Glucocorticoid effects on myocardial performance in patients with systemic sclerosis

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Abstract

Objective

Myocardial inflammation and fibrosis are common autopsy findings in systemic sclerosis (SSc) and, although symptomatic cardiac involvement occurs less often, current therapies remain empiric and do not prevent or modify its course. In this open, uncontrolled study we assessed the short-term effects of glucocorticoid administration on myocardial performance in patients with SSc in the absence of clinically overt cardiac disease.

Methods

Resting radionuclide ventriculography with ^{99m}Tc was performed before and 20 days after the administration of prednisolone, 20 mg daily, in 32 patients with SSc without clinically evident myocardial dysfunction at rest; 13 and 19 patients with systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA), respectively, were studied in parallel as controls.

Results

The mean left ventricular ejection fraction (LVEF) value at baseline was 59% in the SSc group; similar values were found for the SLE (61%) and RA (59%) groups. An impaired LVEF (i.e., < 50%) was found in 6 patients with SSc and in 1 patient with SLE. Prednisolone administration resulted in a significant percent improvement in the baseline LVEF (mean 18%, p = 0.0001) in the SSc group; this improvement was greater in the patients with diffuse SSc than in those with limited skin disease (27% vs 10%, p = 0.02). The improvement was most prominent in the 6 patients with an initial impaired LVEF. No significant improvement was observed in the SLE or RA control groups. The linear trend between the individual baseline LVEF values in patients with SSc and their percent changes after treatment (r^2 = 0.55, p: 0.00001) showed that the lower the initial LVEF, the greater the improvement caused by prednisolone. The degree of LVEF improvement was also associated with the individual erythrocyte sedimentation rate values and serum IgG concentrations at baseline. Prednisolone-induced changes in LVEF were not associated with any changes in blood pressure, heart rate, blood, plasma, or red cell volumes.

Conclusion

Glucocorticoid administration may improve myocardial performance in some patients with SSc. Although further double-blind controlled studies of the long-term effects are warranted, such treatment may be useful in those patients with SSc and documented low LVEF, if they are kept under careful observation for objective improvement.

Key words

Prednisolone, systemic sclerosis, radionuclide ventriculography, ejection fraction, cardiac involvement, systemic lupus erythematosus, rheumatoid arthritis.

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Introduction

Cardiac involvement manifesting as myocardial disease, pericardial disease, conduction system defects or arrythmias is a leading cause of morbidity in patients with SSc and most of the patients who develop clinical manifestations of myocardial involvement die within 5 years (1,2). Pathology studies show that myocardial inflammation and fibrosis is found in the majority of autopsied patients with SSc (3-5), but symptomatic myocardial dysfunction at any time during the course of the disease is present in approximately 20% of patients (1,2). However, clinically unapparent cardiac involvement can be demonstrated frequently by echocardiographic and/or radionuclide imaging studies in SSc (1,2, 6, 7). Diastolic and/ or systolic left ventricular dysfunction may occur at some point in the disease, probably as a result of progressive fibrosis (2,8). On the other hand, left ventricular dysfunction may be due in part to coronary vasospasm and myocardial ischemia (8-11).

Whether structural or functional, vascular abnormalities initiate and/or prevail in the chronic inflammatory process of myocardial damage and fibrosis and the subsequent development of clinical disease remains unclear (2). Although early identification and treatment is crucial, aside from the standard treatment of congestive heart failure, all therapies for cardiac involvement in SSc including vasodilators and immunosuppressive agents remain empiric and are essentially symptomatic at present (1, 2, 12).

Glucocorticoid administration in SSc is currently indicated in isolated cases of severe skeletal and myocardial muscle disease, and especially in those overlapping with polymyositis, in cases of severe serositis, as well as in fibrosing alveolitis combined with cyclophosphamide with variable results (2, 12, 13). Patients with SSc in these situations may benefit from the potent anti-inflammatory, anti-fibrosing and immunomodulatory effects of glucocorticoid administration (14). Therefore, in view of the lack of current specific therapies to prevent or modify the course of cardiac involvement in SSc, we aimed to test the hypothesis that the short-term administration of relatively low doses of prednisolone may beneficially affect the myocardial performance in SSc patients who are at a stage prior to the (possible) development of clinically overt cardiac involvement. Resting radionuclide ventriculography with ^{99m}Tc, which represents the best non-invasive procedure for the assesment of myocardial (LV systolic) performance (15), was used. Disease control patients with systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA) were studied in parallel.

Patients and methods

Patient population

Patients with SSc and age- and sex-matched control disease patients with SLE and RA according to the respective ACR criteria (16-18) without clinically evident cardiac disease attending our clinics, from whom informed consent was obtained, were enrolled in this open study. None of these patients had clinical evidence of polymyositis or was positive for anti-Jo1 antibody. All patients, except for one patient with SSc, had normal creatine phosphokinase (CPK) serum levels; the one SSc patient who had elevated CPK levels (by 40%) underwent a muscle biopsy and electromyography studies with normal findings. Patients with known coronary artery disease, valvular heart disease, atrial fibrillation, current serositis, severe arterial hypertension, severe pulmonary disease, renal failure, thyrotoxicosis or diabetes mellitus, as well as patients on diuretics or cardiotonic medication were excluded.

Thirty-two patients with SSc (27 women, 5 men), aged 18-73 years (mean: 51 years) were studied. Increased titers of antinuclear antibodies were present in 28 out of 32 patients. There were 15 patients with diffuse SSc (19), 11 of whom were tested positive for anti-topoisomarase-I antibodies, and 17 patients with limited skin disease, 12 of whom tested positive for anticentromere antibodies. The disease duration, i.e. from the onset of the first symptom attributed to SSc (Raynaud's phenomenon in 30 patients and swollen

hands in 2 patients), varied from 1 to 22 years (mean± SD: 6.0 ± 4.9 years). The mean disease duration was 2.7 and 8.8 years in patients with the diffuse and the limited form of SSc, respectively. Eleven of 15 patients with diffuse SSc and 6 of 17 with the limited form had early phase disease, i.e. less than 3 years, and less than 5 years, respectively. Treatment within 3 months prior the study included only D-penicillamine, NSAIDs, acetaminophen, ranitidine, and nifedipine.

The disease control group included 13 patients (12 women, 1 man) with SLE of 1 to 5 years duration (mean ± SD: 2.3 ± 1.4 years), aged 19-69 years (mean: 41 years), and 19 patients (18 women, 1 man) with RA of 0.5 to 20 years duration (mean ± SD: 6.2 ± 5.5 years), aged 17-70 years (mean: 55 years) who were studied in parallel. The treatment of these patientst included hydroxychloroquine, azathioprine, NSAIDs, acetaminophen and ranitidine; 7 SLE and 6 RA patients were also receiving oral prednisolone at daily doses ≤ 7.5 mg (mean 4.2 mg).

Protocol

All patients first underwent a detailed clinical examination, chest x-ray, electrocardiogram, and laboratory measurements including hematological, biochemical and serological examinations. Resting equilibrium radionuclide ventriculography was performed at baseline, with ^{99m}Tc pertechnetate labelled autologous red blood cells (20). Briefly, stannous ion (sodium pyrophosphate) was used as the reducing agent. 20 g stannous ion per kg body weight was injected intravenously as a bolus, followed by 800 MBq of ^{99m}Tc pertechnetate 20 minutes later (effective dose equivalent 7mSv, 0.0085 mSv/MBq).

Patients were then positioned supine on the imaging couch of an Anger scintillation camera, with the left arm above the head, standard electrocardiogram leads connected to the trigger device, and instructed to lie still. Prior to starting data acquisition, the heart rate was sampled for 20 seconds and the mean RR interval for sinus rhythm determined. Any beats greater than 10% longer or shorter than the mean RR interval were rejected. The camera was then set in the frame mode, 32 frames per view, peaked at 140keV with a 20% window and a 64 x 64 matrix. A low-energy general purpose collimator was used. 5000 kcounts per view were obtained. Imaging was performed at the left anterior oblique view, with 15° caudal tilt, and repeated at the anterior projection. Images were scaled to the hottest pixel and displayed on a colour scale to represent the count density. Spatial and temporal filtering was applied. Identification of the edges of the blood pool at end-diastole and end-systole was performed manually. The first frame of the study was taken as end-diastole and the frame with the lowest left ventricular count as end-systole. Background correction was applied and a time-activity curve for the left ventricle at each frame in the cardiac cycle was generated. Since a direct relation exists between ventricular activity and its volume, the left ventricular ejection fraction was calculated by dividing the background-corrected difference in end-systolic and end-diastolic counts, by the end-diastolic counts (21).

All 64 patients received 20 mg of prednisolone orally at a single morning dose for the following 20 days, in addition to all other medications. According to the experimental design, placebo-treated or non-treated patients were not studied. Doses of medications, including nifedipine (10, 22), remained stable during the 20-day period. Then, a second radionuclide LVEF measurement was performed, always by the same person, using an identical view. The heart rate and blood pressure were recorded immediately prior to each radionuclide examination.

In addition, blood volumes were measured by a radioimmunoassay method using ^{51}Cr labeling of red cells and dilution analysis, according to the standard protocol, in a representative subgroup of 11 patients with SSc. These were randomly selected from those patients who were willing and able to undergo these procedures. There were 5 patients with diffuse SSc (4 with early disease) and 6 patients with the limited form (3 with early disease). This subgroup was comparable to the whole group of SSc patients in terms of age (mean of 48 years) and duration of the disease (mean of 6.0 years).

Statistical analysis

Analysis of the results was performed using the t-test for either paired or unpaired variables where appropriate. To search for associations between the individual percent change in each patient's LVEF caused by prednisolone administration and various parameters, including the baseline LVEF, we used multiple and simple linear regression analysis.

Results

Baseline LVEF in patients with SSc, SLE and RA

The initial evaluation of patients enrolled in the study confirmed the absence of clinical manifestations of cardiac disease at rest, as well as of advanced electrocardiographic abnormalities in all of them. Among the SSc patients in particular, none had symptomatic cardiac disease, as defined previously (7). Baseline determination of LVEF at rest by radionuclide ventriculography disclosed abnormally low values, i.e. < 50%, in 6 of 32 patients with SSc (4 with diffuse and 2 with limited disease) and in 1 patient with SLE; all patients with RA had normal LVEF values. A LVEF value lower than 50% was considered abnormal based on the parallel study of 14 healthy individuals matched for age and sex (% mean ± SD: 61 ± 5, range 52% to 70%), as well as on published standard values (15, 21) and previous studies of healthy individuals performed in our laboratory (23).

Although the patients' LVEF values at baseline covered a wider range than those routinely observed in healthy individuals, the mean LVEF values in the three patient groups (Table I) were normal and did not differ between patients with SSc, SLE, and RA. The subgroup of patients with the diffuse form of SSc had a lower mean LVEF (56 ± 11) than patients with limited SSc (62 ± 8), but this difference did not reach significance.

Table I. Left Ventricular Ejection Fraction (LVEF) values (% mean ± SD, range) at baseline, after 20 days of prednisolone administration (20 mg, daily), and mean percent improvement of LVEF in patients with SSc, SLE, and RA

	SSc, all (n=32)	SSc, diffuse (n=15)	SSc, limited (n=17)	SLE (n =13)	RA (n=19)
Baseline	59 ± 10 (34 to 71)	56 ± 11 (34 to 66)	62 ± 8 (45 to 71)	61 ± 8 (44 to 73)	59 ± 8 (50 to 82)
After treatment	68 ± 8* (45 to 82)	69 ± 10 * (45 to 82)	67 ± 7 † (52 to 74)	63 ± 8 (45 to 82)	61 ± 8 (43 to 80)
Percent improvement	18 ± 20	27± 19	10± 17	3 ± 11	4 ±14

* p: 0.0001 versus baseline by paired t-test; † p: 0.02 versus baseline by paired t-test.

Changes of LVEF following prednisolone administration in patients with SSc, SLE and RA

A second radionuclide ventriculography at rest was repeated after 20 days of prednisolone administration in all patients. The resting LVEF increased variably in the majority of SSc patients (27/32), as well as in the majority of SLE patients (8/13), and patients with RA (13/19) following prednisolone administration. Two SSc patients had identical LVEF values before and after treatment, while LVEF decreased, remaining within the normal range, in 3 patients. These particular patients had advanced (i.e., > 5 years duration) limited SSc; one had an initial LVEF of 54 that decreased by 3.7%, while the other two patients had initial LVEF measurements of 70 and 67 that decreased by 5.7% and 13.4%, respectively. Although a slight reduction in LVEF values after prednisolone administration was also observed in 5 patients with SLE, none of the post-prednisolone values were abnormal. Three RA patients had slightly abnormal LVEF values after treatment. Statistical analysis by paired t-test revealed that prednisolone administration resulted in a significant percent increase in the baseline LVEF only in the group of SSc patients (mean 18%, p = 0.0001), and not in the SLE (mean of 3%, p = NS) or RA (mean of 4%, p = NS) patients (Table I). To assess whether even the low doses of prednisolone that 13 disease control patients had been receiving prior to the study did not affect these findings, a separate analysis excluding these 13 patients was performed revealing similar results. Prednisolone-associated improvement was most prominent in the subgroup of patients with diffuse skin involvement (mean 27%, p = 0.0001 by paired t-test versus baseline) compared to patients with limited skin disease (mean of 10%, p = 0.02 by paired t-test versus baseline), and this was a significant difference (p = 0.02, by unpaired t-test). Significant side-effects, including exacerbation of Raynaud's phenomenon and scleroderma renal crisis (24), were not observed during the 20-day period of prednisolone administration in any of the studied patients.

Prednisolone effects in patients with SSc and low baseline LVEF

The subgroup of the 6 SSc patients with low LVEF was not different to the whole SSc group in terms of age (mean:53 years), or disease duration (mean ± SD: 7.2 ± 4.5 years). As depicted in Figure 1, the highest percent increases of LVEF following prednisolone administration were observed in all 6 SSc patients with an impaired initial LVEF. In this particular subgroup the mean LVEF increased significantly from 42% ± 5% to 63% ± 11% (mean ± SD at baseline and after treatment, respectively, p:0.002, by the paired t-test).

Correlations of prednisolone-induced individual changes of LVEF in patients with SSc

To evaluate the effects of prednisolone administration on myocardial performance in patients with SSc the individual percent changes of baseline LVEF caused by prednisolone treatment were compared to the baseline LVEF values. As shown in Figure 1, the linear trend between the individual LVEF values at baseline and their changes after treatment indicated that the lower the initial LVEF, the greater the improvement caused by prednisolone. This trend was highly significant within the group of SSc patients as a whole (p = 0.00001), as well as within the subgroups of patients with the diffuse (p = 0.003) or

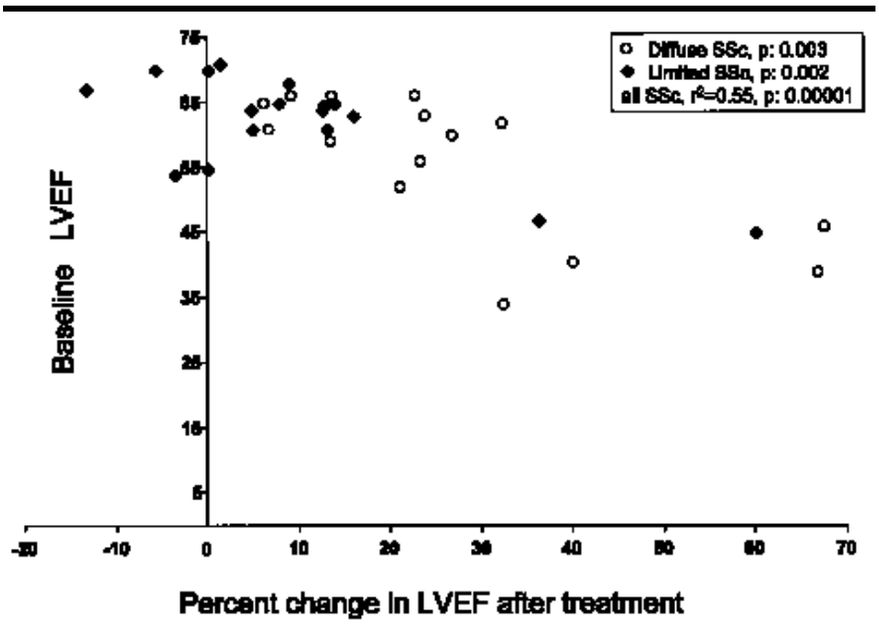

Fig. 1. Percent changes in the left ventricular ejection fraction (LVEF) following prednisolone administration correlate inversely to the baseline LVEF values in patients with SSc.

Table II. Changes in heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP) (n=32), as well as in blood volume (BV), plasma volume (PV) and red cell volume (RCV) (n=11) at baseline and after 20 days of prednisolone administration (20 mg, daily) in patients with SSc.

	Baseline mean ± SD	After treatment mean ± SD	p
HR (beats/min)	80 ± 14	83 ± 16	NS
SBP (mm Hg)	126 ± 17	131 ± 21	NS
DBP (mm Hg)	79 ± 9	79 ± 10	NS
BV (ml)	3753 ± 814	3555 ± 1243	NS
PV (ml)	2353 ± 464	2244 ± 749	NS
RCV (ml)	1400 ± 391	1301 ± 541	NS

* Comparisons were made by the paired t-test. NS denotes non-significant.

the limited form (p = 0.002) of the disease (Fig. 1).

Multiple regression analysis for possible associations between individual changes in LVEF and the patients' age, disease duration, and various biochemical measurements performed at baseline, including CPK serum levels (25), did not reveal significant findings. Given that the mean baseline erythrocyte sedimentation rate (ESR) values at 1st hr were comparable between the groups of patients with SSc, SLE and RA (mean ± SD = 50 ± 10, 59 ± 29, 61 ±35, respectively), we used the individual baseline values of ESR as a surrogate marker of the inflammatory response to assess a possible relationship between ESR and the prednisolone-induced changes in LVEF observed in SSc. Linear regression analysis revealed that the degree of prednisolone-associated improvement of LVEF in patients with SSc was significantly associated with the baseline ESR, showing that the higher the ESR before prednisolone administration, the greater the prednisolone-induced increase in LVEF. This association was highly significant within the whole group of SSc patients (p = 0.0009), as well as within the subgroups with the diffuse (p = 0.005) or limited form (p = 0.02) of the disease. In addition, prednisolone-induced changes in LVEF were associated significantly with the individual serum IgG concentrations measured at baseline only within the whole group of SSc patients (p=0.01), and not within the subgroups of diffuse and limited disease.

LVEF changes were not associated with changes in the heart rate or blood pressure measurements within the 20-day period of treatment (Table II). To evaluate whether possible prednisolone-induced alterations in the blood volume could account for the observed changes in LVEF, blood volumes were determined in a representative subgroup of 11 patients with SSc, including 3 patients with initial low LVEF, before and after prednisolone administration. Mean baseline LVEF values and their changes after treatment did not differ between this subgroup and the whole SSc group. Paired statistical analysis did not reveal any significant changes in blood volumes, nor in the derivative parameters of plasma and red cell volumes, that could be associated with the increase in LVEF caused by prednisolone in these patients with SSc (Table II).

Discussion

As shown by autopsy studies myocardial inflammation and fibrosis, the hallmarks of cardiac scleroderma, occur in the majority of patients with SSc (3-5). However, it is well appreciated that a clinical diagnosis of myocardial involvement in SSc is much less often established, indicating that many patients have clinically unrecognised disease (1, 2, 6, 7). In this study of selected SSc patients without clinical manifestations of myocardial dysfunction at rest, an impaired resting LVEF, a reliable marker of systolic LV dysfunction, was found in 6 of 32 patients (18%). Although resting radionuclide ventriculography is not an adequate measure of cardiac function in isolation, this highly reproducible method represents the best non-invasive procedure for the assesment of myocardial performance (15). Possibly, the presence of extensive skin disease or arthritis could have masked the cardiac symptoms in some of our patients. In a previous study Follansbee *et al.* also reported that 15% of diffuse SSc patients had an abnormal resting LVEF estimated by radionuclide ventriculography, while 46% had an abnormal LVEF response to exercise (26). In contrast to patients with SSc, we found only one out of 32 disease control patients with an impaired LVEF at rest.

To study whether short-term, relatively low doses of prednisolone may have a beneficial effect on myocardial performance in patients with SSc at a stage prior to the possible clinical expession of cardiac involvement, we studied patients with SLE and RA in parallel, instead of using a placebo- or non-treatment controlled approach. Because of the limited number of patients who fullfilled the inclusion criteria, dividing our SSc patients would have resulted in small placebo or non-treatment groups, thus not allowing legitimate clinical correlations. As is well known, in contrast to SSc, a chronic process of myocardial damage and fibrosis is rarely seen in either SLE (27, 28) or RA (29, 30). Our results indicated that a significant increase in myocardial performance after prednisolone administration ocurred only in the group of patients with SSc, and not in the patients with SLE or RA who served as the disease controls.

The prednisolone-induced increase in LVEF in patients with SSc was not associated with any changes in the heart rate or blood pressure measurements, nor in the blood, plasma or red-cell volume parameters, within the 20-day period of treatment. Lenders *et al.* also did not observe any changes in either the heart rate or blood pressure in 15 healthy subjects who took 20 mg of prednisone for a 7-day period (31). On the other hand, single measurements are not adequate to exclude significant changes in pre-load and afterload on

which a resting LVEF depends (15). Therefore, even though glucocorticoids are not known to increase LVEF in general, and prednisolone in particular has a less marked influence on sodium retention comparing to other glucocorticoids (14), our findings can be partly explained by a glucocorticoid treatment-associated volume expansion which could increase the ejection fraction without representing a true change in myocardial function. Probably by such a mechanism prednisolone treatment resulted in slight, non-significant increases in LVEF in the groups of patients with SLE and RA (Table I). Along this line, a volume expansion-associated change in LVEF cannot be excluded in the SSc patients, where the mean LVEF after the 20-day prednisolone treatment (68%) was higher than the normal mean LVEF in 14 healthy subjects (61%) studied previously in our laboratory (23).

However, when the individual percent changes in LVEF before and after treatment were compared to baseline LVEF values in SSc, a linear trend between the individual LVEF values at baseline and their changes after treatment showed that the lower the initial LVEF, the greater the improvement caused by prednisolone. Taken together with the fact that this effect was observed in patients with SSc and not with SLE or RA, this finding may suggest that prednisolone had a direct beneficial myocardial dysfunction, in addition to other possible indirect mechanisms. Furthermore, the more prominent LVEF improvement seen in patients with diffuse SSc than in those with limited disease, as well as the significant correlations between the degree of LVEF improvement and the individual baseline ESR values and serum IgG concentrations, may suggest that the beneficial effect is related, at least in part, to a suppression of occult myocardial inflammation occuring specifically in some patients with SSc and clinically unrecognised cardiac involvement.

Certain histologic features distinguish the myocardial fibrosis present in atherosclerotic disease or in infiltrative disorders from the fibrosis in cardiac scleroderma, where normal heart muscle is destroyed and concommitant collagen deposition occurs. The pathogenesis of myocardial damage is not clear but an immune-mediated inflammatory pathogenetic component involving multiple cytokines certainly contributes to the fibrotic process in SSc (2,32-34). Trials of immunosuppressive therapy in SSc cardiac disease have thus far yielded disappointing results (2, 12). Although the effect of steroids has never been studied systematically, there is evidence suggesting that patients with both skeletal and myocardial muscle disease, including patients with polymyositis in overlap with SSc, should be treated with steroids in sufficient doses to normalize CPK serum levels (12).

Whether in a given patient the inflammatory fibrotic process within the heart will subside or remain stable at some disease stage, or in turn progress to the point that cardiac failure eventually emerges, cannot be forseen or prevented (1,2). In any case, if occult myocardial inflammation contributes significantly to the development of clinical cardiac disease, then antiinflammatory and immunosuppressive treatment may only be effective if initiated much earlier in the disease process. Because our study was confined to patients without clinical manifestations of cardiac disease at rest, the subgrpoup of diffuse SSc patients with impaired baseline LVEF who benefited most from prednisolone treatment may represent those patients with primary myocardial fibrosis at a pre-clinical level. In fact, the presence of subclinical cardiac muscle damage cannot be excluded since aldolase levels and/or serial endocardial biopsies were not obtained in these particular patients.

In conclusion, in the absence of clinically evident cardiac involvement short-term, relatively low doses of prednisolone can significantly improve the resting LVEF in patients with SSc, primarily in those with low LVEF. The degree of prednisolone-associated improvement in myocardial performance was inversely correlated with the baseline ejection fraction and it was most prominent in patients with diffuse skin disease, impaired myocardial performance, and evidence of an inflammatory response. These findings suggest that low-dose prednisolone administration may potentially be beneficial in some patients with SSc with documented myocardial (LV systolic) dysfunction. However, because chronic steroid administration may predispose to premature atherosclerosis (14) and renal crisis (24), further double-blind controlled studies of the long-term effects of glucocorticoid administration on myocardial performance should focus on whether significant improvement in an impaired LVEF after short-term prednisolone administration is an additional indication for such treatment in patients with SSc and impaired LVEF.

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