measured as the E-wave height (Table 1), or as the left ventricular filling time velocity integral during first third of diastole ($P < 0.0005$), the hormone was clearly correlated to the Doppler A/E ratio (Fig. 1).

Mitral regurgitation was considerably more common (>4 times) among the patients than among the controls, and atrial natriuretic peptide was related to the presence as well as to the degree of regurgitation. However, in multivariate analysis, the natriuretic peptide was related to the A-wave height ($P < 0.005$) independently of mitral

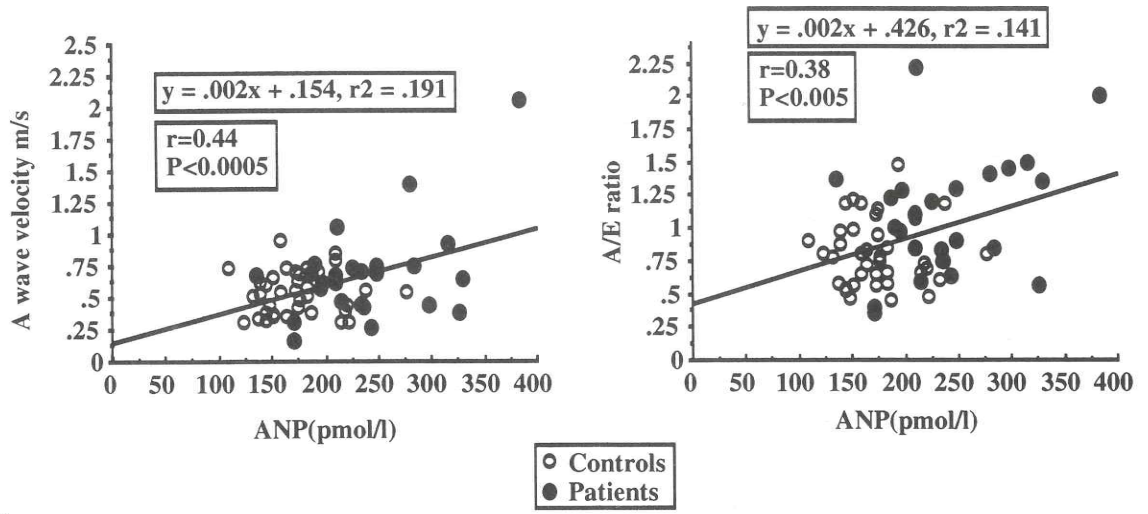

Fig. 1. The relationship between plasma atrial natriuretic peptide and atrial contribution to left ventricular filling as measured by Doppler A-wave height illustrated to the left and by the A/E ratio to the right.

regurgitation, as well as of age, heart rate and systolic blood pressure.

4. Discussion

In the present study we were able to demonstrate the plasma atrial natriuretic peptide in patients with systemic sclerosis to be significantly increased and correlated with the echocardiographic measurements of impaired left ventricular filling, distensibility and hypertrophy.

We have previously shown that impaired left ventricular filling, decreased distensibility and hypertrophy, are common in systemic sclerosis [7,8] and our findings have been confirmed by others [16]. The reduced E/A ratio as well as the increased peak A velocity among our patients indicate an increased atrial contribution to the left ventricular filling, which, together with increased atrial pressure and stretch, may be responsible for the stimulation of atrial natriuretic peptide secretion in systemic sclerosis. This mechanism is suggested by the direct correlation of atrial natriuretic peptide with the peak A velocity and inverse correlation with the E/A ratio.

Atrial distension due to volume overload, atrial tachycardia or mitral obstruction has been shown to increase atrial natriuretic peptide secretion [17]. We found two-thirds of our patients to have mitral regurgitation, which not only distends the left atrium, but also increases the amount of blood entering the ventricle during early left ventricular filling. Therefore, the reduction of early filling velocity in relation to the filling during atrial contraction is probably indicating an even more important diastolic impairment than is directly evident by the Doppler measurements. However, we found the natriuretic peptide to be related not only to impaired left ventricular filling, but also to the presence and degree of mitral regurgitation, which can explain part of the increase in left atrial size in the present study [7,8], as well as part of the increased plasma atrial natriuretic peptide level due to increased atrial wall tension.

The increased wall thickness among patients caused an increase in left ventricular mass index. Left ventricular hypertrophy is usually a consequence of chronic volume or pressure overload of the heart [18]. However, our patients did not differ from the controls regarding blood pressure, preload or afterload. Putative pathophysiologic mechanisms causing the left ventricular hypertrophy may be triggered by small vessels disease or myocardial fibrosis commonly seen in systemic

sclerosis [5]. Atrial natriuretic peptide was found to be significantly related to the measurements of left ventricular hypertrophy. In the human failing ventricle, the natriuretic peptide content is comparable to that of the atrium [19], and in animal models of severe left ventricular hypertrophy, the total atrial natriuretic peptide-mRNA content of the hypertrophied ventricle may even markedly exceed that of the atrium [3]. In the present study we found the plasma atrial natriuretic peptide to be somewhat closer related to echocardiographic measurements of hypertrophy than to the left atrial dimension. This implies the possibility of a ventricular contribution to the increased atrial natriuretic peptide. We were not able to determine the source of the increased plasma atrial natriuretic peptide in this study, since we did not consider intracardiac blood sampling to be ethical. Moreover, it is practically difficult to separate left atrial and left ventricular production of atrial natriuretic peptide, since both chambers drain into the coronary sinus. Proof for left ventricular secretion of atrial natriuretic peptide in systemic sclerosis can only be obtained by atrial natriuretic peptide and ANP-mRNA analysis of left ventricular biopsies. However, we can conclude that the fibrotic process in systemic sclerosis does not prevent synthesis and secretion of atrial natriuretic peptide as in other types of heart failure.

Thus, the plasma atrial natriuretic peptide is increased in systemic sclerosis in relation to left ventricular hypertrophy, diastolic impairment and the presence of mitral regurgitation. The plasma atrial natriuretic peptide level may be used as an index of cardiac involvement in systemic sclerosis since it reflects an integral of factors relating to atrial or ventricular stretch. Although such an indicator of outcome is warranted, because cardiac involvement is the main cause of morbidity and mortality in systemic sclerosis, further studies are needed to elucidate the prognostic value of plasma atrial natriuretic peptide.

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