Percutaneous Myocardial Biopsy of the Left Ventricle

Experience in 198 Patients

By Earl K. Shirey, M.D., William A. Hawk, M.D., Devobroto Mukerji, M.D., and Donald B. Effler, M.D.

SUMMARY

A thin-walled Silverman needle has been used for 254 percutaneous punch biopsies of the left ventricle in 198 patients with closed chests at the Cleveland Clinic. The technic is described. The biopsy specimens were adequate for diagnosis in 192 patients. In all but three patients (who had lupus erythematosus, scleroderma, and chronic glomerulonephritis with congestive heart failure) cardiac catheterization and selective cardioangiographic studies were performed. There was angiographic evidence of primary myocardial disease, coronary atherosclerosis, or both, or rheumatic valvular disease in 175 patients. Cardiac catheterization and angiographic studies demonstrated no evidence of organic heart disease in 20 patients.

Cardiac tamponade was a complication of myocardial biopsy in eight patients. Postpericardiotomy syndrome occurred in four patients and ventricular fibrillation in one patient.

Myocardium with no pathologic diagnosis and interstitial fibrosis or myocardial hypertrophy or both were the light microscopic findings in 165 patients. Representative sections of the biopsy in 27 patients demonstrated small-vessel disease, basophilic degeneration, focal interstitial myocarditis, amyloidosis, Aschoff's nodules, or vacuolar degeneration. The current experience suggests that myocardial biopsy combined with selective cardioangiography is of experimental value, improves the accuracy of diagnosis, and plays a role in the management of some patients.

Additional Indexing Words:
Cardiac catheterization  Rheumatic heart disease  Cinecardioangiography
Coronary atherosclerosis  Light microscopy  Primary myocardial disease
Hemopericardium

Biopsy of the heart has provided a method for evaluating morphology, biochemistry, and other parameters related to normal and abnormal myocardium. Since Casten and Marsh in 1953 reported a series of punch biopsies made with a Vim-Silverman needle in 65 dogs, a variety of technics for obtaining heart muscle tissue from the experimental animal and the human by using an epicardial or endocardial approach has been advocated. This paper describes our experience with biopsies performed with the Vim-Silverman needle in patients with and without angiographic abnormalities. A total of 254 biopsies have been performed on 198 living patients ranging in age from 14 to 66 years. There were 139 males and 59 females. The light microscopic interpretations of the biopsied specimens are presented, and the technic, complications of the procedure, and the...
rode of biopsy in investigation, diagnosis, and management of patients are discussed.

Methods

All patients were evaluated by their histories, physical examinations, electrocardiograms, and X-rays of the chest. In all but three patients (those who had lupus erythematosus, scleroderma, and chronic glomerulonephritis) cardiac catheterization and cineangiography were performed in the manner described elsewhere. The angiographic diagnosis was primary myocardial disease, coronary atherosclerosis, or both, or rheumatic valve disease. In 20 patients with clinical diagnosis of coronary atherosclerosis, left heart catheterization, selective coronary arteriography, and left ventriculography demonstrated no evidence of organic heart disease.

Criteria for Angiographic Diagnosis

The following criteria for diagnosis were employed:

Normal Study

No variations were evident in the lumen diameter in a major trunk or branch of the coronary arteries. Normal size, contour, and contractility of the left ventricle were present, without evidence of a valve lesion or shunt.

Coronary Atherosclerosis

Variations were seen in lumen diameter of a coronary artery.

Primary Myocardial Disease

The criteria for congestive and restrictive myocardial disease consisted of localized or generalized impairment of contractility of the left ventricle without a primary valve lesion or shunt. Obstruction of a coronary artery was less than 50%. In hypertrophic disease a small ventricular cavity, accentuated trabecular pattern, functional constriction of septal perforators during systole were present without arterial hypertension, a fixed subvalvular obstruction, valvular, and supravalvular aortic stenosis.

Rheumatic Valve Disease

Mitral or aortic valve leaflets were thickened with or without calcification with reduced valve orifice or leakage or both.

Technic

All biopsies were performed in the Cardiac Catheterization Laboratory under direct vision using a 6-inch Philips image amplifier and a television fluoroscopic screen, and technic is as follows. The size of the heart, the contour of the cardiac silhouette, and the amplitude of pulsations are reviewed on a fluoroscopic image amplifier television screen with the patient in the supine position and rotated about 5° in the right anterior oblique projection. Then the heart rate and blood pressure are recorded, and the neck veins and peripheral pulses are carefully examined.

The left anterolateral chest wall is cleansed with benzalkonium chloride (tincture of Zephiran) and draped with sterile towels, with only the site for the needle biopsy exposed. The site is determined by locating the apex of the heart on the fluoroscopic image. In most patients with marked cardiomegaly, the apex is easily recognized by visible or palpable cardiac pulsations. The skin and subcutaneous tissue at the biopsy site are infiltrated with 2% procaine hydrochloride. Oxygen is administered by mask, and the electrocardiogram (lead II) is recorded on a multichannel recorder (Electronics for Medicine, model DR 8). The electrocardiogram is constantly monitored by a specifically designated member of the team. Sodium methohexital (Brevital sodium) in doses ranging between 60 and 80 mg is administered intravenously.

The obturator of a 14-gauge thin-walled Silverman needle, which permits the introduction of a 16-gauge split inner stylet, is positioned within the cannula and both are inserted beneath the skin at the predetermined site (fig. 1). The position of the needle is observed on the television fluoroscopic screen and under direct vision advanced into the chest cavity toward the apex of the left ventricle. The tip is directed upward and posteriorly toward the inferior angle of the right scapula. The needle is advanced slowly to the epicardial surface. Contact with this surface is recognized by ventricular ectopic beats, sensation of resistance, or pulsatile movements of the needle synchronous with the cardiac cycle (fig. 2A). Ventricular ectopic beats are controlled by slight withdrawal of the needle. While the cannula is held in place, the obturator is replaced with the split inner stylet or cutting needle (fig. 2B). This is advanced slowly until resistance or pulsatile movements are encountered. In rapid sequence the cutting needle is thrust forward into the myocardium and the cannula is advanced over the needle (fig. 2C and D). A quick withdrawal of both components, while twisting them in a clockwise direction, completes the maneuver (fig. 2E).

The specimen is placed on a saline-moistened gauze sponge and divided into appropriate portions for light microscopy, electron microscopy, and special biochemical and immunologic procedures. The portion for light microscopy is immediately immersed in Zenker's fluid for
Results

A satisfactory myocardial specimen was obtained from 192 of 198 patients. In six patients the specimen was too small for diagnosis. It was usually possible to obtain a slightly flattened cylindrical biopsy specimen measuring $1.5 \times 0.1 \times 0.1$ cm. Although specimens as long as 2.0 cm have been obtained in practice, specimens 0.8 cm in length or greater are satisfactory for light microscopy, electron microscopy, biochemical,

![Figure 1](image1)

*Myocardial biopsy site.*

exactly 90 min. After this, the specimen is washed for 2 hours, dehydrated in graded alcohols, and embedded in paraffin. Because of the thinness of the biopsy specimen almost all of the section in the paraffin ribbon is retained and a battery of special stains is used, rather than cutting the paraffin block at different times with resultant waste of sections. All biopsy specimens have been stained in the same way. Three slides are prepared and stained with hematoxylin and eosin. A Masson trichrome stain for collagen, a phosphotungstic acid-hematoxylin stain for myofibrils, a toluidine blue stain for metachromatic substances, a diastase digest periodic acid Schiff stain and an undigested periodic acid Schiff stain for glycogen, a Verhoeff elastic tissue stain for vessels, and a crystal violet stain for amyloid comprise the routine.

**X-Rays and Electrocardiograms**

Chest X-ray and electrocardiographic findings after myocardial biopsy are shown in table 1. Postbiopsy X-rays were not taken in 14 patients who had no adverse effects. Electrocardiograms in 125 of 198 patients were considered an adequate number to establish the patterns commonly encountered.

For most patients the prebiopsy and postbiopsy electrocardiograms were recorded on high-sensitivity photographic electrocardiographs (Sanborn Twin Beam). Standard unipolar limb leads and eight precordial leads were obtained.

![Figure 2](image2)

*Biopsy technic (A to E); refer to text for description.*

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and immunologic assessment. In 39 patients it was necessary to perform 50 additional biopsies for studies other than histology. In some patients more than one anatomic abnormality was present, but only the major change is recorded. For example, basophilic degeneration, the prominent feature, and interstitial fibrosis occurred in the same patient.

The most frequent tissue diagnosis on 192 patients was interstitial fibrosis or hypertrophy or both (46.3%). Myocardium with no significant change constituted the next largest group (39.5%). The other pathologic findings occurred in 27 of 192 patients (14.2%).

The light microscopic findings in relation to the angiographic diagnosis are shown in table 2. There was no pathologic change in 80% (16 of 20) of those patients with no angiographic evidence of a cardiac abnormality. There was also no pathologic change in 35.6% (48 of 132) of those with primary myocardial disease, in 11% (two of 18) of those with rheumatic heart disease, and in 50% (eight of 16) of those with coronary atherosclerosis.

Interstitial fibrosis or hypertrophy or both were present in 50.7% (67 of 132) of patients with primary myocardial disease, in 61.1% (11 of 18) of those with rheumatic heart disease, and in 31.2% (five of 16) of those with coronary atherosclerosis. Three of these five patients with coronary atherosclerosis had electrocardiographic evidence of an old myocardial infarction. These histologic changes were found in two of three patients with primary myocardial disease and significant coexisting coronary atherosclerosis. Interstitial fibrosis was present in three of 20 patients with no angiographic abnormality.

Small-vessel disease was present in eight patients with angiographic evidence of primary myocardial disease or coronary atherosclerosis or both. In three of these eight patients scarring, manifested as fibrous tissue replacement of myocardium, was so extensive that half of the biopsy specimen was fibrous tissue. The other five biopsy specimens showed only slight interstitial fibrosis with a slight increase in perivascular fibrous connective tissue.

In the three cases showing marked scarring, the vessels involved were from 70 to 150 μ in diameter and the cross diameters of the lumina varied from 15 to 30 μ. The walls of these vessels showed a considerable increase in stainable collagen, particularly beneath the intima and extending in irregular fashion through the muscular coat of the vessel. Not all of the vessels in the biopsy specimens were affected. It was normal to find only one or two showing the sclerotic process. In the other five biopsies showing slight fibrosis, the caliber of vessel involved was somewhat smaller, ranging only to approximately 70 μ in cross diameter, and appeared to have an increased quantity of stainable collagen replacing portions of the muscularis. Masson stains and Verhoeff elastic tissue preparations reinforced these observations.
Of six patients who had microscopic findings of basophilic degeneration, five of these (83%) had angiographic evidence of primary myocardial disease and rheumatic heart disease. Of the five patients who had inflammatory changes manifested by lymphocytic infiltration, three had primary myocardial disease with a specific type of primary myocardial disease recognized in the biopsy specimens of two patients with rheumatic heart disease. Vacuolar degeneration was recognized in two patients with primary myocardial disease and rheumatic heart disease. Aschoff's nodules were recognized in two patients with rheumatic heart disease. Vacuolar degeneration was the major lesion in two patients with primary myocardial disease. Amyloidosis was recognized in four patients with a specific type of primary myocardial disease. Of the five patients who had angiographic evidence of primary myocardial disease or rheumatic heart disease, the biopsy specimens of two patients with primary myocardial disease showed an opportunity to observe the biopsy site with light microscopic findings and to compare the findings with the condition of the myocardium. Biopsy and autopsy histologic findings on all 11 patients are compared in Table 3.

Complications

The most potentially serious complication associated with percutaneous myocardial biopsy is cardiac tamponade. In eight patients, emergency thoracotomies were necessary. In four of these eight patients, distended neck veins and a progressive decline in arterial blood pressure developed within 5 min after the biopsy. Cardiac tamponade occurred after the biopsy, and the defect produced by the biopsy was filled by a blood clot which appeared to seal the defect effectively. Biopsy and autopsy histologic findings on all 11 patients are compared in Table 3.

Table 2

Comparison of Histology with Angiographic Findings in 189 Patients

<table>
<thead>
<tr>
<th>Angiographic diagnosis</th>
<th>Patients (no.)</th>
<th>Myocardium, no significant change*</th>
<th>Hypertrophy and/or fibrosis†</th>
<th>Small-vessel disease</th>
<th>Basophilic degeneration</th>
<th>Lymphocytic infiltration</th>
<th>Amyloidosis</th>
<th>Aschoff's nodule</th>
<th>Vacuolar degeneration of muscle cell</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal study</td>
<td>20</td>
<td>16</td>
<td>3</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary myocardial disease</td>
<td>132</td>
<td>48</td>
<td>67</td>
<td>5</td>
<td>3</td>
<td>3</td>
<td>4</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Rheumatic heart disease</td>
<td>18</td>
<td>2</td>
<td>11</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coronary atherosclerosis</td>
<td>16</td>
<td>8</td>
<td>5</td>
<td>2</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary myocardial disease and coronary atherosclerosis‡</td>
<td>3</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Angiographic studies were not performed on two additional patients (not listed in this table) with lupus erythematosus and chronic glomerulonephritis. Biopsy showed no significant change in the myocardium.
†A single patient with scleroderma was not studied angiographically and consequently is not listed in this table. Biopsy, however, showed hypertrophy and fibrosis.
‡Obstruction > 50% but extent of arterial disease not proportional to the degree of impaired contractions of the left ventricle.
approximately 3 hours after biopsy in one patient. The site of the biopsy may be a significant factor in the development of cardiac tamponade. In five of the eight patients who required emergency thoracotomy, the puncture was made in the anterolateral wall several centimeters above the apex. The insertion of the needle into the myocardium some distance from the apical segment was recognized during the biopsy and confirmed at surgery. Although myocardial tissue has been obtained from the same area in a few patients without causing tamponade, the relationship could be significant. The incidence and degree of hemopericardium is likely to be related to the anatomic and functional status of the myocardium. Seven of the eight patients had primary myocardial disease of the congestive type. The same angiographic diagnosis had been made in four of seven patients who developed signs of hemopericardium but did not require thoracotomy. There was no consistent finding on light microscopy in this group of patients.

Cardiac tamponade has not been reported after the use of the Sakakibara and Konno technic. 6

Postpericardiotomy syndrome occurred within 4 weeks after myocardial biopsy in four patients. Each patient responded to adrenal
steroid therapy. Postpericardiotomy syndrome following left ventricular puncture for left heart catheterization has been described by Peter and associates.15

Ventricular fibrillation was encountered in one patient with severe primary myocardial disease. Sinus rhythm followed the application of a single DC electrical discharge. There were no other untoward reactions.

Regardless of technic, biopsy of the heart carries some risk, but the outcome in terms of morbidity and mortality depends heavily on the experience and the availability of personnel to manage emergencies effectively.

Discussion

The value of myocardial biopsy has been essentially dependent on the proper evaluation of clinical manifestations, which can vary with the experience and competence of the physician. For myocardial biopsy to be of experimental value and to have any practical application, the pathologic changes associated with specific types of cardiac disease must be identified. For this reason, selective cardioangiography, which provides a more dependable diagnostic standard, was performed on all but three patients. The presence or absence of coronary atherosclerosis was clearly defined by selective coronary arteriography.

Postmortem examination in 11 patients offered an opportunity to evaluate the reliability of cardioangiography and percutaneous myocardial biopsy (table 3). There was no difference in the angiographic and postmortem findings. In six of 11 patients (cases 1 through 6) the pathologic changes demonstrated in the biopsy specimen were comparable to the autopsy findings. The disparity in tissue diagnosis in four patients (cases 7 through 10) is probably due to failure to detect focal disease by the biopsy technic. In one patient (case 11) the absence of basophilic degeneration at autopsy suggests that the lesion may not be permanent. The cause of death was congestive failure secondary to a significant periprosthetic leakage. The patient had refused to undergo additional surgery.

In several patients the needle was advanced into the left ventricular cavity, but endocardial tissue was consistently absent in the specimens. This may not be a major disadvantage. Usually the diagnosis of endocardial fibroelastosis is recognized during the first few years of life and can be derived from clinical and angiographic findings. The types of endomyocardial disease described by Davies16 and Becker and associates17 are rarely encountered in the United States. Fibroplastic parietal endocarditis reported by Löeffler,18 like the other types of endocarditis, involves the inner third of the myocardium which is accessible from the epicardial approach. This study suggests that the diagnostic accuracy of percutaneous myocardial biopsy is acceptable but of limited value in patients with focal disease of the myocardium. Also, the thin-walled Silverman needle is of no value in establishing the presence or absence of endocardial disease.

Myocardial biopsy was performed on 19 patients with angiographic evidence of obstructive lesions in the coronary arteries to evaluate the reliability of selective coronary arteriography for the recognition of coronary atherosclerosis. There was evidence of sclerosis of small vessels in three of 19 patients. No atheromatous changes were recognized. Postmortem examination on one patient with coronary atherosclerosis revealed no abnormality of the small vessels (case 6; table 3). These findings indicate that selective coronary arteriography provides an objective diagnostic tool for the recognition of coronary atherosclerosis.19

The role of the microcirculation as a cause of angina pectoris and other clinical syndromes has interested several investigators.20–26 James24 found medical necrosis in the coronary arteries of small vessels in autopsy patients with Friedreich's ataxia, progressive muscular dystrophy, Marfan's syndrome, and familial cardiomegaly, and concluded this process was responsible for arrhythmias, conduction defects, and myocardial insufficiency. Clinical syndromes could be identified in four of our five patients with

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primary myocardial disease and biopsy findings of small-vessel disease. Congestive heart failure, or ventricular arrhythmias, or both were clinical manifestations in these patients. The four patients in this group had no extracardiac features of these heritable diseases. One patient had chest-wall pain. The histopathologic finding was an increase in collagen beneath the intima and throughout the muscular coat of the vessel. The pathology of small vessels of these patients differed from that of patients with hereditary disease, which suggests they have a different etiology. On the basis of morphology alone it is difficult to assess the significance of these vascular changes. In the severely scarred biopsy specimen the vascular changes may be reflective of the severity of the process which produced the scarring and might possibly play a role in the disability noted clinically. In the biopsy specimens with minimal fibrosis, however, the significance of the vascular changes is not clear since not all vessels are involved. The results would suggest that primary nonatherosclerotic changes are rare in the microcirculation and are not a cause of angina pectoris.19

In addition, 20 patients with normal coronary arteriograms and left ventriculograms were investigated because coronary heart disease had been suspected by one or more physicians. Chest pain resembling angina pectoris was the presenting symptom of all but one patient. The biopsy specimens revealed no evidence of any abnormality of the microcirculation. Chest pain interpreted as angina pectoris in patients with normal coronary arteriograms should not be attributed to myocardial ischemia secondary to large- or small-vessel disease. We suspect the error in the diagnosis is related to inadequate angiographic studies or to incorrect interpretation of the angiograms or symptoms in the majority of patients.

The significance of basophilic degeneration in six patients is not known. Five of the six patients had angiographic evidence of primary myocardial disease and rheumatic heart disease. The basophilic granule or crystal-like

Figure 3

(A) Left coronary arteriogram and (B) right coronary arteriogram shown in the left anterior oblique projection demonstrate no evidence of obstruction. The left ventriculogram (C) in the right anterior oblique projection demonstrates an increase in end-systolic volume. The amplitude of pulsations are impaired on motion picture study.
Substance has been found by others in microscopic sections of human myocardium at autopsy and in patients with familial form of myoclonic epilepsy, hypothyroidism, and idiopathic myocardiopathy.27, 28

The value of myocardial biopsy in the living human for investigative purposes when combined with selective angiographic studies is appreciated from this study. The improved accuracy of diagnosis is recognized in four patients with amyloidoses and three of 20 patients with interstitial fibrosis of the left ventricle and normal cardioangiograms. The findings in these three patients suggest primary myocardial disease which was not recognized clinically or by angiographic studies. Another example is illustrated in the following case report.

Case Report

A 42-year-old black female had shortness of breath and easy fatigability for 4 years. At the onset of these symptoms, she was admitted to a hospital and treated for rheumatic heart. On three occasions, she was readmitted to the same hospital because of chest pain attributed to heart attack. In addition to shortness of breath, she complained of a squeezing and burning sensation in the anterior chest during periods of physical and emotional stress, relieved by rest in 4 to 5 min. The physical examination elicited no abnormalities. Blood pressure was 149/90 mm Hg.

The hemoglobin was 12.6 g/100 ml. The leukocyte count was 8,300. Urinalysis was negative. Serum glutamic oxalacetic transaminase (SGOT) and lactic dehydrogenase (LDH) levels were normal. Fasting blood sugar value was 75 mg/100 ml. Levels of serum cholesterol and blood urea nitrogen (BUN) were normal. Serum albumin was 4 g/100 ml, and the alpha-1 and beta globulins were elevated. Chest X-rays showed slight enlargement of the left ventricle. An electrocardiogram showed sinus rhythm and left ventricular hypertrophy.

Left heart catheterization and angiographic studies were performed. The pressures in the aorta and left ventricle were 146/86 and 146/13 mm Hg, respectively. The angiographic findings

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**Figure 4**

Representative sections of the biopsy showing the presence of irregularly distributed broad bands of hyaline connective tissue which tended to separate muscle fasciculi so that several muscle fascicles appeared separated from a segment of apparently unremarkable appearing myocardium. Small vessels did not appear abnormal. The biopsy was interpreted as an example of interstitial fibrosis.
of primary myocardial disease are shown in figure 3, and the biopsy findings supporting the diagnosis, in figure 4. On the basis of these combined studies the likely diagnosis is chronic myocarditis, cause undetermined.

Therapeutic Implications

At present, myocardial biopsy has a minor role in determining the management of patients. A diagnosis of diffuse myocardial degeneration in the form of vacuolar changes observed in one of two patients precluded valve surgery for mitral insufficiency. The recognition of inflammatory changes characterized by lymphocytic infiltration in five patients was considered an indication for steroid therapy. Aschoff's nodules were an indication for steroid therapy and a possibly valid reason for deferring valve surgery in two patients with rheumatic heart disease.

Myocardial hypertrophy and interstitial fibrosis, the most frequent pathologic abnormalities, probably have no therapeutic implication except in the selection of patients for surgery with acquired valvular and coronary heart disease. The same may be true in patients biopsied with no histologic abnormality; however, a negative biopsy does not absolutely exclude myocardial disease. If these specimens are representative of all other myocardial segments throughout the heart, findings could be of value from a therapeutic and prognostic standpoint. A careful follow-up of these patients will be required to determine the validity of such information.

Biopsies for ultrastructural studies and other investigations are in process. Perhaps these other parameters will improve our knowledge and understanding of normal and abnormal myocardium and consequently establish a greater significance to biopsies from the clinical standpoint.

References

1. Casten CG, Marsh JB: Metabolic studies on cardiac tissue obtained by needle biopsy in the intact unanesthetized dog. Circ Res 1: 226, 1953
15. Peter RH, Whalen RE, Orgain ES, McIntosh HD: Postpericardiotomy syndrome as a complication of percutaneous left ventricular puncture. Amer J Cardiol 17: 86, 1966

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