A Comparison of the Pathological Spectrum of Hypertensive, Diabetic, and Hypertensive-Diabetic Heart Disease

K.H. van Hoeven, MD, and Stephen M. Factor, MD

The hearts obtained at autopsy of 67 patients with hypertension, diabetes mellitus, or both were examined microscopically and histochemically, and the amount of fibrosis was determined. Significant differences in heart weight, interstitial fibrosis, replacement fibrosis, and perivascular fibrosis were found among the groups. The mean heart weight of the hypertensive-diabetic patients was significantly greater than that of the hypertensive patients and the diabetic patients. The amount of microscopic fibrosis increased between the groups, the lowest in hypertensive hearts, midrange in diabetic hearts, and highest in hypertensive-diabetic hearts. Total fibrosis correlated with heart weight among diabetic and hypertensive-diabetic patients and was significantly greater among patients with congestive heart failure, most of whom had histories of both hypertension and diabetes. The microscopic grade of fibrosis correlated significantly ($p<0.01$) with a quantitative, histochemical determination of the amount of collagen per milligram of total noncollagenous protein in the heart tissue. Myocardial fibrosis may contribute to the diastolic dysfunction typical of hypertensive-diabetic cardiomyopathy, in which congestive heart failure is a common sequela. The importance of hypertension in the pathogenesis of severe diabetic heart disease is discussed. (Circulation 1990;82:848–855)

Since the initial description of the clinical and morphological features of hypertensive-diabetic cardiomyopathy a decade ago, there has been much interest in identifying and evaluating the cardiac complications of combined hypertension and diabetes. It is particularly important to study the effects of these two diseases together, because more than half of all American diabetics are hypertensive.

In the initial study on hypertensive-diabetic cardiomyopathy, a specially selected group of diabetic patients with congestive heart failure and absence of coronary artery disease was studied; coincidentally, all were discovered to have superimposed hypertension. The clinical and morphological features of heart disease in this group of hypertensive-diabetic patients were more severe than that of comparison groups of hypertensive patients or diabetes mellitus patients. In this study, we examined a larger group of unselected patients with hypertension, diabetes mellitus, or both, and we found a significant spectrum of clinical and pathological differences.

**Methods**

**Case Selection**

The autopsy records of the Bronx Municipal Hospital Center and the Hospital of the Albert Einstein College of Medicine were reviewed for the years 1978 through 1983. Patients older than 40 years of age with a documented clinical history of hypertension, diabetes mellitus, or both were prescribed pharmacological therapy for their disease(s) were selected for further study. A data base was constructed that included the following data for each patient: age; sex; body weight; diagnosis of hypertension, diabetes, or both; number of years diagnosed with diabetes; diabetic therapy with insulin or oral hypoglycemic agents; antihypertensive drugs prescribed; presence or absence of chronic congestive heart failure requiring long-term pharmacological treatment on an outpatient basis before terminal admission; right and left ventricular free wall thickness at the outflow tract; heart weight; cause of death; and location and percent obstruction of any coronary lesion identified at autopsy during serial 3-mm sections of the epicardial arteries.

Fourteen patients met the criteria for hypertension alone, twenty-eight patients met the criteria for dia-
betes alone, and twenty-five patients met the criteria for both hypertension and diabetes. From the autopsy slide files for these 67 patients, all representative, formalin-fixed, paraffin-embedded tissue blocks and all hematoxylin-eosin–stained tissue sections of the free wall of the left ventricle were obtained, and the area of the tissue section on the slide was recorded. Two pathologists independently reviewed the cardiac histology. They reviewed the 180 slides in a blind fashion, without prior knowledge of the clinical or postmortem findings. Only sections taken across the full thickness of the ventricle, which included endocardium, myocardium, and epicardium were reviewed. Sections that had acutely or remotely infarcted myocardium were so recorded and were not further examined or graded microscopically. Acutely infarcted myocardium was identified by histological features such as wavy myocardial fibers, interstitial infiltration by neutrophils and other inflammatory cells accompanying frank coagulative necrosis of myocytes, and ingrowth of fibrovascular tissue. Remotely infarcted myocardium was defined as a macroscopic fibrotic scar.

**Microscopic Analysis**

A semiquantitative scale was developed to measure the amount of interstitial, perivascular, and replacement fibrosis seen at low power (×10) scanning light microscopy. Interstitial fibrosis was graded on a scale of 0 to 3+, with 0 representing the absence of pathological interstitial fibrosis, 1+ representing mild interstitial fibrosis, 2+ representing moderate separation of cells and groups of cells, and 3+ representing interstitial fibrosis that was severe and, at low power, reminiscent of cirrhosis (Figure 1). These and the other microscopic changes were generally diffuse, but when multifocal, the highest grade of any multifocal lesion was recorded. Subendocardial regions and papillary muscles were not included in the microscopic grading.

Perivascular fibrosis was graded on a scale of 0 to 2+, with 0 representing the absence of pathological perivascular fibrosis and 1+ representing encroachment of perivascular fibrosis into the adjacent first few layers of myocytes. Encroachment by perivascular fibrosis into more than three adjacent layers of myocytes was graded as 2+ perivascular fibrosis (Figure 1).

"Replacement fibrosis" is another term for "microscopic fibrosis," that is an area of scar formation in the heart not visible to the naked eye, scar that has replaced viable muscle cells. Areas of replacement fibrosis in the myocardium were individually...
counted. Each area of replacement fibrosis less than 50 \( \mu \)m in greatest dimension was given a score of 0.01. Areas 50 to 500 \( \mu \)m in greatest dimension were given a score of 0.1. Areas of replacement fibrosis greater than 500 \( \mu \)m in greatest dimension were given a score of 0.2 (Figure 1). The scores of the areas of replacement fibrosis were summed and divided into the summed tissue area in square centimeters on all slides for each patient. A quotient greater than 0.3 was graded as 3+, greater than 0.2 was graded as 2+, greater than 0.1 was graded as 1+, greater than 0.05 was graded as 0.5+, and less than 0.05 was graded as 0 replacement fibrosis.

A mean grade of interstitial fibrosis, perivascular fibrosis, and replacement fibrosis was calculated for each patient by summing the individual grades from each slide and dividing by the number of slides per patient. A total fibrosis score for each patient was calculated by summing the mean interstitial fibrosis grade, the mean perivascular fibrosis grade, and the mean replacement fibrosis grade. Thus, the maximum total fibrosis score for a single patient was 8.0, and the minimum was 0.0.

**Chemical Analysis**

There were 174 formalin-fixed, paraffin-embedded tissue blocks on 64 cases that were recut on a microtome (model 820, American Optical) to make tissue sections 10 \( \mu \)m in thickness. In some cases, the paraffin of the original block was melted; noninfarcted cardiac tissue was reembedded in one block, and infarcted cardiac tissue or noncardiac tissue was embedded in a second block. The noninfarcted cardiac tissue was analyzed for micrograms of collagen content per milligram of noncollagenous protein according to the method of Lopez-de Leon and Rojkind. All analyses were performed in the laboratory of Dr. M. Rojkind. In brief, tissue sections were deparaffinized and stained for 30 minutes with a mixture of Sirius red F3BA and fast green FCF in saturated picric acid. After numerous water washings, the stain was eluted from the tissue with 2 ml of 0.1N NaOH in absolute methanol (1:1 vol/vol), and the optical density of the eluted color was read immediately in a spectrophotometer at 605 and 540 nm (559A Perkin-Elmer Corp., Norwalk, Conn.), which are the respective maximal absorbancy wavelengths of fast green FCF and Sirius red F3BA. Micrograms of collagen per milligram of noncollagenous protein were calculated according to the previously described method.12

**Statistical Analysis**

The few, scattered, missing clinical data points were deleted from the analysis and are so noted in the text. All means are immediately followed by the standard error of the mean. For the comparison of means between three groups (hypertensive, diabetic, and hypertensive-diabetic patients), a one-way analysis of variance was performed. Either unpaired two-tailed Student's \( t \) tests or Wilcoxon's tests were used to compare means of two groups; the latter was used for nonparametric data. The \( \chi^2 \) test was used to test differences between groups when counts were compared. Linear regression and Pearson's correlation coefficients were used to evaluate trends. All statistical data were calculated with the statistical software package EPISTAT. A \( p \) value less than 0.05 was considered significant; however, for analysis between pairs in groups of three or more, lower \( p \) values were required for acceptance of significance, with Bonferroni's criteria (\( p<0.05/n \), where \( n \) represents the total number of comparisons).

### Table 1. Clinical and Pathological Features of Hypertensive, Diabetic, and Hypertensive-Diabetic Patients

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Hypertensive</th>
<th>Diabetic</th>
<th>Hypertensive-diabetic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients (n)</td>
<td>14</td>
<td>28</td>
<td>25</td>
</tr>
<tr>
<td>Men (n)*</td>
<td>7</td>
<td>14</td>
<td>10</td>
</tr>
<tr>
<td>Mean age at death (yr)*</td>
<td>65±3</td>
<td>69±2</td>
<td>65±2</td>
</tr>
<tr>
<td>Mean body weight (kg)*</td>
<td>79±6</td>
<td>72±3</td>
<td>82±5</td>
</tr>
<tr>
<td>Heart weight (g)*†</td>
<td>451±29</td>
<td>430±16</td>
<td>591±36</td>
</tr>
<tr>
<td>Mean wall thickness (cm)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LV†</td>
<td>1.8±0.1</td>
<td>1.6±0.07</td>
<td>2.0±0.1</td>
</tr>
<tr>
<td>RV†</td>
<td>0.44±0.04</td>
<td>0.48±0.05</td>
<td>0.67±0.05</td>
</tr>
<tr>
<td>Mean microscopic grades</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Interstitial fibrosis</td>
<td>0.97±0.2</td>
<td>1.4±0.2</td>
<td>1.8±0.2</td>
</tr>
<tr>
<td>Perivascular fibrosis</td>
<td>0.77±0.2</td>
<td>0.97±0.1</td>
<td>1.2±0.1</td>
</tr>
<tr>
<td>Replacement fibrosis</td>
<td>0.75±0.3</td>
<td>1.2±0.2</td>
<td>1.4±0.3</td>
</tr>
<tr>
<td>Total fibrosis score†</td>
<td>2.2±0.3</td>
<td>3.5±0.4</td>
<td>4.4±0.5</td>
</tr>
</tbody>
</table>

Values are mean±SEM. LV, left ventricular; RV, right ventricular. *Not significant (\( p>0.05 \)); †Analysis of variance; significant (\( p<0.05 \)) difference between the three means. See text for analysis of pairs.
**Results**

Table 1 lists the number of patients, mean age, number of males, mean body weight, mean heart weight, mean ventricular wall thickness, and microscopic findings for each patient group. There were no significant differences between the mean ages or body weights among the patient groups. Although there were slightly more women than men in the hypertensive-diabetic group, there were no significant differences in the distribution of the sexes between the groups.

The mean heart weights of the groups were significantly different. The mean heart weight of the hypertensive-diabetic group was significantly greater than that of the hypertensive (p=0.01) and of the diabetic groups (p<0.001). The mean heart weights of the diabetic and of the hypertensive groups were not significantly different (p>0.05). Despite the lower mean baseline heart weight of normal women compared with that of normal men and the inclusion of slightly more women in the hypertensive-diabetic group, the mean heart weight of the hypertensive-diabetic group was still significantly more than that of the other groups.

There were significant differences in the means of the right and left ventricular wall thicknesses among the three groups. Closer analysis revealed that significant differences in the left ventricular wall thickness were found only between the diabetic and the hypertensive-diabetic groups (p<0.01). Likewise, significant differences in the right ventricular wall thicknesses were found between the diabetic and the hypertensive-diabetic groups (p=0.01) and also between the hypertensive and the hypertensive-diabetic groups (p=0.01).

Table 2 reveals that the insulin-compared with noninsulin-dependent status of the diabetic patients yielded no difference in heart weight. Among insulin-dependent diabetic patients, the mean heart weight of those with superimposed hypertension was significantly greater than those with normal blood pressure (p=0.02). There were no differences in the reported years of diabetes between the insulin-dependent and noninsulin-dependent groups.

Information on the specific types of antihypertensive therapy was available for 22 hypertensive-diabetic patients, of whom five no longer were prescribed antihypertensive drugs secondary to heart failure. The remaining 17 patients were prescribed 27 antihypertensive drugs, an average of 1.6 drugs/patient. Among the hypertensive patients, similar information was available for all 14 patients, one of whom no longer was prescribed antihypertensive therapy because of congestive heart failure. The remaining 13 hypertensive patients were prescribed 20 drugs, an average 1.5 drugs/patient. There is no significant difference between these two groups.

The mean interstitial fibrosis grades, mean perivascular fibrosis grades, mean replacement fibrosis grades, and mean total fibrosis scores are shown in Table 1. From Table 1, it is notable that the means for each type of fibrosis and the fibrosis score progressively increase across the groups, lowest for the hypertensive, midrange for the diabetic, and highest for the hypertensive-diabetic group. Analysis of paired groups revealed that the total fibrosis scores were significantly different between the hypertensive and the hypertensive-diabetic groups (p<0.01) and approached significance between the hypertensive and the diabetic groups (p=0.04). The mean total fibrosis score of the hypertensive-diabetic group was higher than that of the diabetic group and approached, but did not reach, significance (p=0.17).

Figure 2 reveals the distribution of total fibrosis scores for patients within each of the clinical groups. There is a wide range of fibrosis scores, particularly in the hypertensive-diabetic group, but the clustering around the mean is evident in the hypertensive and the diabetic groups. There is a trend toward increasing total fibrosis scores from the hypertensive, to the diabetic, and, finally, to the hypertensive-diabetic group.

Analysis of pairs of means in the constituent types of fibrosis revealed that the hypertensive-diabetic patients have statistically more interstitial and replacement fibrosis than do hypertensive patients (p<0.01). Other analyses by pairs were not significantly different.

Figure 3 reveals the correlation between heart weight and total fibrosis scores in diabetic and hypertensive-diabetic patients. There was a significant positive association between the heart weight and fibrosis scores of the diabetic patients (r=0.41, p=0.03, y=0.01x−1.2) and the hypertensive-diabetic patients (r=0.42, p=0.03, y=0.006x+1). No such association was found for the hypertensive patients (p=0.63).

Congestive heart failure was more common in hypertensive-diabetic patients (13 of 25) than in diabetic patients (six of 28, p=0.04) or in hypertensive patients (two of 14, p=0.05). Among the 21

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**Table 2. Mean Heart Weights and Clinical Histories Among Insulin- and Noninsulin-Dependent Diabetic Patients**

<table>
<thead>
<tr>
<th></th>
<th>Insulin-dependent</th>
<th>Noninsulin-dependent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total (n)</td>
<td>25</td>
<td>28</td>
</tr>
<tr>
<td>Mean length of diabetes (yr)*</td>
<td>11.5±1.3</td>
<td>8.7±1.2</td>
</tr>
<tr>
<td>Mean heart weight (g)*</td>
<td>510±35</td>
<td>502±27</td>
</tr>
<tr>
<td>Hypertensive-diabetic patients (n)</td>
<td>11</td>
<td>14</td>
</tr>
<tr>
<td>Mean heart weight (g)*</td>
<td>624±59</td>
<td>565±43</td>
</tr>
<tr>
<td>Normotensive-diabetic patients (n)</td>
<td>14</td>
<td>14</td>
</tr>
<tr>
<td>Mean heart weight (g)*</td>
<td>421±23</td>
<td>439±24</td>
</tr>
</tbody>
</table>

Values are mean±SEM. *Not significant (p>0.05).
patients with congestive heart failure, the mean values for heart weight and all pathological types of fibrosis were significantly greater than those of patients without congestive heart failure (Table 3).

Data points concerning percent obstruction of the large coronary arteries were recorded in 12 hypertensive, 25 diabetic, and 24 hypertensive-diabetic patients. Luminal narrowing of at least 70% was present in one hypertensive, 17 diabetic, and 13 hypertensive-diabetic patients. Table 4 reveals that among all diabetic patients with or without hypertension (n=49), there is no significant difference in mean total fibrosis scores and mean heart weights (p>0.05) between diabetic patients with and those without 70% luminal narrowing. However, analysis of the mean constituent fibrosis scores revealed significantly increased amounts of replacement fibrosis in diabetic patients with compared with those without coronary artery disease.

Among 24 patients with acutely infarcted myocardium, the mean fibrosis score in the noninfarcted myocardial tissue of these patients was 3.9±0.4, and the mean heart weight was 524±33 g. For patients without acute infarcts, the mean fibrosis score was 3.4±0.4, and the mean heart weight was 478±22 g. There were no significant differences in the means between these two patient groups.

The cause of death was cardiovascular and cerebrovascular related in 18 of 25 (72%) hypertensive-diabetic patients, significantly more frequent than that of hypertensive patients who died of the same causes (three of 14, 21%). Cardiovascular deaths were noted in 11 of 28 (39%) diabetic patients, which was significantly less than in the hypertensive-diabetic patients (p<0.01).

To validate the semiquantitative fibrosis scale, a quantitative chemical measurement of the concentration of collagen was obtained, measuring micrograms of collagen per milligram of noncollagenous protein in the tissue sections. Figure 4 depicts the correlation between the chemical method and the semiquantitative, microscopic grading. There is a highly significant positive association between the two methods (y=0.25x−2.1, r=0.74, p<0.01).

**Discussion**

Cardiovascular disease is the major cause of mortality in diabetic patients. Diabetic patients with

**Figure 2.** Plot of distribution of total microscopic fibrosis scores for hypertensive (H), diabetic (D), and hypertensive-diabetic (HD) patients. No single hypertensive patient had a fibrosis score greater than 4. Mean score of the diabetic patients was 3.5, and clustering around this mean occurred. Scores of hypertensive-diabetic patients are widely distributed.

**Figure 3.** Plot of relation between the microscopic total fibrosis score and heart weight for diabetic and hypertensive-diabetic (Htn diabetic) patients. Both correlations are significant.
TABLE 3. Mean Heart Weights and Microscopic Grades Among Patients With and Without Congestive Heart Failure

<table>
<thead>
<tr>
<th></th>
<th>Congestive heart failure</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>With</td>
<td>Without</td>
</tr>
<tr>
<td>Patients (n)</td>
<td>21</td>
<td>46</td>
</tr>
<tr>
<td>Mean heart weight (g)*</td>
<td>613±34</td>
<td>441±17</td>
</tr>
<tr>
<td>Microscopic grade</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Interstitial fibrosis*</td>
<td>1.8±0.4</td>
<td>1.3±0.1</td>
</tr>
<tr>
<td>Perivascular fibrosis*</td>
<td>1.5±0.3</td>
<td>0.89±0.1</td>
</tr>
<tr>
<td>Replacement fibrosis*</td>
<td>1.8±0.3</td>
<td>0.78±0.1</td>
</tr>
<tr>
<td>Total fibrosis score*</td>
<td>5.0±0.5</td>
<td>3.0±0.3</td>
</tr>
</tbody>
</table>

Values are mean±SEM. *Wilcoxon’s ranked-sum test; significant difference (p<0.05) between the two means.

TABLE 4. Mean Heart Weights and Microscopic Grades Among All Diabetic Patients With and Without Coronary Artery Lesions of 70% or More

<table>
<thead>
<tr>
<th></th>
<th>Coronary lesion</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>≥70%</td>
<td>&lt;70%</td>
</tr>
<tr>
<td>Patients (n)</td>
<td>30</td>
<td>19</td>
</tr>
<tr>
<td>Mean heart weight (g)*</td>
<td>519±29</td>
<td>493±35</td>
</tr>
<tr>
<td>Microscopic grade</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Interstitial fibrosis*</td>
<td>1.6±0.2</td>
<td>1.5±0.2</td>
</tr>
<tr>
<td>Perivascular fibrosis*</td>
<td>1.2±0.1</td>
<td>0.99±0.2</td>
</tr>
<tr>
<td>Replacement fibrosis*</td>
<td>1.5±0.2</td>
<td>0.79±0.3</td>
</tr>
<tr>
<td>Total fibrosis score*</td>
<td>4.3±0.4</td>
<td>3.3±0.5</td>
</tr>
</tbody>
</table>

Values are mean±SEM. *Not significant (p>0.05); †Wilcoxon’s ranked-sum test; significant difference (p<0.05) between the two means.

hypertension have an increased risk of developing congestive heart failure\textsuperscript{15} and myocardial infarction\textsuperscript{2} over and above the risk of developing these complications in patients with hypertension or diabetes alone. The search for factors that can reduce the excess morbidity and mortality due to cardiovascular disease in diabetic patients is, therefore, important. Hypertension has been identified as a major, if not the major, risk factor in the pathogenesis of retinopathy\textsuperscript{16} and nephropathy\textsuperscript{17} in certain diabetic groups. A decade ago, one of us (S.M.F.) with others proposed that hypertension is a significant factor in the pathogenesis of another diabetic complication, severe diabetic heart disease.\textsuperscript{1} The present study confirms these earlier findings and also lends support to other related studies published during this 10-year interval.\textsuperscript{2–9}

Noninvasive testing has demonstrated left ventricular diastolic abnormalities in hypertensive-diabetic patients greater than those found in patients with hypertension alone.\textsuperscript{3} Systolic hypertension independently contributes to diastolic dysfunction in diabetic patients.\textsuperscript{4} These findings have led to the suggestion that treatment of even mild hypertension in diabetic patients may forestall the development of hypertensive-diabetic cardiomyopathy.\textsuperscript{4} Diabetic patients with hypertension are excluded at times from studies that specifically examine cardiac function in diabetes,\textsuperscript{18} thus hampering evaluation of hypertension as a risk factor for the development of diabetic cardiomyopathy.

Rat models of hypertension and diabetes have demonstrated the dysfunctional aspects\textsuperscript{5} and abnormal histological features by light\textsuperscript{7} and electron\textsuperscript{6} microscopy that are noted in human hypertensive-diabetic cardiomyopathy as well. In particular, the cardiomegaly and the increased interstitial and replacement fibrosis seen in the rat model recapitulate the findings seen in human hypertensive-diabetic cardiomyopathy. Recently, electrophysiological and contractile protein biochemical studies on rats with hypertension, diabetes, or both revealed progressive cellular dysfunction among these groups, sufficient to cause cardiomyopathy and congestive heart failure in the hypertensive-diabetic rat.\textsuperscript{9}

None of the microscopic features that we have described are specific for hypertensive-diabetic cardiomyopathy. All of these fibrotic changes can be seen in other types of cardiomyopathy.\textsuperscript{11} However, in patients who have hypertension, diabetes, or both, the extent and the progressive increase in these microscopic abnormalities are noteworthy and are likely contributors to the measurable diastolic dys-

FIGURE 4. Plot of relation between the microscopic total fibrosis score and the chemical determination of micrograms of collagen per milligram of noncollagenous protein. Correlation is highly significant.
function in these patients. Because the function of the normal connective tissue framework of the heart is primarily to ensure proper diastolic alignment of the myocytes, abnormalities of connective tissue have been proposed as a pathophysiological mechanism for the development of diastolic dysfunction and the stiff consistency of the ventricle noted grossly at autopsy of patients with hypertensive-diabetic cardiomyopathy.

The development of a semiquantitative scale for evaluation of total fibrosis was necessary, because all types of fibrosis are generally included in purely quantitative methods in which morphometric or biochemical and spectrophotometric methods are used to measure the amount of fibrosis in the heart. These more purely quantitative methods have been used to correlate heart weight and percent cardiac fibrosis in various types of heart diseases. We postulated that a semiquantitative evaluation of total cardiac fibrosis would be more likely to correlate with functional deficits than would any single fibrosis component, that is, replacement, interstitial, or perivascular fibrosis. In this study, patients with congestive heart failure had significantly greater total fibrosis scores than did patients without congestive heart failure. We believe that the greater amounts of fibrosis in the hearts of hypertensive-diabetic patients are largely responsible for the diastolic dysfunction measured noninvasively in these patients.

With the semiquantitative scale, positive associations were found between heart weight and total fibrosis for patients with diabetes alone and with both hypertension and diabetes. Because hypertensive patients had the least amount of fibrosis, the inability to detect a correlation could have been due to inadequate sensitivity of the scale to measure small amounts of fibrosis. Other investigators have found that with strict quantitative methods, the percent area of fibrosis in hearts of hypertensive patients is relatively small (mean, 2.6%) but does correlate with heart weight. With these same methods, hearts of hypertensive patients have been found to have significantly more fibrosis than do hearts of normal patients, which have a mean of 1.1% fibrosis. However, the role of myocardial hypertrophy as the major contributor to increased heart weight in hypertensive patients cannot be overemphasized.

The chemical method validated the semiquantitative microscopic findings, showing a significant correlation between the two methods. This quantitative method, like other chemical methods, is limited by its inability to delineate the distribution of collagen. Therefore, the collagenous components of, for instance, subendocardial fibrosis, resolving subacute myocarditis, and epicardial perivascular fibrosis are included within the quantitative measurements, thus contributing to some of the "noise" in the data. These components were screened out in the microscopic evaluation.

Epidemiological studies have revealed that hypertension and diabetes are independent risk factors for the development of coronary artery disease. The risk of coronary artery disease is further increased when both of these factors are present in a single patient. The first study of hypertensive-diabetic cardiomyopathy specifically examined a group of patients without coronary artery disease. Coronary artery disease was not a restriction to entry in the present study and, in fact, had no significant influence on the total amount of fibrosis or on mean heart weight among the diabetic patients.

There are several potential explanations for the wide variation in fibrosis scores and heart weight within groups of patients with the same disease. Within these groups of autopsied patients, disease duration varied widely, from at least 1 year of recognized, treated disease(s) to more than 25 years. Although all patients were prescribed medications, their compliance with their therapeutic regimen is unknown, as is their blood pressure or metabolic control. Furthermore, antihypertensive treatment can affect the amount of myocardial fibrosis. For instance, after treatment-induced regression of hypertensive hypertrophy in rats, the myocardial collagen content of treated rat hearts was significantly less than that of untreated hypertensive rat hearts. However, hypertensive-diabetic patients often have poorly controlled hypertension.

Another possibly important reason for the variation in scores within the diabetic group is the high probability of several cases of clinically undiagnosed or untreated hypertension among these diabetic patients. Outpatient studies have revealed that 20% of hypertensive-diabetic patients are unaware of their hypertension. To explore this possibility, we reviewed the autopsy reports on the 28 diabetic patients and discovered that in 16, sections of the kidneys disclosed renal hyaline arteriolosclerosis, which is a pathological finding highly correlated with hypertensive disease. Thus, we suspect that subclinical or undiagnosed hypertension was an important contributor to higher fibrosis values in patients with diabetes alone.

We recognize the possibility that extracellular deposits of glycosaminoglycans could have been misinterpreted as fibrosis by light microscopy on hematoxylin-eosin–stained sections and could account for some of the scatter in Figure 4. However, previous observations emphasized the focality of glycosaminoglycan deposition in hearts of diabetic patients. Thus, these deposits are thought to be unrelated to diffuse myocardial disease.

All tissue samples used in this study were transmural sections of left ventricular free wall in areas free of any focal disease process (e.g., infarct and tumor). The assumption was made that several random sections taken at multiple locations along the left ventricular free wall are representative of pathology equally distributed along the wall. Indeed, the gross pathology of hearts of hypertensive-diabetic patients generally reveals the myocardium to be diffusely firm, almost waxy in consistency, without any grossly visi-
ble lesion. The rat model of hypertensive-diabetic cardiomyopathy also reveals that the myocardial pathology is diffuse in nature.6,7

The development of scars of replacement fibrosis is largely attributable to coronary artery disease;11 our results among the diabetic patients are certainly supportive of this tenet. However, in hearts of patients without coronary artery disease, areas of replacement fibrosis were occasionally found. Evidence of remote and acute myocytolysis may be responsible in part. Among the hypertensive patients, the group that had the least number of patients with luminal narrowing of 70% or more, mean replacement fibrosis scores were lowest.

The development of hypertension in diabetes mellitus has been variably attributed to genetic predisposition particularly in juvenile diabetic patients and to microangiopathy.25 The development of fibrosis in the heart of hypertensive patients may be largely attributable to increased wall stress.21 The pathogenesis of fibrosis in the heart of diabetic patients is unknown, but this fibrosis has been recognized for many years and is postulated to be due, at least in part, to diabetic microangiopathy.26 When the heart of a diabetic patient is affected by hypertension or coronary artery disease, there may be additive microangiopathy and large vessel-induced ischemia that results in diffuse myocardial scarring. The generalized fibrosis may lead to increased wall stiffness, diastolic dysfunction, and ultimately greater rates of congestive heart failure and cardiac mortality. As our population ages and becomes increasingly susceptible to both diabetes mellitus and hypertension, the public health implications take on even greater importance.

Acknowledgment
We thank Dr. Marcos Rojkind for his kind assistance and use of his laboratory in making possible the histochemical collagen determination.

References

Key Words • cardiomyopathy • congestive heart failure • myocardial fibrosis • histomorphometry
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K H van Hoeven and S M Factor

Circulation. 1990;82:848-855
doi: 10.1161/01.CIR.82.3.848

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1990 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

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