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Endothelin may be pathogenic in systemic sclerosis of the heart[1]

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Abstract

We evaluated 30 consecutive patients and 48 age- and sex-matched controls to explore the possibility of a pathogenic contribution by plasma endothelin-1 in the cardiac expression of systemic sclerosis. Venous plasma endothelin-1 was measured by radio-immunoassay and left ventricular function by echocardiography. The patient group had elevated plasma endothelin-1 (2.6±0.2 vs. 1.8±0.1 pmol/l, $P<0.001$), but endothelin-1 was not related to age, heart rate, blood pressure, total peripheral resistance, disease duration or systemic sclerosis score. Endothelin-1 was related to left ventricular hypertrophy in terms of septal thickness ($r=0.33$, $P<0.01$) and left ventricular mass index ($r=0.32$, $P<0.01$). Plasma endothelin-1 was further related to measures indicating reduced left ventricular filling; left atrial emptying index ($r=-0.50$, $P<0.0005$), the first third filling fraction ($r=-0.31$, $P<0.05$) and the time velocity integral of Doppler early/late filling velocity ($r=-0.40$, $P<0.001$). Furthermore, circulating endothelin-1 was related to impaired left ventricular contractility as estimated by pre-ejection period/left ventricular ejection time ($r=0.32$, $P<0.01$) and end-systolic wall stress/volume index ($r=-0.30$, $P<0.05$). We conclude that plasma endothelin-1 is elevated in relation to the degree of left ventricular hypertrophy, diastolic dysfunction and impaired contractility in systemic sclerosis. It may be of pathogenic importance to the cardiac involvement in systemic sclerosis which is not mediated via an increase in systemic blood pressure. It is not yet clear whether our findings are exclusive to systemic sclerosis patients or represent a generalized phenomenon in patients with impaired left ventricular function.

Keywords: Atrial natriuretic peptide; Echocardiography; Endothelin; Systemic sclerosis

1. Introduction

The endothelin family of peptides possesses potent vasoconstrictor properties in both veins and arteries [1]. Endothelin-1 is released by endothelial cells and endothelin mRNA is widely expressed in human tissues. Endothelin-1 binding sites have been demonstrated in blood vessels, the heart and kidneys and there are two subtypes of the endothelin receptor, an E1A and an E1B binding site [2]. The exogenous administration of endothelin to animals results in pronounced systemic, coronary and renal vasoconstriction [3]. Furthermore, circulating concentrations of endothelin were reported to be increased three-fold in congestive heart failure [4], two-fold in essential hypertension [5] and three-fold in cardiogenic shock [6]. Thus, measurements of plasma endothelin-1 may be important in the pathophysiologic evaluation of patients with cardiovascular diseases.

Systemic sclerosis is a multisystemic disease characterized by fibrotic, inflammatory and degenerative changes in the skin and other organs including the

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heart [7]. Cardiac involvement in particular appears to be associated with a poor prognosis and is a major cause of morbidity and mortality [8,9]. We have previously been able to demonstrate an increased prevalence of left ventricular hypertrophy, reduced distensibility, impaired filling properties, as well as slightly reduced contractility, in a consecutive series of patients with systemic sclerosis [10–12], findings which have been confirmed by others [13].

The pathogenesis of cardiac involvement in systemic sclerosis is as yet poorly understood. Myocardial fibrosis and/or ischemia are possible etiologic factors [14,15]. We have previously shown that myocardial perfusion abnormalities are common in systemic sclerosis and that a cold-induced vasospastic process in the myocardial circulation might contribute to the development of the patchy myocardial fibrosis in these patients [16].

The current study was performed to determine whether circulating endothelin-1 may be increased in patients with systemic sclerosis in comparison to carefully selected controls and whether the plasma endothelin-1 level is related to functional cardiac abnormalities in systemic sclerosis.

2. Materials and methods

2.1. Subjects

Thirty consecutive patients (15 males and 15 females; age range 25–77, mean 54.5 years), with systemic sclerosis according to the American Rheumatism Association criteria [17], were studied. Their disease had been recognized for a mean of 5.6 (range 0.5–23) years. For purposes of comparison, age- and sex-matched control subjects were selected from the general population. A sample of 90 age- and sex-matched subjects (3 for each patient) was drawn from the population register kept by the County Census Bureau. All the controls were informed about the investigation protocol and 55 of them consented to participate in the study. Controls were excluded if they were being treated for hypertension, if they had coronary or rheumatic heart disease according to their clinical history or electrocardiogram (ECG), or if they had known renal or pulmonary disease. Controls were not excluded on the basis of current blood pressure levels or right bundle branch block (1 subject). No control had left bundle branch block. Of the 55 subjects willing to participate, 2 were excluded because of previous antihypertensive treatment, 1 because an ECG indicated coronary heart disease, 1 since the clinical history suggested ischemic heart disease, 2 subjects because of a history of rheumatic heart disease and 1 subject due to inadequate recordings. The remaining 48 subjects (26 males and 22 females, age range 25–77 years, mean 54.6 years) constituted a healthy control group. All the patients and controls gave their informed consent to participate in this study and the study protocol was approved by the ethics committee.

2.2. Blood analysis

For the measurement of plasma endothelin-1, blood samples were drawn from an antecubital vein with the patient in the recumbent position (08:00–10:00 h) at rest after 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 stored at −70°C until the time of analysis. Plasma levels of endothelin-1 [18] and atrial natriuretic peptide [19] were measured using specific radioimmunoassay techniques, as described previously.

2.3. Pulse curves

A standard 12-lead resting ECG, carotid pulse tracings and apexcardiograms were recorded using a direct writing ink-jet 7-channel Mingograph (Siemens Elema, Sweden) as described previously [10,11].

2.4. Echocardiography

We used a Hewlett Packard ultrasound imaging system model 77020A, equipped with a 2.5 or 3.5 MHz phased array transducer. The two-dimensional echocardiographic recordings of the routine projections were stored on VHS 0.5-inch video tapes using a Panasonic NV 8100 video recorder. 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 [10,11]. 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 at 50 mm/s from the apical approach as was previously described [12]. Investigations were performed with the subjects lying in the left lateral position.

2.5. Measurements

M-mode echocardiographic measurements were obtained from three beats, using the leading edge to leading edge method, and the mean was used for further calculations according to the recommendations of the American Society of Echocardiography [20].

The left ventricular internal diameter, interventricular septal thickness and posterior wall thickness were measured at end-diastole and end-systole [10,11]. Ejection fraction, mean velocity of circumferential fiber shortening, left ventricular meridional end-systolic wall stress and end-systolic volume index (end-systolic volume/body surface area) were calculated [10]. As additional measures of contractility, we calculated the ratio end-systolic wall stress/end-systolic volume index and measured systolic time intervals [10]. Left ventricular mass and ventricular mass index were calculated from end-diastolic M-mode measurements of left ventricular dimension, septal and posterior wall thicknesses [11]. The left atrial emptying index was obtained from the posterior aortic wall motion as an estimate of early left ventricular filling properties [11]. The left atrial M-mode echocardiographic diameter was measured at the aortic valve closure and adjusted for body surface area [11]. From the Doppler spectral recording of the mitral flow profile, we measured the peak velocity of atrial (A) contribution to left ventricular filling and its relationship to early (E) peak velocity by means of a computer technique [12]. We also measured the time velocity integrals of the first third of diastole and of the E- and A-waves [12]. Total peripheral resistance was calculated as mean arterial blood pressure $\times 1.33$ (60/cardiac output) [10,11]. The left and right atrial areas and long axes were measured from the two-dimensional apical four-chamber view [21]. One investigator carried out all the recordings, measurements and interpretations. Measurement points were agreed upon by two observers and only beats of acceptable or good quality were used for measurements.

2.6. Severity of skin lesions

The severity of skin lesions was assessed by a simple scoring system; skin thickening was estimated at 18 anatomic sites using 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.

2.7. Statistical analysis

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

3. Results

3.1. General characteristics

In spite of being similar in height, the patients weighed less than the controls and had a smaller body surface area ($P<0.05$). Heart rate was increased in patients compared with controls (68±2 vs. 62±1 beats/min, $P<0.01$). Blood pressure and total peripheral resistance were similar in the two groups (Table 1).

3.2. Plasma endothelin-1 level

The mean venous endothelin-1 concentration was significantly increased in the patient group as compared to controls (2.6±0.2 vs. 1.8±0.1 pmol/l, $P<0.0005$) (Fig. 1).

3.3. Plasma endothelin-1 and clinical data

Plasma endothelin-1 was not related to systolic or diastolic blood pressure, mean arterial blood pressure, total peripheral resistance, heart rate, body weight,

Table 1
Plasma ET-1 was only related to heart rate among clinical variables

	Controls	P value	Patients	Correlation to plasma ET-1	
				r value	P value
Systolic blood pressure (mmHg)	135±3	NS	133±4	0.05	NS
Diastolic blood pressure (mmHg)	81±1	NS	79±2	0.04	NS
Mean blood pressure (mmHg)	99±2	NS	97±2.1	0.01	NS
TPR (dynes s cm^{-5})	1604±59	NS	1723±132	0.11	NS
Heart rate (beats/min)	62±1	<0.01	68±2	0.26	<0.05
Age (years)	55±2	NS	55±2	0.02	NS
Height (cm)	173±1	NS	171±2	0.14	NS
Weight (kg)	73±2	<0.05	65±2	0.02	NS
Body surface area (m^2)	1.86±0.03	<0.05	1.74±0.04	0.02	NS
Body mass index (kg m^{-2})	24.3±0.5	<0.01	22.3±0.9	0.06	NS

ET, endothelin; TPR, total peripheral resistance. Values are expressed as mean±S.E.

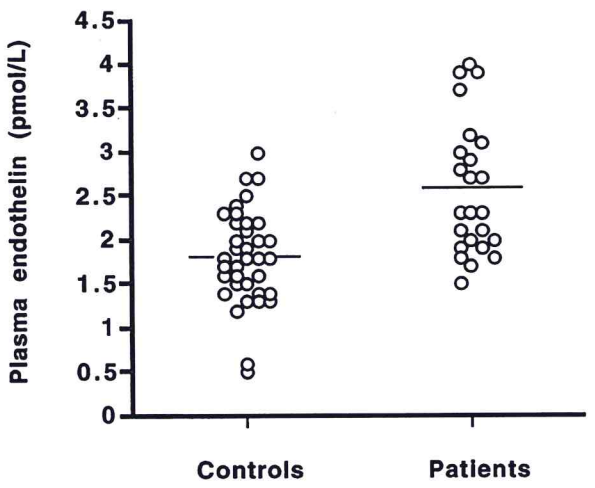

Fig. 1. The plasma level of endothelin-1 among patients and controls.

body surface area, body mass index, duration of the disease or scleroderma score (Table 1).

3.4. Plasma endothelin-1 and left ventricular systolic function

There was a significant relationship between plasma endothelin-1 and the ratio pre-ejection period/left ventricular ejection time (Table 2). Plasma endothelin-1 was also inversely correlated with the end-systolic wall stress adjusted for end-systolic volume index, which was lower among patients. There was no relationship between plasma endothelin-1 and load-dependent echocardiographic indexes of left ventricular contractility (left ventricular end-systolic diameter, stroke volume, ejection

Table 2
The relationship of plasma ET-1 to the echocardiographic indexes of LV systolic function

	Controls	P value	Patients	Correlation to plasma ET-1	
				r value	P value
PEP/LVET	0.30±0.01	P<0.005	0.37±0.02	0.32	P<0.01
ESWS/ESVI (10^3 dyn $cm^{-1}ml^{-1}cm^2$)	3.3±0.1	P<0.5	2.9±0.2	−0.30	P<0.05
Ejection fraction	0.72±0.01	NS	0.69±0.03	0.07	NS
Mean Vcf (circ s^{-1})	1.07±0.03	NS	1.11±0.05	0.09	NS
Stroke volume (ml)	94.5±4.9	NS	80.4±5.0	0.02	NS
EPSS (mm)	4.8±0.3	P<0.001	8.3±1.3	0.24	NS

ET, endothelin; PEP, pre-ejection period; LVET, LV ejection time; ESWS, end-systolic wall stress; ESVI, end-systolic volume index; Vcf, velocity of circumferential fibre shortening; EPSS, E-point septal separation. Values are expressed as mean±S.E.

fraction and velocity of circumferential fiber shortening), which were similar in the two groups.

3.5. Plasma endothelin-1 and left ventricular hypertrophy

The plasma endothelin-1 correlated to various measures of left ventricular hypertrophy, such as interventricular septal thickness and left ventricular mass index (Table 3), which were higher among the patients.

3.6. Plasma endothelin-1 and early left ventricular filling properties

Early left ventricular filling properties were impaired among patients, with a reduction in left atrial emptying index, a reduced Doppler E-wave velocity/A-wave velocity ratio and a reduced first third filling fraction (Table 3). This reduction in early filling was found despite the fact that 2/3 of the patients displayed some degree of mitral regurgitation, which in itself increases early left ventricular filling. Endothelin-1 was inversely related to left atrial emptying index (Fig. 2), the pulsed wave mitral Doppler early/late filling velocity and first third filling fraction (Table 3). Although the time velocity integral of the first third of diastole and the time velocity integral of the early filling/total diastolic flow profile were not significantly lower among

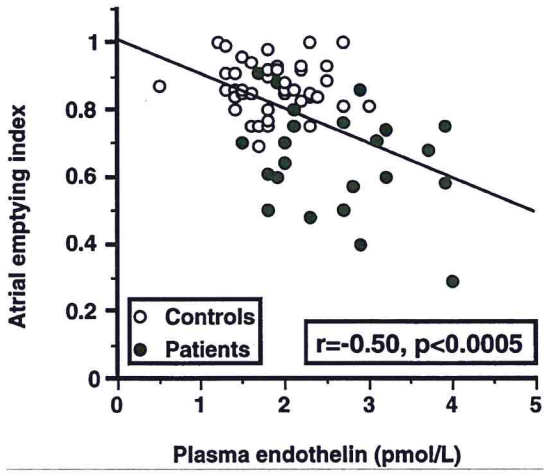

Fig. 2. The relationship between plasma endothelin-1 and left atrial emptying index.

Table 3
The relationship of plasma ET-1 to the echocardiographic indexes of LV hypertrophy and diastolic function

	Controls	*P* value	Patients	Correlation to plasma ET-1	
				r value	*P* value
LV hypertrophy					
Septal thickness (mm)	12.2±0.5	<0.0005	9.9±0.3	0.33	<0.01
Posterior wall (mm)	10.1±0.4	<0.05	9.1±0.3	0.15	NS
LV mass index (g/m^2)	951±3	<0.005	116±7	0.32	<0.01
Early LV filling					
LAEI	0.87±0.01	<0.0005	0.63±0.03	−0.50	<0.0005
VTI-33% (m)	9.53±0.75	NS	8.99±1.17	−0.29	<0.05
VTI-33%/total diastole	0.48±0.01	<0.001	0.41±0.02	−0.31	<0.05
VTI-E/total diastole	0.64±0.01	NS	0.61±0.01	−0.32	<0.01
VTI-E/A	2.86±0.24	<0.05	2.15±0.16	−0.40	<0.005
Velocity E/A	1.33±0.06	<0.05	1.09±0.10	−0.27	<0.05
Mitral regurgitation (%)	15	<0.001	67	0.30	<0.05
Left atrial dimensions/BSA					
M-mode (mm/m^2)	19.3±0.4	<0.005	21.9±1.0	0.14	NS
2D long axis (mm/m^2)	26.5±0.6	<0.005	29.1±1.0	0.40	<0.005
2D area (mm^2/m^2)	748±25	<0.005	913±43	0.36	<0.005
Right atrial dimensions/BSA					
2D long axis (mm/m^2)	27.4±0.5	<0.05	29.6±1.0	0.28	<0.05
2D area (mm^2/m^2)	917±30	NS	929±56	0.10	NS

ET, endothelin; A, atrial contribution to LV filling; BSA, body surface area; E, early part of LV filling profile; 33%, the first third of the diastolic flow profile; VTI, velocity time integral. Values are expressed as mean±S.E., or as % of subjects.

patients, the plasma endothelin-1 level was inversely related to both these measurements (Table 3).

3.7. Plasma endothelin-1 and left atrial dimensions

The atrial short-axis dimension index was larger among patients and plasma endothelin-1 was not related to it. However, the indexed 4-chamber left atrial long axis and area were increased in patients and plasma endothelin-1 was related to these measurements (Table 3).

3.8. Plasma endothelin-1 and right atrial dimensions

The 4-chamber right atrial systolic long axis was increased among patients and plasma endothelin-1 was related to it. However, there was no relationship between plasma endothelin-1 and right atrial area, which did not differ between patients and controls even when the body surface area was taken into account.

3.9. Plasma endothelin-1 and plasma atrial natriuretic peptide

Since plasma endothelin-1 was related to atrial dimensions, we evaluated the possibility of a relationship between endothelin-1 and atrial natriuretic peptide. However, there was no such relationship ($r=0.07$, ns), (Fig. 3). When the controls were considered separately, however, there was a significant inverse relationship.

3.10. Comparison of functional abnormalities related to plasma endothelin-1

Multivariate analysis was used to evaluate the strength of the relationship between plasma endothelin-1 and various parameters, which in univariate analyses indicated a possible influence by endothelin-1 on the heart. Left ventricular mass index was taken as a measurement of hypertrophy, left atrial emptying index as a measurement of left ventricular diastolic dysfunction and the pre-ejection period/left ventricular ejection time ratio as a measurement of left ventricular systolic function. The relationships between plasma endothelin-1 and the pre-ejection period/left ventricular ejection time as well as left ventricular mass index were abolished when the left atrial emptying index was taken into account (Table 4).

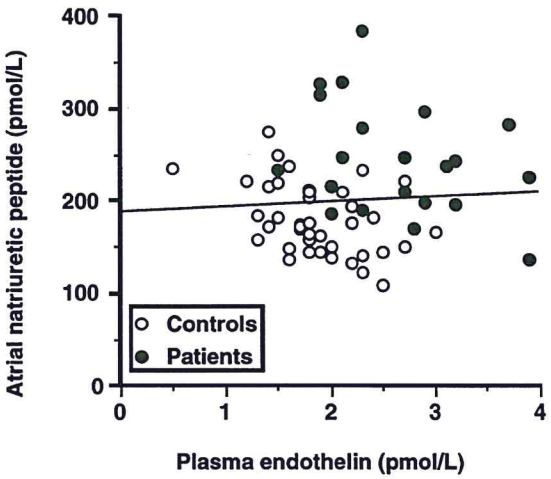

Fig. 3. There was no obvious relationship between plasma endothelin-1 and the plasma concentration of atrial natriuretic peptide among patients ($r=-0.19$, $P=0.38$) or in the combined group of patients and controls. However, a relationship was found among controls ($r=-0.38$, $P=0.01$).

4. Discussion

In this study, we were able to demonstrate a 44% increase in circulating endothelin-1 among patients with systemic sclerosis as compared to controls. Furthermore, the circulating endothelin-1 correlated significantly with the echocardiographic measurements of left ventricular hypertrophy, as well as with the degree of abnormal diastolic and systolic left ventricular properties.

A possible pathophysiologic role for endothelin-1 in various cardiovascular diseases has been proposed [1–6]. The ability of the endothelin family of pep-

Table 4
Multivariate analysis of LV mass, diastolic function (atrial emptying index) and LV systolic function as predictors of plasma ET-1 concentration

	β-coefficient	t value	P value
LV mass index	2.015	1.89	0.1277
Left atrial emptying index	−1.666	3.02	0.0037
PEP/LVET	0.004	1.55	0.0641

ET, endothelin; PEP, pre-ejection period; LVET, LV ejection time.

tides to stimulate mitogenesis in smooth muscle and fibroblasts, coupled with their contribution to the regulation of gene expression and secretion of other neurohumoral mediators, raises the possibility that endothelin-1 may contribute to the development of the cardiovascular disease process in systemic sclerosis [22].

The mechanism behind the increased plasma endothelin-1 concentration in patients with systemic sclerosis is unclear. Microvascular endothelial cell damage has been suggested as a likely cause of increased endothelin-1 levels in systemic sclerosis [23,24], leading to fibrosis [25], the main component of cardiac involvement in systemic sclerosis [14,26–28], through a collagen synthesis-enhancing effect, which may even be dose- dependent [24,29]. Interestingly, Kawaguchi et al. [30] recently reported that the level of endothelin-1 protein was significantly higher in systemic sclerosis fibroblast cultures than in those of normal fibroblasts, as was the expression of endothelin-1 mRNA. They concluded that the endothelin-1 induced by fibroblasts may play a role in fibrosis development and Raynaud's phenomenon of systemic sclerosis. Furthermore, Petersen et al. [31] recently showed that inhalation of cold air during exercise, which increased the degree of regional myocardial ischemia, may involve endothelin-1 in the ischemic response. These latter reports are interesting, since we have recently documented the fact that in patients with systemic sclerosis, cold provocation induced an intermittent vasospastic process causing myocardial perfusion defects secondary to abnormal intramyocardial circulation [16]. The mechanism is not known, but endothelin-1 is a possible key factor as it is a potent vasoconstrictor, which is increased among systemic sclerosis patients.

It is therefore possible to hypothesize that cardiac abnormalities in systemic sclerosis are primarily due to myocardial fibrosis [14,27,28], due at least in part to the increase in fibroblast activity promoted by endothelin-1. As it is a potent vasoconstrictive agent [2] endothelin-1 may contribute to the myocardial ischemia which we have demonstrated to be an important feature of the cardiac involvement in systemic sclerosis [16]. The potential of endothelin-1 to cause myocardial ischemia and vascular damage generating a further release of vasoactive substances including endothelin-1 itself [32] creates a vicious circle. Since endothelin-1 [33] and other vasoactive substances like angiotensin II may promote myocardial hypertrophy, this may, in addition to fibrosis, explain the increase in wall thickness and diastolic dysfunction we have found among our patients with systemic sclerosis [11,12]. We found only a moderate impairment in myocardial contractility, not expressed as a reduction in ejection fraction and related measurements [10]. One possible explanation for this is the positive inotropic action of endothelin-1 on the myocardium [34] and another is the increased wall thickness. An increase in wall thickness in relation to left ventricular dimension reduces the afterload imposed on the ventricle, further alleviated by the presence of a mild to moderate mitral regurgitation in two-thirds of the patients. Measurements accounting for afterload may therefore provide more reliable information on the true status of the myocardium, which is consistent with the data we present.

Some in vitro studies suggest that endothelin-1 may stimulate the release of atrial natriuretic peptide from atrial myocytes [35] and a physiologic antagonism between atrial natriuretic peptide (vasodilator) and endothelin-1 (vasoconstrictor) has been postulated [36]. Since atrial distension and stretch are believed to be the main stimuli for atrial natriuretic peptide secretion, a relationship between plasma endothelin-1 and atrial natriuretic peptide can be expected. In the present study, we found a highly significant relationship between plasma endothelin-1 and measurements of atrial distension (left atrial long axis diameter and area as well as right atrial long axis diameter). In the same patient group, we have previously found a significant relationship between these atrial measurements and atrial natriuretic peptide [18]. There was a (possibly random) relationship between atrial natriuretic peptide and endothelin-1 among controls (Fig. 3). However, we did not find any relationship between plasma endothelin-1 and atrial natriuretic peptide among patients or in the complete study population (Fig. 3). This is in agreement with published data. For example, McMurray et al. [1] did not find any relationship between atrial natriuretic peptide and plasma endothelin-1 in patients with congestive heart failure and Shichiri et al. [37] also found no relationship between plasma atrial natriuretic peptide and endothelin-1 in patients with renal failure. However, the relationship between

plasma endothelin-1 and atrial distension requires further investigation.

Since endothelin-1 is a potent vasoconstrictor in the peripheral vasculature in systemic sclerosis as well [29], it was surprising to find that high circulating endothelin-1 was not related to an increase in peripheral resistance and elevated blood pressure. However, in an animal model of ischemic heart failure, vascular, but not myocardial, endothelin receptor binding and function was downregulated [38]. Thus, in response to high circulating endothelin concentrations, there is a downregulation of the vascular endothelin-1 response, resulting in a lack of peripheral vascular responses.

We have found a beneficial effect by ACE-inhibitors (captopril) on both systolic and diastolic dysfunction in patients with systemic sclerosis, most probably as a result of vasodilatation at the micro circulatory level, leading to an improvement in myocardial perfusion by decreasing the circulating angiotensin II level or as a result of a direct effect on the local angiotensin system in the heart [39]. It has recently been shown that endothelin-1 is produced by cardiomyocytes [32,40]. Like ACE-inhibitors, endothelin-1 converting enzyme inhibitors and receptor antagonists may have therapeutic potential as vasodilators in the near future [41,42] and it seems likely that they could be particularly suited to the treatment of systemic sclerosis.

Further studies are needed to elucidate the mechanism responsible for the elevation of the plasma level of endothelin-1 and its pathophysiologic importance in systemic sclerosis, as well as its possible role as a marker of involvement or a predictor of the prognosis in systemic sclerosis.

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