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Plasma Noradrenaline and Neuropeptide-Y may not be of Primary Importance in the Pathophysiology of Cardiac Involvement in Systemic Sclerosis

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Objective. The present study was performed to measure concentrations of plasma noradrenaline and neuropeptide-Y-like immunoreactivity in relation to cardiac function in patients with systemic sclerosis (SSc).
Methods. Plasma noradrenaline was measured by high performance liquid chromatography and neuropeptide-Y by radioimmunoassay in 30 consecutive patients with SSc and 48 sex and age matched controls. Left ventricular (LV) function was evaluated by Echocardiography.
Results. There were no significant differences between patients and controls in either plasma noradrenaline or plasma neuropeptide-Y. LV dysfunction and hypertrophy were common among patients. Plasma Neuropeptide-Y was related only to systolic function, while noradrenaline was related to both systolic and diastolic function as well as to LV hypertrophy.
Conclusion. Patients with SSc develop different forms of myocardial dysfunction without activation of the sympathetic nervous system as evaluated by plasma noradrenaline and neuropeptide-Y; leaving vascular disease of the heart to be a main candidate.

Key words: diastolic function, Doppler/echocardiography, left ventricle, neuropeptide-Y, noradrenaline, systolic function, systemic sclerosis

Recent studies indicate that neurohumoral activation is observed early in, and is related to asymptomatic left ventricular dysfunction (LV). The balance between the vasodilative-natriuretic and vasoconstrictive anti-natriuretic mechanisms is important for the prevention of cell injury and preservation of cardiac function in different cardiac diseases.

Systemic sclerosis (SSc) is a multisystemic disease characterized by fibrotic, inflammatory, and degenerative changes in the skin and other organs including the heart (1). The clinical expression of myocardial disease in SSc include chest pain, dyspnea, congestive heart failure, and sudden death (2, 3). Cardiac involvement in SSc is a major cause of morbidity and mortality and is an indicator of poor prognosis (4, 5). We have previously demonstrated that LV hypertrophy, diastolic and systolic dysfunction are commonly seen in patients with SSc (6-9). The pathogenesis of cardiac involvement in SSc is as yet poorly understood. Myocardial fibrosis, hypertrophy, and ischemia are possible etiological factors behind myocardial dysfunction in SSc (1, 2, 11–12). Abnormalities of the coronary circulation at the level of the intramyocardial vasculature is a possible cause of myocardial ischemia (13). Plasma noradrenaline levels have long served as a marker of sympathetic nervous activity (14, 15) and has been found to be elevated, not only in patients with overt heart failure (16), but also in individuals with LV dysfunction in the absence of symptoms (17). The sympathetic nervous system is important in controlling vascular tone, heart rate, contractility, and blood pressure (18, 19). In some publications a sympathetic overactivity was reported in patients with SSc (20). In general, myocardial dysfunction leads to activation of multiple neuroendocrine pathways in an attempt to compensate for the depressed cardiac function. Recently, we were able to show that atrial natriuretic peptide (a potent vasodilator) and plasma endothelin-1 (a potent vasoconstrictor) were found to be increased in the present study population (21, 22). Therefore, we were interested to know whether the plasma levels of noradrenaline and neuropeptide-Y are also elevated. If so would be the case, it could have prognostic and therapeutic implications.

Material and methods

Subjects

Thirty consecutive patients (15 men and 15 females, age range 25–77, mean 54.5 years), with SSc according to the American Rheumatism Association criteria (23) were included in the study. Their disease had been recognized for 5.6 (range 0.5–23) years. For comparative purposes 48 (26 men and 22

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females, age range 25-77, mean 54.6 years), age- and sex-matched control subjects were drawn from the general population register as previously described (7). All patients and controls gave their informed consent to participate in this study after approval of the study protocol by the ethics committee.

Blood sampling and analysis

Blood samples were drawn from an antecubital vein at rest in the recumbent position (8 – 10 a.m.) after an overnight fasting. Blood was collected in EDTA coated tubes, immediately put on ice, centrifuged at 4°C for 10 min and aliquots of plasma were rapidly transported and stored at −70°C until the time for analysis. Concentrations of noradrenaline were measured by high performance liquid chromatography and neuropeptide-Y-like immunoreactivity by radioimmunoassay as previously described (24, 25).

Electrocardiography, pulse curves, and Echocardiography

A standard 12-lead rest ECG, pulse curves, and phonocardiograms were recorded using a direct writing ink-jet 7-channel Mingograph as previously described (7, 8). Echocardiography was performed using Hewlett Packard ultrasound imaging system model 77020A, equipped with a 2.5 or 3.5 MHz phased array transducer. M-mode echocardiogram, guided by 2-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 (8). A Doppler system (Alfred®, Vingmed A/S, Trondheim, Norway) was used to record aortic and mitral flow spectrums for the measurements of systolic and diastolic parameters as previously described (7, 9).

Measurements

Echocardiographic M-mode measurements obtained from three beats, leading edge to leading edge method, and the mean used for further calculations, systolic time intervals (five beats), were measured by means of a digitizing table-minicomputer system as previously described (7, 8). The LV internal diameter, interventricular septal thickness, and posterior wall thickness were measured at end-systole and end-diastole (7, 8). LV-ejection time, pre-ejection period, LV isovolumic contraction time, mitral E-point septal separation, ejection fraction, cardiac output, LV meridional end-systolic wall stress (10^3dyn/cm^2), septal fraction thickening, and the time to peak aortic flow acceleration were calculated as measurements of LV systolic function as previously described (7, 8, 12). Apexcardiographic a/H (%) ratio, LV mass index, left atrial diameter adjusted for body surface area, left atrial emptying index, isovolumic relaxation time and – from the Doppler spectral recording of the mitral flow profile –, the peak velocity of atrial (A) contribution to LV filling and its relation to early (E) peak velocity (A/E) and the time velocity integrals (''area'') of the first third of diastole and of the E and A-waves (TVI33%/TA) were calculated as measurements of LV diastolic function as previously described in detail (7-5).

Statistics

Data are presented as mean and standard error of the mean (SEM). Unpaired two-sided t-test was used to compare differences between patients and controls. P values <0.05 were considered significant. Pearson's correlation coefficients were computed to illustrate certain relationships, as indicated. Abnormal values were defined by two standard deviations of the control group.

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 ($P<0.01$). Blood pressure and total peripheral resistance were similar in the two groups.

Plasma noradrenaline and neuropeptide-Y levels

There was no significant difference between patients and controls in the plasma levels (mean, sem) of noradrenaline (0.25 ± 0.02 vs 0.13 ± 0.09 ng/l, $P=0.403$) or neuropeptide-Y (121 ± 3 vs 119 ± 5 pmol/l, $P=0.613$). Furthermore, no correlation was found between the levels of these two peptides ($r=0.17$, $P=$NS). Only one patient had increased level of plasma noradrenaline and two patients had increased levels of neuropeptide-Y (value more than two standard deviations). Two controls had abnormal neuropeptide-Y values, but none of the controls had abnormal value of noradrenaline.

The relation between plasma noradrenaline and neuropeptide-Y levels and hemodynamics

There was no difference in systolic and diastolic blood pressures, mean arterial blood pressure, or total peripheral resistance between patients and

Table I. Relation between plasma NA and NPY and left ventricular systolic function.

	Controls	P	Patients	Correlation to NA		Correlation to NPY	
				r	P	r	p
LVET (ms)	323±4	0.01	303±6	r=−0.30	p<0.05	r=0.40	p<0.01
PEP/LVET	0.30±0.01	p<0.005	0.37±0.02	r=0.23	NS	r=−0.30	p<0.05
ICT/LVET	0.12±0.01	p<0.01	0.17±0.02	r=0.06	NS	r=−0.30	p<0.05
MEPSS/LV dimension (Q)	0.098±0.01	p<0.0005	0.162±0.02	r=0.28	p<0.05	r=−0.40	p<0.005
EF%	0.72±0.01	NS	0.69±0.03	r=0.33	p<0.05	r=0.11	NS
ESWS (10^3dyn cm^{-2})	62.9±2.2	p<0.005	51.3±2.8	r=0.25	p<0.05	r=0.10	NS
Septal Fractional thickening%	43±3	p<0.01	30±4	r=−0.30	p<0.05	r=0.12	NS
Time to Peak acceleration (% of systole)	9.1±0.3	p<0.01	10.6±0.6	r=0.44	p<0.0005	r=0.21	NS
CO Doppler	5.22±0.2	NS	4.9±0.3	r=−0.45	p<0.005	r=0.04	NS

LVET=left ventricular ejection time; PEP=pre-ejection period; ICT=isovolumetric contraction time; MEPSS=mitral E-point septal separation; EF=ejection fraction; ESWS=end systolic wall stress; Co=cardiac out put.

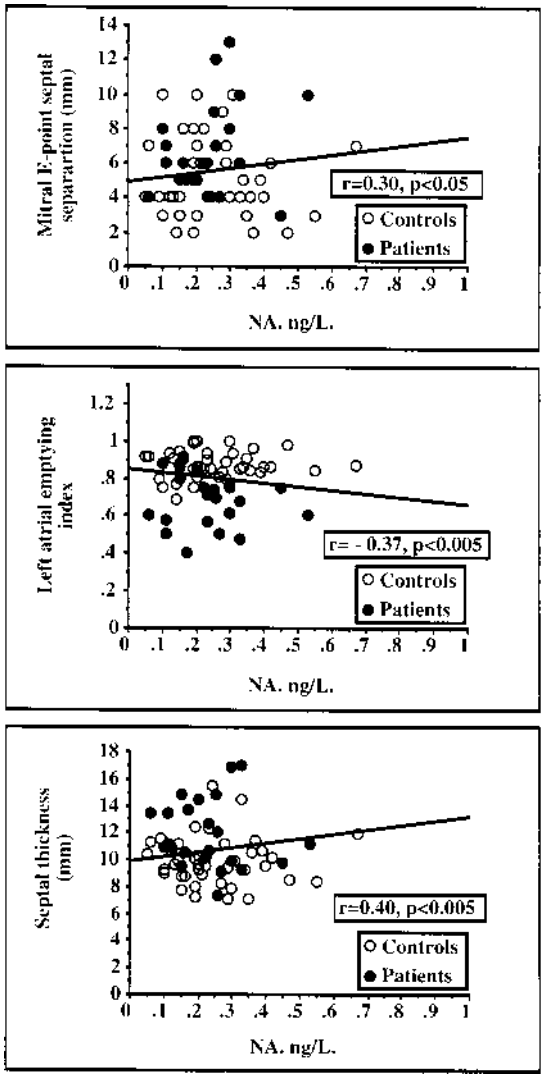

Fig. 1. The relationship between plasma noradrenaline and left ventricular systolic function (mitral E-point septal separation) upper panel, left ventricular diastolic function (left atrial emptying index) middle panel and left ventricular hypertrophy (septal thickness) lower panel.

controls. However, plasma noradrenaline was significantly related to the diastolic blood pressure ($r=0.30$, $P<0.05$) and mean arterial blood pressure ($r=0.25$, $P<0.05$).

The relation between plasma noradrenaline and neuropeptide-Y levels and the duration of disease and the severity of skin lesion

The plasma levels of noradrenaline and neuropeptide-Y were not related neither to the duration of the disease nor to the severity of skin lesions.

The relation between plasma noradrenaline and neuropeptide-Y levels and left ventricular systolic function.

In the patient group, LV ejection time was significantly shorter ($P<0.01$) and the ratios pre-ejection period/LV ejection time as well as isovolumetric contraction time/LV ejection time were significantly higher ($P<0.001$ and $P<0.01$). Plasma nor-

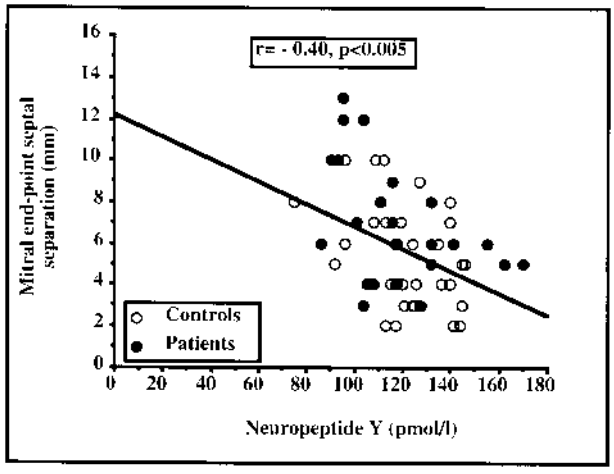

Fig. 2. The relationship between plasma neuropeptide-Y and left ventricular systolic function (mitral E-point septal separation).

Table II. Relation between PNA and PNPY and measurements of left ventricular hypertrophy and diastolic function.

	Controls	P	Patients	Correlation to NA		Correlation to NPY	
				r	P	r	p
Measurements of LV hypertrophy:							
IVSD	9.9±0.3	p<0.0005	12.2±0.5	r=0.38	p<0.005	r=0.11	NS
PWD	9.1±0.3	p<0.05	10.1±0.4	r=04	NS	r=0.12	NS
LVMI (g/m^2)	94.8±3.2	p<0.005	115.6±6.5	r=0.27	p<0.05	r=0.17	NS
Measurements of LV diastolic function:							
Apexcardiographic a/H (%)	9.6±0.6	p<0.05	11.9±0.9	r=0.40	p<0.005	r=0.17	NS
AC-MO	100±8.4	NS	106.2±10.5	r=0.06	NS	r=−0.43	p<0.005
Left atrial index (mm/m^2)	19.3±0.4	p<0.005	21.9±1.0	r=0.14	NS	r=−0.28	p<0.05
Atrial emptying index	0.87±0.01	p<0.0005	0.63±0.03	r=−0.37	p<0.005	r=0.02	NS
A/E	0.80±0.04	p<0.0005	1.09±0.08	r=0.25	p<0.05	r=0.13	NS
TVI (A/E)	0.41±0.02	p<0.005	0.54±0.04	r=0.30	p<0.05	r=0.19	NS
TVI 33%/TA	0.48±0.01	p<0.005	0.41±0.02	r=−0.30	p<0.05	r=0.18	NS

IVSD=inter-ventricular septal thickness end diastole; PWD=posterior wall end diastole; LVMI=left ventricular mass index;AC-MO=isovolumic relaxation time; TVI=time velocity integral; A/E=Doppler early to late velocity; TVI 33% /TA=the first-third filling fraction/ total area.

adrenaline was significantly related to LV ejection time ($r=-0.30$, $P<0.05$) as was the plasma neuropeptide-Y ($r=0.40$, $P<0.01$). Furthermore plasma neuropeptide-Y alone was significantly related to pre-ejection period/LV ejection time ($r=-0.30$, $P<0.05$) and isovolumetric contraction time/LV ejection time ($r=-0.30$, $P<0.05$) (Table I). The echocardiographic mitral E-point septal separation was increased in patients ($P<0.005$), also after adjustment for LV dimension ($P<0.0005$). Both plasma noradrenaline (Fig. 1) and plasma neuropeptide-Y (Fig. 2) concentrations were related to the mitral E-point septal separation ($r=0.28$, $P<0.05$ and $r=-0.37$, $P<0.005$, respectively) even when adjusted to the end diastolic diameter ($r=0.28$, $P<0.05$ and $r=-0.40$, $P<0.005$ respectively) (Table I). Other indices of the LV contractility such as ejection fraction and stroke volume tended to be lower (no significant difference) in patients. The plasma levels of noradrenaline was significantly related to these indices ($r=0.33$, $P<0.05$ and $r=0.25$, $P<0.05$), but they were not related to neuropeptide-Y (Table I). Septal fractional thickening was found to be lower in the patient group (Table I), and was significantly related to plasma noradrenaline ($r=-0.30$, $P<0.05$). The time to peak aortic flow acceleration ($P<0.01$) and also the time to peak aortic flow velocity ($P<0.0005$) were longer in the patient group in spite of no significant difference regarding peak velocity of LV emptying (aortic flow acceleration) as calculated from Doppler recording (Table I). Plasma noradrenaline concentration was significantly related to both measurements ($r=0.44$, $P<0.0005$ and $r=0.30$, $P<0.05$), while plasma neuropeptide-Y was only significantly related to the time to peak acceleration ($r=0.30$, $P<0.05$). Cardiac output as estimated by Doppler was found be significantly related to plasma noradrenaline ($r=-0.45$, $P<0.005$) (Table I).

The relation between plasma noradrenaline, plasma neuropeptide-Y, and measurements of left ventricular hypertrophy.

Measurements of LV hypertrophy (Table II), were increased among patients as compared to controls, such as interventricular septal thickness ($P<0.0005$) and LV mass index ($P<0.005$). The plasma noradrenaline (Fig. 1) but not plasma neuropeptide-Y was related to the septal thickness ($r=0.38$, $P<0.005$) and LV mass index ($r=0.27$, $P<0.05$), (Table II).

The relation between plasma noradrenaline, plasma neuropeptide-Y, and left ventricular diastolic function.

The measurements of LV distensibility increased as evaluated by the apexcardiographic a/H% ($P<0.5$) and left atrial index ($P<0.005$) among the patients. Plasma noradrenaline levels were only related to the apexcardiographic a/H% ($r=0.40$, $P<0.005$) and plasma neuropeptide-Y levels were related to the left atrial index ($r=-0.28$, $P<0.05$), (Table II). The LV isovolumic relaxation time was slightly prolonged among the patients but it did not reach a significant level ($P=0.63$), (Table II). However, plasma neuropeptide-Y was significantly related to LV isovolumic relaxation time ($r=-0.43$, $P<0.005$). Plasma noradrenaline levels significantly correlated (Fig. 1) to the left atrial emptying index ($r=-37$, $P<0.005$), (Table II) which was lower ($P<0.0005$) in the patients group indicating impaired early LV filling. Furthermore, LV early diastolic filling investigated by pulsed Doppler showed an increase

in the Doppler A/E ratio among the patients ($P < 0.0005$). The situation was similar when using time velocity integral (A/E) of early and late atrial filling ($P < 0.0005$). The time velocity integral of the first-third filling fraction /to the total time velocity integral of the diastole was also markedly lower among patients ($P < 0.005$). Plasma neuropeptide-Y levels were not related to any of these measurements of LV filling. On the other hand, plasma noradrenaline levels were related to the Doppler A/E ratio ($r = 0.25$, $P < 0.05$) and significantly to the time velocity integral of early and atrial filling ($r = -0.30$, $P < 0.05$) as well as the first-third filling fraction ($r = 0.30$, $P < 0.05$), (Table II).

Discussion

In the present study there was no evidence for an increased sympathetic nervous system activity in SSc patients as measured by plasma noradrenaline and plasma neuropeptide-Y levels, contrary to what was found by Dessein et. al (20). However when sympathetic nervous system activity was related to cardiac function and LV mass irrespective of disease (both patients and controls included), neuropeptide-Y was related only to systolic function while noradrenaline was related to both systolic and diastolic function as well as to LV mass.

The sympathetic nervous system is an important regulator of cardiac function during physiological conditions and plays a significant role in pathophysiological alterations such as remodelling in various disease processes. Neuropeptide-Y is co-stored with noradrenaline and co-released upon sympathetic activation (26). Neuropeptide-Y is released only in states of high sympathetic activity while noradrenaline is the primary mediator during conditions of low sympathetic activity (27). Such differences in noradrenaline and neuropeptide-Y release and function could possibly explain why plasma noradrenaline and not plasma neuropeptide-Y was related to measurements of LV mass and diastolic dysfunction.

Åkesson and Ekman (28) have studied 43 consecutive patients with systemic sclerosis where plasma neuropeptide-Y levels were significantly higher than in controls. The lack of difference in the present study might be due to different stage and duration of disease. The sympathetic system might be less activated in our patients at rest explaining why no difference in plasma noradrenaline levels was found. Another explanation for the lack of statistically significant elevation in plasma noradrenaline in our patients might be due to a type 2 error due to small number of patients. Moreover, a local release of noradrenaline from the myocardium might be hidden due to dilution in peripheral blood.

For many years, cardiac failure has been regarded as a hemodynamic disorder (29) however, in several reports, concerns were raised about the neurohormonal theory suggesting that heart failure develops and progresses due to activation of endogenous neurohormonal systems (29). Neurohormonal activation is observed already in asymptomatic LV dysfunction although being more pronounced in overt failure. The vasoactive effect of atrial natriuretic peptide is antagonized by vasoconstrictive antinatriuretic mechanisms (30).

Today, heart failure is described in terms of both diastolic and systolic heart dysfunction (31). The end result of a systolic contractile dysfunction is a drop in cardiac output which is counteracted by the Frank-Starling mechanism and activation of the sympathetic nervous system resulting in secondary increase of heart rate and inotropic state (32). This leads to myocardial hypertrophy and activation of the baroreceptor reflex and release of atrial natriuretic peptide (31). In fact, we were able to demonstrate LV hypertrophy in about 43% of patients with SSc (8). Moreover, atrial natriuretic peptide was significantly increased and this increase was related to the measurements of LV hypertrophy and diastolic function rather than to systolic function (21). Based on these findings, we were expecting to see a significant activation of the sympathetic nervous system, but this was not the case. In the present study, the patients had only moderately impaired systolic function (7) while 77% had moderate LV hypertrophy and/or diastolic impairment (8). This might explain the lack of increased sympathetic nervous system activity and is in agreement with the report by Kubo et. al who did not find increased plasma levels of noradrenaline in patients with mild to moderate congestive heart failure (32). Further, our findings indicate that sympathetic nervous activation is not a likely primary event nor a likely etiological factor in cardiac function of this disease.The exact role of sympathetic nervous system in cardiac involvement in SSc needs further studies.

Clinical Implications of the present Study

The present study demonstrate that patients with SSc develop myocardial dysfunction without major elevation of plasma noradrenaline or neuropeptide-Y. Still, mortality in SSc patients is mainly related to cardiac involvement. However, the present study suggests that β-blocker treatment may not be beneficial in patients with SSc. The present findings, together with our previous results about the beneficial effect of ACE-inhibitors on cardiac func-

tion (33), increased levels of atrial natriuretic peptide (21), and endothelin-1 (22) in the present patients group might be relevant when trying to understand the pathogenesis of the cardiac disease and to find suitable therapeutic options. A prospective placebo controlled treatment study is needed to address the question of prolonged survival.

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