occur at the same time as zidovudine absorption, greatly inhibited presystemic hepatic glucuronidation of zidovudine. Such presystemic inhibition might be the primary mechanism for the rise in systemic zidovudine concentrations.

Our data suggest that probenecid could be used to reduce the daily dose of zidovudine, by allowing the dose interval of zidovudine to be doubled from 4 to 8 h. This combination should improve convenience and compliance, should reduce drug costs by nearly half, and should not substantially change the mean, peak, or trough plasma zidovudine concentrations. Even if the recommended dose of zidovudine were changed, a probenecid and zidovudine combination has the potential to halve the required zidovudine dose and to halve the cost of any regimen compared with full-dose zidovudine alone.

Quinine sulphate, surprisingly, failed to reduce the renal elimination of zidovudine. This finding suggests that zidovudine is not secreted by the organic cation transport system; or that quinine's inhibitory effect on the transport system is lost in these patients in the presence of zidovudine; or that inadequate plasma concentrations of quinine were achieved. We cannot distinguish among these possibilities.

The addition of quinine to zidovudine plus probenecid did not potentiate the reduction of total zidovudine clearance caused by probenecid. In fact, quinine reversed the effect of probenecid. The reversal of the effect of probenecid on zidovudine elimination without change in its effect on the renal clearance of zidovudine glucuronide or uric acid suggests that quinine impairs probenecid's effect on glucuronidation but not renal transport. We are not aware of any other data on this possible effect.

The toxicity of probenecid given long-term to HIV-infected patients is not known. Patients with gout, however, have received probenecid for years with minimal toxic effects. The effects of probenecid on the pharmacokinetics of other drugs taken by AIDS patients must also be considered and appropriate dose adjustments may be necessary as they are for certain drugs in patients with substantial renal failure or hepatic dysfunction. Furthermore, not all drug interactions can be accurately predicted; in this study the interactions of quinine and zidovudine, with and without probenecid, differed from what we predicted.

In summary, our study supports the use of probenecid in combination with zidovudine in the treatment of patients with human immunodeficiency virus infection. We believe that the potential benefits to patients of this combination are substantial. However, the long-term safety and efficacy of zidovudine in combination with probenecid have yet to be established. Further studies should address the tolerance, toxicity, and efficacy of the combination.

We thank Mr Steven Good (Burroughs Wellcome Company) for authentic zidovudine and zidovudine glucuronide and the internal standard used in the HPLC assay; the AIDS Clinical Trials Program for logistic support; Mary Williams for secretarial assistance; and the volunteers. Clinical studies were carried out in the Johns Hopkins Clinical Research Center and laboratory studies in the Alan Bernstein Laboratories for Clinical Pharmacology.

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COLD-INDUCED REVERSIBLE MYOCARDIAL ISCHAEMIA IN SYSTEMIC SCLEROSIS

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Summary The effect of cold provocation on myocardial perfusion was studied in 21 patients with systemic sclerosis and 8 healthy controls. The cold provocation was designed not to cause a pain reaction, and no rise in heart rate/blood pressure product occurred during provocation. Myocardial perfusion was assessed by measurement of thallium uptake by imaged single photon emission computed tomography. No patient had clinical evidence of cardiac involvement, but abnormal electrocardiographic (ECG) findings were found in 5. In 12 patients cold-induced reversible perfusion defects were found; 9 of these also had permanent defects. A further 3 patients had permanent perfusion defects but no reversible defects. The permanent and/or reversible perfusion defects were not related to age among the patients and were not seen in any of the healthy controls, whose age distribution was similar. The reversible and permanent defects were not related to other features of systemic sclerosis, nor to the ECG findings. It is concluded that abnormalities in myocardial perfusion are common in systemic sclerosis and may be present without apparent clinical myocardial involvement. A cold-induced vasospastic process in the myocardial circulation might contribute to the development of the patchy myocardial fibrosis seen in patients with systemic sclerosis.

Introduction

THE cardiac symptoms and signs found in systemic sclerosis include arrhythmias, congestive heart failure, angina pectoris with normal coronary arteries, and sudden death. The origin of the myocardial disease in systemic sclerosis is uncertain but it may be secondary to vascular lesions. Various vasomotor changes are seen in this disorder, including Raynaud's phenomenon,[1] development of trophic

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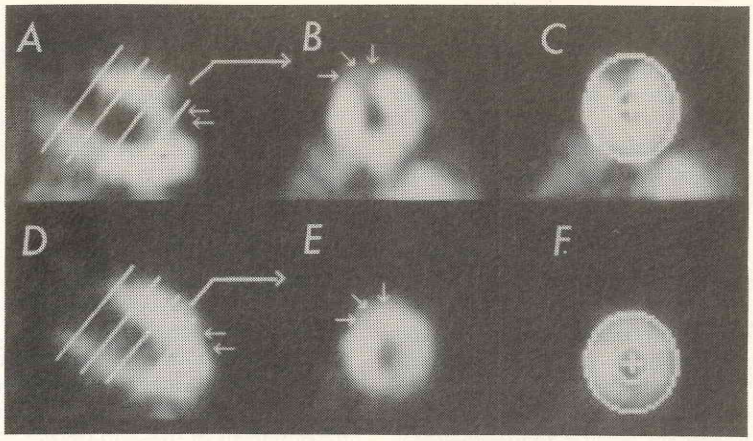


Fig 1—Images of myocardial ^{201}Tl distribution immediately after cold provocation (A-C) and 3 h later (D–F) in a patient with systemic sclerosis.

A = sagittal view of left chamber in three equal portions plus apex; perfusion defect antero-apically indicated by small arrows. B = coronal view at area indicated in A; perfusion defect in anterior wall indicated by arrows. C = computerised definition of epicardium, endocardium, and centre cavity for coronal slices. D–F = corresponding images 3 h later.

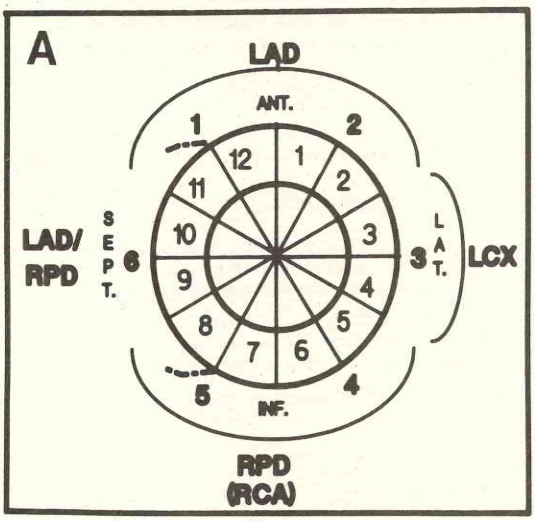
ulcers of the digits,[2] structural changes in the capillaries of skin and muscle,[3] and disturbances of cutaneous blood flow in response to cooling.[4] The pathological features of the myocardial lesions in systemic sclerosis have been established at necropsy. Focal fibrosis randomly distributed throughout the myocardium is a frequent finding, but the epicardial arteries generally appear normal on histology.[4] The occurrence of myocardial contraction band necrosis in systemic sclerosis may be due to a "Raynaud's phenomenon" of the intramural vessel.[4]

We have studied the myocardial distribution of blood flow in patients with systemic sclerosis by single photon emission computed tomography (SPECT). Our aim was to assess in vivo the frequency of abnormal myocardial perfusion in patients with systemic sclerosis and to see whether a myocardial vasospastic reflex could be induced by a cold provocation test which caused minimum discomfort and interference with blood pressure and heart rate.

Patients and Methods

Patients

21 patients (11 women, 10 men) aged 26–76 (mean 52) years, with systemic sclerosis according to the American Rheumatism Association criteria[5] were studied. So that other disease processes should not influence the myocardial evaluation, we excluded patients who had renal insufficiency, hypertension, diabetes mellitus, or previous treatment with cardiotoxic drugs. At the time of the study, no patient was receiving drug treatment. There were no smokers but 4 ex-smokers. 8 healthy subjects (3 women, 5 men; mean age 49 years, range 28–64) were studied as a reference group. 2 of the controls were smokers and 2 ex-smokers.



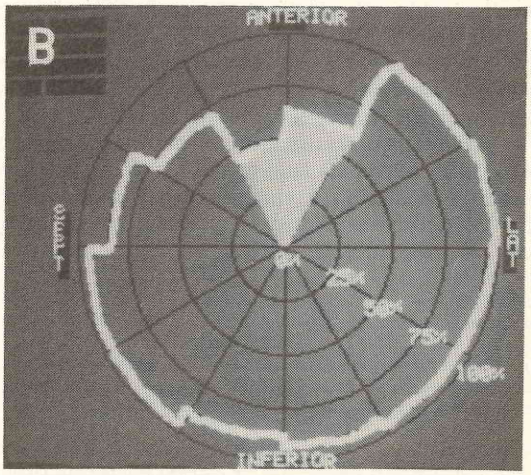


Fig 2—A = model used for dividing myocardium into 12 sectors (30°) for quantification of myocardial activity between epicardial and endocardial borders (heavy lines) and B = activity during cold provocation of a patient with systemic sclerosis.

A: six anatomical portions and coronary arteries supplying them are marked; LAD = left anterior descendent; LCX = left circumflex; RPD = ramus posterior descendent, most probably right coronary artery (RCA). Centre = 0%, first circle = 25%, next circles = 50%, 75%, and 100% of sector with maximum activity; mean activity in each sector is plotted in a polar coordinate system, with the same anatomical orientation as coronal slices. Activity in anterior wall is below lower normal limit.

CLINICAL AND LABORATORY FINDINGS

Patient	Age (yr)	Sex	Duration of disease (yr)	Pulmonary function tests (% predicted)			ESR (mm/h)	Raynaud score	Skin score	Perfusion defects on SPECT*	ECG findings
				FVC	FEV_1	TL_{CO}					
1	50	F	25	112	90	79	95	3	31	None	Normal
2	51	M	10	76	75	83	8	1	18	None	LV-strain
3	66	F	10	57	57	..	20	2	28	None	Normal
4	73	F	2	70	71	52	54	3	34	None	Normal
5	66	F	15	86	91	..	56	1	21	None	Normal
6	66	M	2	57	72	30	95	3	34	None	Normal
7	34	F	13	88	88	87	3	2	28	R	Normal
8	47	F	15	90	113	62	14	3	15	R	LV-strain
9	26	M	6	64	70	64	5	2	28	R	Normal
10	66	F	7	76	76	94	22	2	25	R/P	Normal
11	60	M	6	111	80	..	7	1	24	R/P	Normal
12	39	M	1	59	66	28	18	1	11	R/P	LBBB
13	51	F	8	66	66	44	34	3	28	R/P	Normal
14	56	M	3	92	73	75	8	2	29	R/P	LV-strain
15	44	F	8	90	93	82	8	2	27	R/P	Normal
16	43	F	4	57	66	..	22	2	16	R/P	Normal
17	47	F	10	109	109	64	10	2	31	R/P	Normal
18	44	M	15	75	77	42	12	3	16	R/P	Normal
19	46	M	1	58	63	50	4	2	37	P	Normal
20	76	M	15	89	86	55	8	2	20	P	Q-wave
21	43	M	6	..	..	..	8	3	16	P	Normal

*R = reversible; P = permanent; LBBB = left bundle branch block.

Cold Provocation Test

The subjects were studied in the fasting state, and in the supine position. After baseline electrocardiography (ECG) and blood pressure measurements, plastic bags filled with ice-water were placed on the patient's trunk for 4 min; three medium-sized bags were placed on the right and left side covering the upper thorax, mid-abdomen, and groin. A six-lead ECG was continuously recorded. Heart rate was measured from the continuous ECG recordings, and blood pressure was measured at the start of the cold provocation test, after 2 and 4 min, and after the test. After 4 min of cold provocation, 90 MBq thallium-201 was injected into an antecubital vein through an intravenous catheter which was then flushed with 10 ml saline. The subject was kept resting for a few minutes and then transferred to the imaging room for recording of "early" myocardial perfusion; the "late" recordings were done 3 h later.

Cardiac Imaging and Analysis

With the patient in the supine position the myocardial ^{201}Tl distribution was studied by SPECT. SPECT data collection was started within 10 min of injection of ^{201}Tl according to our standard protocol. A rotating head camera (Picker SX-300, 'Digital Dyna Camera', Cleveland, Ohio, USA) equipped with a low-energy, high-resolution collimator was used. Data were collected from 32 angles, 30 s per angle over 180° rotation from 45° left posterior oblique to 45° right anterior oblique. The camera was rotated in the body contour mode after initial body outlining. Two symmetrical 20% windows were centred at the 75 keV and 167 keV peaks. Data were collected in a 64 × 64 word mode.

The data were prefiltered with a Metz filter[6] and reconstructed by means of the SPETS-TSX software package (Nuclear Diagnostics, Stockholm, Sweden). Briefly, an arithmetic back-projection reconstruction algorithm was used, attenuation correction guided by the body outline was applied with an attenuation coefficient of 0·19,[7] and 1 pixel wide 6·5 mm transverse slices were reconstructed. Based on these data, oblique sagittal and oblique coronal 1 pixel wide slices were generated according to the true anatomical heart axis.

Corresponding parts of the myocardium from the two studies (early and late) were selected and displayed side by side on a high resolution monitor connected to an eight-bit video board. Images were analysed for permanent or reversible perfusion defects by an observer-independent quantitative technique.[8] Briefly, the myocardium was divided into equal thirds plus apex. In each corresponding coronal pair the inner and outer borders of the myocardium were delineated by a semiautomatic algorithm, with access to manual correction in cases of extensive and deep perfusion defects, and the centre of the cavity was defined (fig 1). The area between the inner and outer borders was defined as myocardium and divided into sectors by an angle of 30° (12 sectors per coronal slice). The counts per pixel in each sector were computed by the algorithm (fig 2). The computed values of myocardial activity in each sector in the early and late studies were plotted in a polar coordinate system with the same anatomical orientation as the coronal slices. The computed values for each sector were compared with the corresponding values for the specific sector and portion of the heart obtained from the data base of myocardial activity distribution in the healthy controls. The controls' mean value minus 2 SD for each sector and portion of the myocardium was defined as the lower normal limit. Sectors with values below the lower normal limit were automatically identified; in the late studies such sectors were taken as defining areas with permanent perfusion defects; sectors with abnormally low activity in the early studies, but activity within the normal range in the late studies were taken to define areas with reversible defects.

Clinical Studies

Lung volume and lung function were determined by measurements of the total lung capacity (FVC), forced expiratory volume in 1 s (FEV_1), and transfer factor (TL_{CO}) or diffusing capacity for carbon monoxide (single-breath test). The lower normal values of these measurements in our laboratory are 80% of the predicted value.[9] The erythrocyte sedimentation rate (ESR) was read after 1 h (Westergren) and serum creatinine was measured at the Department of Clinical Chemistry.

Raynaud's phenomenon was scored on a scale of 0–4; 0 for no signs of the phenomenon and 4 for the most severe form with cyanotic fingers at 20°C. The severity of skin lesions was assessed by a simple scoring system; skin thickening was estimated at 18 anatomical sites on a scale of 0–3; 0 for normal skin and 3 for the most severe thickening and induration of the skin. The maximum score was therefore 54.

Results

The mean duration of systemic sclerosis in the 21 patients was 8 years (see table). No patient had a history of systemic hypertension or blood pressure above 150/90 mm Hg

during the study. No patient suffered from arrhythmias requiring treatment or had clinical symptoms or signs suggesting cardiac involvement. 3 patients had ST-T changes indicating left ventricular strain (table). 1 patient had a ventricular conduction abnormality and 1 patient an abnormal Q-wave. All patients had Raynaud's phenomenon of the fingers. 15 patients had signs of impaired lung volume or function (table). Laboratory signs of increased inflammatory activity defined by high ESR were present in 10 patients (table).

Persisting abnormal ^{201}Tl distribution in the myocardium was found in 12 of the 21 patients by computerised quantitative analysis of the thallium distribution. The effects of cold provocation on myocardial perfusion were studied by the same observer-independent technique and based on the data base of the controls. Cold-induced reversible perfusion defects were seen in 9 of the 12 patients with permanent perfusion defects and in 3 of the 9 patients without permanent defects (fig 1). The data for the individual patients are given in the table.

Neither reversible nor permanent defects were related to the age of the patients, previous smoking habits, disease duration, skin involvement, severity of Raynaud's phenomenon, pulmonary function, or abnormal ECG findings. No patient or control had arrhythmias or chest pain during the cold provocation. No significant changes in heart rate or mean blood pressure were seen before, during, or after the cold provocation procedure and no ECG changes were induced by cold. Patient 18 underwent cardiac catheterisation and coronary angiography according to standard techniques. The coronary angiogram was normal but thallium distribution studies showed a small permanent non-transmural perfusion defect in the posterior myocardial wall. Cold provocation induced large reversible perfusion defects in the posterior wall and the posterior septum.

Discussion

In this study, in contrast to cold pressor tests, cooling of the trunk with ice-bags did not increase the blood pressure/heart rate product yet resulted in reversible perfusion defects of the myocardium in 12 of 21 patients with systemic sclerosis. Most of the patients with reversible defects also had permanent perfusion defects. Isolated permanent perfusion defects were seen in only 3 of the 21 patients. The reversible perfusion defects observed in systemic sclerosis were not related to age and were not seen in healthy controls with a similar age distribution to the patients. Furthermore, we were able to exclude smoking, hypertension, diabetes mellitus, and drugs as other possible factors underlying the observed perfusion abnormalities.

Follansbee and colleagues[10] reported that in systemic sclerosis patients reversible perfusion defects were induced by physical exercise and there was a close relation with permanent perfusion defects. The patients who had exercise-induced defects had normal coronary angiograms and none showed ST-segment elevation on ECG during exercise. Follansbee et al therefore postulated the presence of an abnormality of the coronary circulation at the level of the intramyocardial vasculature in these patients.[10] However, they could not assess whether the perfusion defects were due to induced vasospasm or to a low coronary reserve.

Myocardial perfusion abnormalities are obviously common in systemic sclerosis. So far there is little evidence to substantiate the much discussed "myocardial Raynaud's phenomenon". We have shown, for the first time, that cold can induce true vasospasm in cardiac vessels in patients with systemic sclerosis. The cold pressor test, used by others, induces pain and an increase in heart rate/blood pressure product when the hand is immersed in ice-water. Our cold provocation was designed not to cause a pain reaction or an increase in cardiac workload, so that we could discriminate between limited coronary reserve and vasospasm. It is possible that our patients suffered from substantial coronary disease and that the cold provocation test induced a normal degree of vasoconstriction that in areas of stenosis may have produced loss of perfusion. However, this possibility seems unlikely based on previous studies. Firstly, coronary artery disease with stenosis is not commonly found at necropsy in systemic sclerosis with myocardial fibrosis,[4] and secondly, exercise-induced perfusion defects may occur in the absence of narrowing of the coronary arteries in this disorder.[10] Furthermore, in our patient with the largest reversible perfusion defects after cold provocation coronary angiography was normal.

The SPECT method used in this study is better than the planar imaging technique for the evaluation of myocardial thallium uptake, having greater spatial resolution and sensitivity. This might explain why Siegel and colleagues[11] were unable to show reversible perfusion defects by the cold pressor test in 2 patients with systemic sclerosis by planar thallium imaging. Finally, our quantitative technique is observer independent, since we use a computerised interpretation of SPECT data with an integrated data base of healthy controls.

Since the early work of Weiss et al[12] it has been established that cardiac involvement in systemic sclerosis is a distinct clinical and pathological entity. Primary cardiac involvement is common in systemic sclerosis, being present in up to 50% of subjects undergoing necropsy.[4,13–16] Clinical signs of cardiac involvement indicate a poor prognosis.[17] The symptoms and signs of myocardial disease in systemic sclerosis include chest pain, dyspnoea, congestive heart failure, and sudden death.[5,15,18,19] None of our patients had any of these symptoms but 5 had ECG abnormalities. An abnormal Q-wave was seen in 1 patient. This patient had no history suggesting myocardial infarction and, according to previous studies on ECG changes in systemic sclerosis,[20] it is more likely that the finding reflects a patch of myocardial fibrosis rather than the result of atherosclerosis. Other abnormal electrocardiac findings were ventricular conduction abnormalities and ST-T wave changes indicating left ventricular strain. In this context, we should mention that none of our patients had, during or after the cold stimulation, symptoms of angina pectoris or findings of ST-segment changes, suggesting that the cold-induced perfusion defect was not severe enough to induce anaerobic metabolism or to affect the myocardial action potential.

The pathogenic mechanisms of the scleroderma lesions in various organs are poorly understood. The extent to which immunological mechanisms are important is widely debated but is still largely unresolved. On histopathology systemic sclerosis is characterised by microvascular abnormalities and by excessive fibroblast activity and collagen deposition. We have reported increased expression of platelet derived growth factor (PDGF) B-type receptors in dermal lesions in systemic sclerosis[21] and increased PDGF release from platelets has been indirectly shown.[22] The enhanced platelet degranulation in systemic sclerosis may be induced by changes in the microcirculation, particularly during

episodes of vascular spasm and ischaemia. Thus, altered PDGF control of connective tissue cell growth may be involved in the development of the lesions.[21] The characteristic manifestation of myocardial involvement in systemic sclerosis is myocardial fibrosis unrelated to narrowing of either the intramural or the epicardial coronary arteries.[4] These areas of fibrosis tend to be patchy and small. The permanent perfusion defects observed in our patients could reflect such islands of fibrosis, which might have been undetected by planar thallium imaging since it cannot resolve this type of lesion. Bulkley et al[4] emphasised the paucity of small vessel abnormalities in the myocardium at necropsy of systemic sclerosis patients. They noted when such abnormalities were present, distinct focal myocardial lesions ranging from myofibrillar degeneration with contraction band formation (a histological lesion seen in the setting of reperfusion injury[23]) to replacement fibrosis.

Some investigators have suggested that the myocardial fibrosis in systemic sclerosis is secondary to disease in other organs, principally the lungs and the kidneys.[13,24,25] None of our patients had signs of renal malfunction but reduced pulmonary function was common. However, we found no connection between the pulmonary changes and the myocardial perfusion defects and it is unlikely that pulmonary involvement would affect left ventricular myocardium or perfusion. Others have also reported no association between myocardial abnormalities and pulmonary disease.[4,14,26,27] Our documented intermittent vasospastic process in the myocardium and the features of the myocardial lesions mimicking ischaemic heart disease suggest that myocardial disease in systemic sclerosis is due to abnormal intramyocardial circulation. It remains to be shown whether a myocardial vasospastic reflex induced by cold is a unique finding in systemic sclerosis or is present in other diseases affecting the coronary circulation.

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Reviews of Books

Pathology of the Skin with Clinical Correlations

Phillip H. McKee. Philadelphia: Lippincott; London: Gower Medical. 1989. Pp 648. £120. ISBN 0-397446012.

PATHOLOGISTS are often baffled by the arcane terms used on skin biopsy request forms, and dermatologists are in turn exasperated when they receive a histological diagnosis that is totally at variance with the clinical picture. In some hospitals personal contact solves the problem, but in smaller centres the peripatetic dermatologist is all too often at his "other" hospital when clarification is required.

Dr McKee has now made a brave attempt to bring about a rapprochement by producing an excellent colour atlas of histopathology which is unique in having a brief account of the clinical features of each condition together with numerous clinical photographs. Refinements in microphotography have led to striking improvements in colour reproduction of histology photographs, and the author has taken full advantage of these to produce an unrivalled collection of first-class pictures of skin histopathology. The histological descriptions are also good, and although the text perhaps provides fewer details than its rivals such as "Lever" (*Histopathology of the Skin*, Lippincott) it is certainly adequate for most purposes.

Some of the clinical photographs are less good, and the choice is in some cases idiosyncratic. Why does such a book need two pictures of retinal angioid streaks, or a picture of a normal hand with its fingerprints, or a pickled plexiform neurofibroma of the spermatic cord? The clinical text generally suffices, although the claim in the foreword that much of the recent progress in dermatological research, including molecular biochemistry, is included, seems extravagant and the weakest sections of the book are those on pathogenesis. If we are to believe figure 8.23, for example,

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