Myocardial Lesions of Progressive Systemic Sclerosis

A Cause of Cardiac Dysfunction

BERNADINE H. BULKLEY, M.D., REN L. RIDOLFI, M.D., WILLIAM R. SALYER, M.D., AND GROVER M. HUTCHINS, M.D.

SUMMARY The nature, prevalence, functional significance, and indeed existence of myocardial disease in progressive systemic sclerosis (PSS) has been debated. In this study the clinical and pathological features of 52 autopsied patients were analyzed in an attempt to resolve these questions. A distinctive focal myocardial lesion ranging from contraction band necrosis to replacement fibrosis throughout both ventricular walls was present in 23 patients who had widely patent extramural coronary arteries. There were no morphologic abnormalities of the intramyocardial coronary arteries to account for these lesions. Comparing those patients having severe (13), mild (10), or no (24) PSS myocardial lesions, and patent extramural coronary arteries, there were no major differences in age, sex, frequency and severity of pulmonary, renal or hypertensive disease which could account for the myocardial necrosis and fibrosis. The three groups did differ, however, with regard to clinical cardiac abnormalities: ventricular arrhythmias and conduction disturbances were six and two times as frequent, respectively, in those with severe myocardial PSS compared to the other two groups. A pattern of primary myocardial disease with intractable congestive heart failure resulted from severe myocardial PSS in four patients, angina pectoris with normal coronary arteries was associated with severe myocardial lesion in three patients, and sudden death in five. The occurrence of contraction band necrosis suggests that the myocardial damage in PSS might be due to intermittent vascular spasm of the type recognized in the digits and possibly kidneys and lungs, i.e., an intramyocardial Raynaud's phenomenon. The findings in our patients clearly show that myocardial progressive systemic sclerosis is a distinct entity with relatively frequent occurrence which may lead to arrhythmias, congestive heart failure, angina pectoris with normal coronary arteries and sudden death.

THE NATURE AND FUNCTIONAL SIGNIFICANCE of myocardial disease in progressive systemic sclerosis (PSS), or scleroderma, are uncertain and have been the subject of controversy. Some studies have minimized or denied the clinical significance of the myocardial lesion, and others have attributed the cardiac abnormalities to associated pulmonary and renal disease.

The present study was undertaken to determine if there is primary myocardial involvement in PSS and, if so, its pathogenetic basis. The clinical and pathological features of 52 patients with PSS were analyzed. The findings suggest that some patients with scleroderma develop clinically significant myocardial injury, and that this injury may be a consequence of a "Raynaud's phenomenon" of the intramyocardial vasculature.

Materials and Methods

The autopsy files of The Johns Hopkins Hospital were reviewed for all patients with PSS. A case was included in this study if there was a clinical diagnosis of definite or probable PSS (scleroderma) and if consistent pathological findings were present. Particular attention was directed to lesions in the lungs, kidneys, and gastrointestinal tract, especially the esophagus, in confirming the diagnosis.

In the 52 patients included in the study the clinical and autopsy records and all histological sections, including an average of eight from the heart, were reviewed. Thirty-six hearts were available for gross review, and 12 had been examined after postmortem arteriography and fixation in dissection. Multiple additional blocks of the heart were taken for histological examination. The specialized conduction tissues were removed and examined by serial histological sectioning. An average of 150 sections were studied from each. Microangiograms were performed, using a low kilovoltage, small, focal spot X-ray machine and high resolution photographic emulsion on glass plates, on transverse 4 to 6 mm thick sections of the ventricles of the 12 hearts with PSS and five normal hearts which had had arterial injections of radiopaque material.

Results

Clinical Findings

The 52 patients with PSS ranged in age from 15 to 74 years (avg. 45), and 35 were women. The duration of clinical illness exceeded 36 months in 28 patients. The skin was abnormal in all 52 patients. Clinical evidence of renal disease was present in 28 patients and of pulmonary involvement in 36 patients, including five patients with a clinical picture of primary pulmonary hypertension. The gastrointestinal tract was abnormal in 50 patients clinically, and in six severe gastrointestinal dysfunction was the major manifestation of PSS. Raynaud's phenomenon was present in 47 patients and was the first symptom of disease in 90% of them. Three patients had a CRST (calcinosi, Raynaud's phenomenon, sclerodactyly, telangectasia) syndrome. Systemic hypertension was present in 28 patients. Congestive heart failure was present in 25 patients: in eight it was associated with renal disease or hypertension; in seven, with severe pulmonary disease, in six, with uremia and pulmonary disease, in four patients there was no apparent cause. Angina pectoris was present in seven patients, and clinical evidence of myocardial infarcts in three. The primary cause of death included renal failure in 14 patients, pulmonary disease in five, cerebrovascular accidents in five, sepsis in five, complications related to bowel malfunction in four, and congestive heart failure in four. Eleven patients died suddenly at...
home or in the hospital; ventricular arrhythmias including frequent premature ventricular contractions (PVCs) were present in seven patients and ventricular tachycardia in three, and three had a history of angina pectoris. In four patients the cause of death was uncertain.

**Morphologic Cardiac Findings**

The 52 hearts ranged in weight from 225 to 640 grams (avg. 399), and 28 (54%) exceeded 350 grams. Left ventricular hypertrophy was present in 22 patients, and marked right ventricular hypertrophy in 13. In five patients with severe pulmonary hypertension documented clinically and anatomically, right ventricular hypertrophy was severe. Five other patients had coronary artery disease with greater than 75% narrowing of epicardial vessels.

**Myocardium**

The myocardium in 26 of the 52 patients showed areas of fibrosis. Of these 26 patients, 23 with normal coronary arteries had a myocardial lesion consisting of focal fibrosis randomly distributed throughout the myocardium. In 13 cases foci of fibrosis were visible by gross inspection of the heart (fig. 1) as well as by histologic examination. The fibrosis was as severe in the right as in the left ventricle and frequently extended to the endocardium. The focal scars bore no relationship to specific extramural vasculature. The three other patients had transmural left ventricular myocardial infarcts associated with atherosclerotic coronary disease.

Foci of contraction band necrosis1,13 were identified in 16 patients; focal fibrotic changes were present in 14 as well (fig. 2). A spectrum of myocardial change was identifiable (fig. 3), ranging from muscle cell necrosis with contraction band formation through a standard response of inflammation and repair to replacement fibrosis. Foci of contraction band necrosis were found in all parts of the myocardium including the immediate subendocardial area.

For the purpose of evaluating the myocardial lesion, five patients were excluded because of coexistent extramural coronary artery disease. In the remaining patients with widely patent extramural coronary arteries, the extent of myocardial fibrosis was evaluated on a scale of 0 to 4+. Thirteen patients had severe (3-4+), ten had moderate to mild (1-2+), and 24 had no myocardial fibrosis. Contraction band necrosis was present in ten (77%) patients with severe myocardial fibrosis, four (40%) patients with mild involvement and in two (8%) patients without PSS type myocardial fibrosis (table 1).

**Coronary Arteries**

The extramural coronary arteries were widely patent in 47 patients and were narrowed by severe atherosclerosis in four patients and by thrombotic occlusions in one. In the latter patient with polyarteritis nodosa as well as PSS, arteritis of the extramural coronary arteries associated with thrombotic occlusions was observed.

The intramural coronary arteries in the 52 patients were generally normal histologically. An occasional vessel (i.e., two or three intramural arteries in the myocardial arteries of that case) was narrowed by cellular intimal proliferation in six patients, and by small thrombotic occlusions in nine patients, but in none of these 15 patients was there diffuse in-

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**FIGURE 1.** A) Base of heart fixed in distention following coronary arteriography. There is marked dilatation of both right (RV) and left (LV) ventricles. The myocardium shows severe focal replacement fibrosis especially involving the interventricular septum and subendocardial muscle of the free wall of the right ventricle. The epicardial coronary arteries are normal. LAD = left anterior descending coronary artery; PV = pulmonary valve. A portion of right ventricular myocardium is shown in B. Myocardial replacement fibrosis extends to the endocardium of the right ventricle (PTAH x 8). The intramural coronary arteries filled with injection mass are widely patent.
Pericardium

Seventeen patients had focal or diffuse fibrous or fibrinous pericarditis. Pericarditis was associated with uremia in ten patients, with infection in one patient, and with a myocardial infarct in one. Fibrous pericarditis was present in the five other patients, of which four had associated severe PSS-type myocardial lesions. The fifth patient had clinical as well as morphologic evidence of constrictive pericarditis, without myocardial or renal disease or any other evident explanation for the pericardial disease.

Endocardium and Valves

The cardiac valves were unremarkable in all 52 patients. Although the myocardial lesions frequently extended to the endocardium, the latter did not show any abnormality.

Cardiac Conduction System

The conduction systems were studied in 35 patients: the sinoatrial node in 32 patients, and the atrioventricular (A-V) node, His bundle, and bundle branches in 31 patients. Anatomic lesions of the sinoatrial node were identified in 13 patients. These consisted of varying degrees of node fibrosis which was mild in 11, and marked in two. These changes were unassociated with electrocardiographic rhythm disturbances. No fibrosis or necrosis was identified within the A-V node or His bundle, but two patients had interruptions within their proximal bundle branches: one had a right bundle interruption (and right bundle branch block clinically) in association with severe PSS type myocardial scarring of the interventricular septum; the other had idiopathic atrophy of the left bundle, a left anterior hemiblock clinically, and no PSS type myocardial lesions. Except for the two patients noted above, electrocardiographic rhythm and conduction disturbances were not accounted for on the basis of pathologic changes within the conducting systems. None of the hearts of the three patients with complete heart block, however, were studied.

Analysis of Clinical and Pathologic Findings Relative to the PSS Myocardial Lesions

The clinical and pathologic findings were evaluated with regard to the severity of the morphologic myocardial lesions and are summarized in Table 2. There were no differences between the three groups with severe, mild, and absent PSS myocardial lesions with regard to age, sex, duration of illness, incidence of severe pulmonary disease, or Raynaud's

Table 1. Frequency of the Myocardial Lesion in 47 Patients

<table>
<thead>
<tr>
<th>Myocardial Lesion</th>
<th>Severe (3-4+</th>
<th>Mild (1-3+)</th>
<th>Absent (0)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>13</td>
<td>10</td>
<td>24</td>
</tr>
<tr>
<td>Contraction band necrosis (%)</td>
<td>(77)</td>
<td>(40)</td>
<td>(8)</td>
</tr>
</tbody>
</table>

*Five patients excluded because of coexisting severe epicardial coronary artery disease.

Figure 2. A) Focal myocardial scars in the right ventricular outflow tract producing small whitish depressions of the endocardium (arrows). B) Section through a lesion shown in A. Note that muscle cell loss extends to the endocardium (H&E X 40). C) Margin of lesion shown in B, demonstrating contraction band necrosis. (H&E, X 400).
phenomenon. Systemic hypertension, pulmonary hypertension, and renal disease were somewhat less frequent in the patients with severe myocardial involvement.

Clinical cardiac abnormalities (table 3) were more frequent in patients with severe PSS lesions. Congestive heart failure without renal or lung disease was present in four patients with severe myocardial scarring but in none of the patients in the other two groups. Despite the presence of morphologically normal extramural and intramural coronary arteries three patients with severe myocardial PSS had angina pectoris documented by a positive exercise stress test in one and transient, ischemic ST-T wave changes during pain in the other two. Ventricular arrhythmias, present in over 60% of those with the severe myocardial lesion, were infrequent in the other two groups. Similarly, conduction abnormalities were more than twice as frequent in the patients with severe PSS type fibrosis compared to those with mild or absent lesions. Death was attributed to a cardiac cause in eight of the 13 patients with severe myocardial disease but in only three of the other 35 patients with mild or absent PSS myocardial lesions. Sudden death of presumed cardiac cause occurred in five of the 13 patients with severe PSS lesions: four patients had a history of ventricular arrhythmias including documented ventricular tachycardias and frequent multifocal PVCs; one patient had angina pectoris with documented ST-segment depression during pain. In three other patients with severe PSS type lesions death was related to intractable congestive heart failure. Of the three patients with mild or absent PSS lesions who died of cardiac causes, one had severe right-sided congestive heart failure due to pulmonary hypertension and one had constrictive pericarditis. The third patient died suddenly and had severe parenchymal lung disease and mild PSS type myocardial changes with foci of interstitial inflammation in the heart. The latter was thought to have contributed to his sudden death.

Discussion

For over 30 years it has been recognized that progressive systemic sclerosis may be associated with myocardial fibrosis. In 1943 Weiss et al. described myocardial "scars of unusual type" in two patients without associated coronary disease and recognized this form of heart disease as a specific entity associated with scleroderma. A few years later
Pulmonary Renal disease
Predominant gastrophenomena
Raynaud's hypertension
Systemic Duration
Sex Age
"CRST" disease.
Myocardial lesion

Table 2. Clinical Features of 47 Patients*

<table>
<thead>
<tr>
<th>Myocardial lesion</th>
<th>Severe (3+)</th>
<th>Mild (1-2+)</th>
<th>Absent (0)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>13</td>
<td>10</td>
<td>24</td>
</tr>
<tr>
<td>Age (years)</td>
<td>29-70 (51)</td>
<td>35-64 (47)</td>
<td>15-74 (43)</td>
</tr>
<tr>
<td>Sex - male/female</td>
<td>6:7</td>
<td>3:7</td>
<td>7:17</td>
</tr>
<tr>
<td>Duration of illness &lt;36 months</td>
<td>8 (62%)</td>
<td>6 (90%)</td>
<td>10 (42%)</td>
</tr>
<tr>
<td>&quot;CRST&quot; syndrome</td>
<td>0</td>
<td>0</td>
<td>3 (13%)</td>
</tr>
<tr>
<td>Predominant gastrointestinal disease</td>
<td>0</td>
<td>0</td>
<td>4 (17%)</td>
</tr>
<tr>
<td>Renal disease (severe)</td>
<td>4 (31%)</td>
<td>6 (60%)</td>
<td>12 (50%)</td>
</tr>
<tr>
<td>Systemic hypertension</td>
<td>2 (15%)</td>
<td>7 (70%)</td>
<td>16 (67%)</td>
</tr>
<tr>
<td>&quot;Primary&quot; pulmonary hypertension</td>
<td>0</td>
<td>1 (10%)</td>
<td>4 (17%)</td>
</tr>
<tr>
<td>Pulmonary parenchymal disease (severe)</td>
<td>4 (31%)</td>
<td>2 (20%)</td>
<td>5 (21%)</td>
</tr>
<tr>
<td>Raynaud's phenomena</td>
<td>12 (92%)</td>
<td>9 (90%)</td>
<td>21 (88%)</td>
</tr>
</tbody>
</table>

*Five patients excluded because of coexisting severe epicardial coronary artery disease.

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Figure 4. Postmortem arteriogram of heart of patient with PSS showing: A) normal epicardial coronary arteries, and B) normal intramyocardial arterioles on microangiography. RA = right atrium; RV = right ventricle; LA = left atrium; LV = left ventricle; LAD = left anterior descending, LC = left circumflex and RC = right coronary arteries.

Others described clinical cardiac dysfunction as a consequence of this peculiar PSS-associated myocardial fibrosis. D'Angelo et al. demonstrated that in autopsy reports myocardial fibrosis was increased in a group of patients with PSS compared to matched controls. Despite recognition of primary myocardial involvement in PSS, there has been some controversy over the frequency, clinical significance, and cause of this lesion. Some have maintained that primary cardiac involvement is infrequent and by itself rarely produces clinical manifestations. It has also been claimed that pulmonary and systemic vascular disease are the major cause of cardiac dysfunction in PSS.

Findings from our 52 autopsied patients indicate that primary myocardial disease in PSS is a definite pathologic

Table 3. Clinical Cardiac Abnormalities in 47 Patients*

<table>
<thead>
<tr>
<th>Myocardial lesion</th>
<th>Severe (15 pts)</th>
<th>Mild (10 pts)</th>
<th>Absent (24 pts)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Congestive heart failure (CHF)</td>
<td>11 (85%)</td>
<td>3 (30%)</td>
<td>8 (33%)</td>
</tr>
<tr>
<td>CHF w/o renal or lung PSS</td>
<td>4 (31%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Angina pectoris</td>
<td>3 (23%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Ventricular irritability</td>
<td>8 (62%)</td>
<td>1 (10%)</td>
<td>1 (4%)</td>
</tr>
<tr>
<td>Conduction abnormality</td>
<td>8 (62%)</td>
<td>3 (30%)</td>
<td>6 (25%)</td>
</tr>
<tr>
<td>RBBB</td>
<td>5</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>LAH</td>
<td>2</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>L* HB</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>CHB</td>
<td>3</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Cardiac death</td>
<td>8 (62%)</td>
<td>2 (20%)</td>
<td>1 (4%)</td>
</tr>
<tr>
<td>Sudden death</td>
<td>5 (38%)</td>
<td>1 (10%)</td>
<td>0</td>
</tr>
<tr>
<td>CHF</td>
<td>3 (23%)</td>
<td>1 (10%)</td>
<td>1 (4%)</td>
</tr>
<tr>
<td>Constrictive pericarditis</td>
<td>0</td>
<td>0</td>
<td>1 (4%)</td>
</tr>
<tr>
<td>Total with clinical cardiac</td>
<td>11 (79%)</td>
<td>4 (40%)</td>
<td>10 (42%)</td>
</tr>
<tr>
<td>abnormalities</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Five patients excluded because of coexisting severe epicardial coronary artery disease.
Abbreviations: CHB = complete heart block; L* HB = first degree heart block; LAH = left anterior hemiblock; RBBB = right bundle branch block; w/o = without.
entity which may lead to significant clinical cardiac dysfunction, and that the clinical cardiac dysfunction due to the myocardial lesion is not a rare finding.

The Primary Myocardial Lesion of PSS

Of the 52 patients studied, 26 (50%) had foci of myocardial fibrosis of varying magnitude randomly distributed throughout the heart. Twenty-three of the 26 patients had widely patent extramural coronary arteries. In 13 of these 23 patients the myocardial fibrosis was extensive, involving an estimated 10% or more of the myocardium, and in ten patients the lesions were mainly evident on microscopic examination.

Unlike the scarring associated with atherosclerotic coronary artery disease, the PSS-type myocardial fibrosis was as severe in the right ventricle as in the left, and the scars bore no relationship to extramural coronary artery distribution. In addition, the fibrosis frequently extended to the endocardium without a superficial layer of myocardium in the immediate subendocardium being spared as is generally seen in the replacement fibrosis of a healed myocardial infarct. In some patients this pattern of destruction of myocardium led to grossly visible depressions or “pockmarks” where the focal myocardial scars could be easily seen through the unaltered endocardium.

Focal myocardial necrosis of contraction band type was also present in over half of the patients with PSS type fibrotic lesions, but in only two (8%) of the patients who had no PSS-type scar. The morphologic findings suggest that myocardial contraction band necrosis was the precursor of the myocardial fibrosis. Thus, among the patients with the PSS myocardial lesion a spectrum of myocardial changes could be identified: focal contraction band necrosis eliciting a standard inflammatory cell response followed by macrophagic removal of necrotic cells and ending in replacement fibrosis.

Other types of myocardial disease of unknown etiology do not show the pattern of injury present in patients with PSS. Necrosis and fibrosis is generally slight in idiopathic cardiomyopathy; the characteristic finding is marked dilatation and hypertrophy of the left ventricle. In systemic lupus erythematosus valvular changes overshadow the mild and infrequent focal myocardial injury. Rheumatoid arthritis may show an interstitial myocardial inflammatory reaction and sometimes rheumatoid nodules. By comparison, the pathological features of the heart in PSS appear distinctive, but are not pathognomonic since contraction band necrosis and replacement fibrosis are the nonspecific responses to a variety of insults.

Clinical Significance of the PSS Myocardial Lesion

Clinical features of the 47 patients without occlusive coronary disease shown in table 2 indicate that there were no major differences between the three groups with severe, mild or absent PSS myocardial lesions with regard to age, sex and duration of illness. Systemic and pulmonary hypertension and renal disease were less frequent in patients with severe myocardial involvement. Severe parenchymal lung disease was somewhat more frequent in the patients with severe PSS lesions. Thus the primary myocardial lesions in PSS patients appear to be independent of pulmonary, renal, or hypertensive vascular disease.

Clinical cardiac abnormalities (table 3) were more frequent in patients with severe PSS lesions. Intractable congestive heart failure leading to death was present in four patients (9% of the 47 patients without coronary artery disease) with severe myocardial fibrosis. None of them had significant pulmonary or renal disease contributing to the congestive heart failure, and during life the etiology of their heart failure was obscure. Three patients (6%) had equivocal angina pectoris documented by transient ischemic ST-T wave changes during pain. Although angina was attributed to probable atherosclerotic coronary artery disease during life, the extramural coronary arteries in all three patients were widely patent at autopsy.

Electrocardiographic abnormalities occurred more often in patients with myocardial PSS. Ventricular irritability, including unifocal and multifocal premature ventricular contractions and paroxysmal ventricular tachycardias, were far more frequent in the patients with PSS type myocardial lesions. Of those with severe myocardial disease eight patients (62%) had ventricular irritability. Over 60% of patients with severe PSS lesions also had some form of ventricular conduction abnormality, and these were twice as frequent in those with severe as compared to those with mild or absent PSS myocardial lesions.

Although conduction abnormalities were more frequent in those with severe myocardial fibrosis, detailed examination of the conduction system in 36 patients failed to reveal a specific anatomic lesion within the proximal conduction tissue itself to account for the conduction block, suggesting that the conduction abnormalities were a manifestation more of diffuse myocardial damage rather than of specific conduction fiber interruption.

Thus, clinical cardiac dysfunction (including congestive cardiac failure, angina pectoris and arrhythmias), which could be attributed in whole or in part to the primary myocardial disease, was present in ten of the 13 patients (77%) with severe myocardial PSS and in 19% of the entire unselected group of 52 patients with PSS. These findings indicate that involvement of the heart by scleroderma is a common pathologic finding and a cause of significant clinical cardiac dysfunction.

Mechanics in the Production of the Primary Myocardial Disease of PSS

There has been considerable speculation as to the etiology of progressive systemic sclerosis and of the associated unusual primary myocardial changes. Abnormal collagen proliferation has been proposed as one possible explanation for the myocardial changes, as well as the fibrotic changes elsewhere in the body. East and Oram suggested that muscle fiber atrophy resulted from pressure from the rapidly proliferating sclerodermatous tissue. Although collagen deposition appears to be increased there is no evident qualitative abnormality of collagen in PSS. Little is known about control mechanisms in collagen turnover, and as yet
there is no firm evidence to support the notion that the basic derangement in PSS is primary rather than secondary connective tissue proliferation.20

     There is also no evidence to support the notion that the myocardial changes are secondary to renal, lung, or hypertensive vascular disease.4 The presence of renal, pulmonary or hypertensive vascular disease did not correlate with the presence or severity of the PSS myocardial lesion in our patients.

     Another possible explanation for the myocardial changes of PSS is vascular disease. The extramural coronary arteries are usually patent in PSS.3 The earliest reports of myocardial PSS commented on the unusual finding of myocardial infarcts without coronary disease.1 3 Extramural coronary disease was infrequent in our patients as well. Five of the 52 patients had extramural coronary artery disease and of these five, only two had PSS type scars in the myocardium; whereas 23 patients had such myocardial "infarcts" and widely patent extramural coronary arteries.

     Microvascular disease has been invoked as an underlying disease mechanism in PSS, particularly in the kidneys, lungs, and extremities.17 Although most morphologic studies indicate no such vessel disease in PSS,1 3 6 19 extramural coronary artery disease has been suggested as an explanation for the myocardial lesion of scleroderma by some.21 24 In a study of eight patients James44 described focal narrowing of the intramural coronary arteries and in part attributed the myocardial scars to small vessel disease. He did note, however, that scarring was out of proportion to the degree of vessel disease, suggesting the added possibility of a concomitant degenerative collagen process of unknown etiology.

     Examination of the intramural coronary arteries in our 52 patients with PSS failed to reveal evidence of significant small vessel disease. An occasional small vessel was narrowed by cellular intimal proliferation or thrombotic occlusions but these findings were as frequent in those patients with as in those without PSS myocardial disease. Microangiograms in 12 patients also failed to show anatomic abnormalities of the small coronary arteries.

     How then can we interpret the clinical and pathologic findings in the myocardium in scleroderma? As described above, myocardial PSS is characterized morphologically by a spectrum of focal myocardial injury ranging from contraction band necrosis to replacement fibrosis, without extra or intramural vascular abnormalities to account for the damage.

     It is suggested that the pattern of necrosis observed in our patients, i.e., contraction band necrosis, may be a clue to the pathogenesis of the myocardial lesion. Contraction band necrosis is a distinctive form of myocardial cell injury the significance of which has been appreciated only within the past decade.11 12 The commonly recognized form of ischemic damage to myocardium is coagulation necrosis, which can be produced experimentally by permanent occlusion of a coronary artery. Contraction band necrosis, also known as "myofibrillar degeneration" or "accelerated necrosis," is a less frequently recognized form of myocardial necrosis which differs in part from coagulation necrosis in that the cytoplasm develops dense eosinophilic transverse bands. At one time thought to be artifactual or agonal changes, contraction band necrosis is now recognized as a reperfusion lesion. Contraction band necrosis is frequently found in patients after cardiac surgery with cardiopulmonary bypass,12 20 at the borders of acute myocardial infarcts,25 26 and may be produced experimentally with temporary coronary artery occlusion followed by 20 minutes or more of reperfusion.11 26

     Contraction band necrosis could be observed in myocardial cells immediately beneath the endocardium. This observation seemed unusual if the lesion does develop from transient nonperfusion with reperfusion, since intraventricular blood should sustain the subendocardial muscle cells as it usually does in a myocardial infarct. However, we examined the myocardium of other patients with contraction band necrosis either secondary to episodes of hypoperfusion from ventricular fibrillation or associated with calcific aortic stenosis and found that this type of muscle cell injury commonly extends to the endocardium.

     Contraction band necrosis was present in 77% of our patients with severe PSS lesions, 40% with mild and in only 8% without PSS type myocardial change. The last figure corresponds closely to the frequency of occurrence of focal contraction band necrosis in a general autopsy population without cardiovascular disease.12 Thus, in scleroderma, as in other situations in which contraction band necrosis has been observed, it is possible that the myocardial injury is due to reperfusion of transiently unperfused myocardium. Raynaud's phenomena is present in 90% of patients with PSS and for most is the presenting symptom. Vascular spasm in the kidneys and the lungs has been considered as a mechanism of pulmonary and renal involvement in PSS.27 28

     It is suggested that a likely explanation for the myocardial lesion of scleroderma is an intermittent functional occlusion of intramyocardial coronary arteries. Although little is known about the physiology of the small coronary vessels in PSS, Gupta et al.20 recently performed coronary angiography in a patient with scleroderma and cardiomyopathy and found normal extramural coronary arteries with unusually slow clearance of contrast material from the coronary vessels suggesting increased resistance of the capillary bed. They concluded that some morphologic abnormality of the myocardial microcirculation probably accounted for the poor runoff and the diffuse myocardial dysfunction. Alternatively, intermittent vascular spasm at some level of the microcirculation, i.e., a myocardial Raynaud's phenomenon, would also account for this functional abnormality.

     As in the other organs in PSS, a myocardial Raynaud's phenomenon would likely be a chronic intermittent process producing the cumulative injury evident at autopsy. On-going piecemeal myocardial necrosis and fibrosis could well account for the angina pectoris, congestive heart failure, ventricular irritability, and sudden death prevalent in the group of patients with severe myocardial PSS disease.

References


Reflex Vasodilation Induced By Coronary Angiography in Human Subjects

ROBERT ZELIS, M.D., CHRISTOPHER C. CAUDILL, KATHLEEN BAGGETTE, AND DEAN T. MASON, M.D.

SUMMARY In order to evaluate the reflex peripheral vascular effects of coronary arteriography, forearm blood flow was measured plethysmographically and forearm vascular resistance calculated before and during coronary angiography with Hypaque-M, 75%, and Renografin-76. The injection of Hypaque into the left coronary artery resulted in a forearm vasodilation which could not be duplicated by an injection of a comparable amount of contrast into the ascending aorta, three centimeters above the coronary ostia. Forearm blood flow rose from 2.95 to 5.41 ml/min/100 ml (83.4%) and forearm vascular resistance fell from 35.8 to 19.9 mm Hg/ml/min/100 ml (44.4%). Renografin injected into the left coronary artery resulted in less forearm vasodilation (21% increase in forearm blood flow and 32% decrease in forearm vascular resistance). When coronary arteriography was repeated following injection of atropine into the brachial artery, no forearm vasodilation occurred. It is suggested that in human subjects myocardial or coronary artery receptors can be activated by the intracoronary injection of iodinated contrast media which results in a forearm vasodilation.

CURRENT INTEREST in ventricular receptors stems from the possibility that they might play a role in the hypotension accompanying acute myocardial infarction. Although the loss of extensive areas of myocardium is a major reason for shock accompanying acute coronary occlusion, it has been suggested that perhaps a depressor reflex secondary to stimulation of ventricular receptors could lead to a failure of the regional circulations to constrict appropriately during systemic hypotension. Although this hypothesis has been tested in experimental animals and found to be valid, only fragmentary evidence has been presented to suggest that such a mechanism is operative in humans. That this mechanism may be operative in humans is suggested by the frequent finding of low blood pressure readings co-existing with a normal cardiac output in patients with acute myocardial infarction. In addition, only one study has been reported in humans to show that myocardial

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