Critical analysis of endomyocardial biopsies from patients suspected of having cardiomyopathy

II: Comparison of histology and clinical/haemodynamic information

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SUMMARY Endomyocardial biopsies showing histological evidence of "ordinary" hypertrophy or changes compatible with congestive cardiomyopathy (COCM) were obtained from 125 patients.

Statistical analysis compared histological/morphometric data with clinical/haemodynamic findings such as ejection fraction, left ventricular end-diastolic pressure, and length of history. Patients were grouped either according to the histological description or the clinical diagnosis. Comparison of the morphological description with the final clinical diagnosis was also undertaken. Follow-up of the patients was between two and 66 months.

The results of the statistical analyses showed no correlation between quantitative, morphological assessment and either clinical information, that is length of history and subsequent course, or the haemodynamic variables.

In 86 per cent of cases a rough agreement between the morphological description and the clinical diagnosis was obtained, but no specific pattern permitting a morphological diagnosis of COCM was established.

The findings suggest that pronounced topographic variation in biopsy material exists and that, therefore, the severity of COCM or its prognosis cannot be assessed from histological changes.

Since the introduction of the biopome technique by Sakakibara and Konno¹ ² this method of obtaining fresh endomyocardial tissue has been used with increasing frequency, particularly in the last decade. The analyses to which the samples have been subjected have been manifold and include diagnostically descriptive aspects,³–⁵ biochemical analyses,⁶–⁸ and immunological studies.⁹ ¹⁰ Correlative studies comparing morphological features and clinical variables have been undertaken with differing results.¹¹ ¹²

The purpose of this investigation was to ascertain whether or not morphology could predict the functional state of the myocardium, as expressed by ejection fraction of the left ventricle, left ventricular end-diastolic pressure, and length of history, and the prognosis. The comparability of descriptive morphology and the final clinical diagnosis were also assessed.

Subjects and methods

Biopsies were obtained from 143 male and 58 female patients with an average age of 43.7 years (range 4 to 72 years) suspected of having some form of cardiomyopathy.

In order to compare histological/morphometric data with clinical/haemodynamic information, patients with either histological "ordinary" hypertrophy or with changes usually agreed to be compatible with congestive cardiomyopathy were selected. Endomyocardial biopsies were obtained by the small Konno-Sakakibara or the King's instrument. The tissue was frozen in melting "Freon"
(BOC) precooled in liquid nitrogen or fixed in
3 per cent cacodylate buffered glutaraldehyde.
Frozen sections, 5 μm thick, were cut on a
Bright’s cryostat with a chamber temperature of
-20°C, and paraffin-embedded material fixed in
glutaraldehyde were cut on a Jung’s base sledge
microtome.

In every instance haemotoxylin-eosin and elastic
van Gieson stains were used.

Morphological assessment included structural
changes in the myocardium, the endocardium, and
the interstitium. Quantitative measurements of
fibre diameter, volume fraction of collagen tissue,
and interstitium were also undertaken.

Experience from a pilot study of endomyocardial
biopsies from 150 patients formed the basis for
the descriptive terms employed:

Hypertrophy: hypertrophy of myocardial fibres
and nuclei, and no other significant changes.

Congestive cardiomyopathy (CCOM): this cannot
be conclusively diagnosed from histological ex-
amination as no single feature or features are path-
ognomonic. Biopsies showing either hypertrophy
plus attenuation of muscle fibres, or hypertrophy
plus smooth muscle cell hypertrophy (hyperplasia)
of endocardium, or hypertrophy plus attenuation
of muscle fibres plus smooth muscle cell hyper-
trophy of the endocardium were included, these
features being compatible with such a diagnosis.

CATHETERISATION, HAEMODYNAMIC
MEASUREMENTS, AND FOLLOW-UP OF
PATIENTS

The Seldinger technique or cutdown had been
used for right- or left-sided catheterisation. Left
ventricular end-diastolic pressures and the find-
ings on selective coronary angiography were ob-
tained from the catheterisation reports but the
former were ignored in patients with significant
valve gradients. In none of the patients were there
any anatomical or significant pathological abnormali-
ties of the coronary arteries.

Left ventricular angiography was performed in
the right anterior oblique projection at 35°, and
angiograms were used to calculate the ejection
fraction by the area-length method of Sandler and
Dodge.

The electrocardiogram was either normal or,
more often, showed non-specific changes.

Clinical and follow-up information was obtained
from the case notes and from the responsible
physicians. Though at the time of the biopsy
cardiomyopathy was the provisional diagnosis in
all patients, in some this was changed later, either
because the biopsy was diagnostic of some other
heart disease, or because hypertension developed,
or because repeat coronary angiography showed
coronary arterial disease, and so forth.

Functional grouping (New York Heart Associa-
tion) was not undertaken by all departments
involved in the study.

STATISTICAL METHODS

The tests carried out included χ² test, t test, one-way
analysis of variance, two-way analysis of variance,
correlation analysis, and multivariate techniques
(multilinear regression or cluster type of analysis)
to investigate if any particular pattern would
emerge on follow-up of the patients.

Mathematical values were assigned to the various
groups: dead = 1, deterioration = 2, a stable course
= 3, and improvement = 4.

Throughout the study the null hypothesis was
used—that there was no difference between the

* In all cases this method was compared with the width/length
method described by Greene et al. The correlation between the
two methods is excellent (r = 0.96, p < 0.001); the line of regression
is coincident with a 45° slope, but does not pass through the origin
(Y Greene = 1.05 × S-D -10.46).

Table 1 Information on morphology and haemodynamics

<table>
<thead>
<tr>
<th>Diam (μm)</th>
<th>VFC (%)</th>
<th>EF (%)</th>
<th>LVEDP (mmHg)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>Range</td>
<td>No.</td>
</tr>
<tr>
<td>Hypertrophy</td>
<td>16.6</td>
<td>0.3-22.5</td>
<td>52</td>
</tr>
<tr>
<td>COCM</td>
<td>15.9</td>
<td>10.1-25.3</td>
<td>82</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>134</td>
</tr>
<tr>
<td>Death</td>
<td>16.4</td>
<td>10.8-22.8</td>
<td>16</td>
</tr>
<tr>
<td>Deterioration</td>
<td>14.6</td>
<td>9.2-20.8</td>
<td>12</td>
</tr>
<tr>
<td>Stable course</td>
<td>15.5</td>
<td>10.0-25.9</td>
<td>52</td>
</tr>
<tr>
<td>Improvement</td>
<td>16.8</td>
<td>10.7-24.7</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td>92</td>
<td></td>
<td>88</td>
</tr>
</tbody>
</table>

Note: Information on the subsequent course is available in 69 per cent of patients (92/134). In 37 of these 92 patients a histological picture of
"ordinary" hypertrophy was found in the biopsies, and in 55 the morphology was compatible with COCM.

VFC, volume fraction of collagen tissue.
Critical analysis of endomyocardial biopsies from patients suspected of having cardiomyopathy

...samples or results in question; consequently two-tailed tests were appraised. A p value of less than 0.05 was accepted as the limit of significance.

Results

MORPHOLOGICAL QUANTIFICATION COMPARED WITH CLINICAL/HAEMODYNAMIC INFORMATION

This is set out in Table 1. Possible differences in subsequent clinical course between the histological groups are set out in Table 2.

Death and deterioration tended to occur more frequently in the group with clinical congestive cardiomyopathy. One-way analysis of variance of diameter of muscle fibres, volume fraction of collagen tissue, ejection fraction, and left ventricular end-diastolic pressure was undertaken in respect of the subsequent course of the patients in the two histological groups.

The diameter of muscle fibres and the volume fraction of collagen tissue show no statistically significant difference in either group (Table 3) but analysis of the ejection fraction and left ventricular end-diastolic pressure showed some statistically significant differences (Table 4).

Multivariate analysis of these variables was undertaken in order to ascertain if this would predict differences in the subsequent course of the disease but there was no difference in the two histological groups.

Ejection fraction, left ventricular end-diastolic pressure, and length of history were each correlated with the diameter of the muscle fibres, and volume fraction of collagen tissue. The data showed total scatter and no correlations were established. Three graphs from the groups compatible with COCM illustrate these findings (Fig. 1 to 3).

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Table 2 Patients with "ordinary" hypertrophy and congestive cardiomyopathy analysed according to subsequent course of disease

<table>
<thead>
<tr>
<th>Clinical progress</th>
<th>COCM</th>
<th>Hypertrophy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dead, deterioration</td>
<td>22</td>
<td>6</td>
</tr>
<tr>
<td>Stable improvement</td>
<td>33</td>
<td>31</td>
</tr>
<tr>
<td></td>
<td>55</td>
<td>37</td>
</tr>
</tbody>
</table>

χ² = 4.84, p < 0.05.

Table 3 Diameter of muscle fibres (mean, µm) and VFC (mean, %) analysed by one-way analysis of variance

<table>
<thead>
<tr>
<th>Clinical progress</th>
<th>Hypertrophy</th>
<th>COCM</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Diameter</td>
<td>Diameter</td>
</tr>
<tr>
<td>Dead</td>
<td>18-4</td>
<td>15-3</td>
</tr>
<tr>
<td>Deterioration</td>
<td>17-1</td>
<td>NS</td>
</tr>
<tr>
<td>Stable</td>
<td>15-6</td>
<td>15-5</td>
</tr>
<tr>
<td>Improvement</td>
<td>17-7</td>
<td>17-5</td>
</tr>
<tr>
<td></td>
<td>VFC</td>
<td>VFC</td>
</tr>
<tr>
<td>Dead</td>
<td>1-6</td>
<td>1-5</td>
</tr>
<tr>
<td>Deterioration</td>
<td>1-2</td>
<td>NS</td>
</tr>
<tr>
<td>Stable</td>
<td>1-6</td>
<td>1-9</td>
</tr>
<tr>
<td>Improvement</td>
<td>1-3</td>
<td>NS</td>
</tr>
</tbody>
</table>

NS: no statistically significant difference.

VFC, volume fraction of collagen tissue.

Table 4 Ejection fraction (EF) (mean, %) and left ventricular end-diastolic pressure (LVEDP) (mean, mmHg) analysed by one-way analysis of variance

<table>
<thead>
<tr>
<th>Clinical progress</th>
<th>Hypertrophy</th>
<th>COCM</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>EF</td>
<td>EF</td>
</tr>
<tr>
<td>Deterioration</td>
<td>&lt;0-001</td>
<td>37-0</td>
</tr>
<tr>
<td>Improvement</td>
<td>41-4</td>
<td>NS</td>
</tr>
<tr>
<td>Stable</td>
<td>46-1</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>&lt;0-01</td>
<td>&lt;0-01</td>
</tr>
<tr>
<td>Dead</td>
<td>67-5</td>
<td>NS</td>
</tr>
<tr>
<td>Stable</td>
<td>25-3</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>&lt;0-01</td>
<td>&lt;0-01</td>
</tr>
<tr>
<td>Improvement</td>
<td>21-4</td>
<td>NS</td>
</tr>
<tr>
<td>Dead</td>
<td>18-0</td>
<td>NS</td>
</tr>
<tr>
<td>Stable</td>
<td>13-1</td>
<td>NS</td>
</tr>
</tbody>
</table>

NS: No statistically significant difference.

Analysis based on clinical diagnosis rather than that based on histological description was undertaken. It was necessary to regroup a few patients, as the two were not always identical. This resulted in two groups, one of 58 patients with COCM and the other with 34 patients who were finally considered not to have this, that is after further...
investigations and follow-up. Multivariate analysis, however, failed to establish any positive correlation.

Twenty-six patients with "ordinary" hypertrophy were separated according to the final clinical diagnosis; 13 patients with clinical congestive cardiomyopathy and 13 patients who were subsequently found to have coronary heart disease and hypertension and/or valvar lesions, and no cardiomyopathy. There was no statistically significant difference (t test) between the data in these two groups (Table 5).

**COMPARISON OF HISTOLOGICAL DESCRIPTION WITH FINAL CLINICAL DIAGNOSIS**

Provided that the sample is representative, a biopsy from conditions such as hypertrophic cardiomyopathy or myocarditis shows a specific morphology: "histological description" can be replaced by "histological diagnosis". In other conditions no specific changes exist and the histological descriptions compatible with clinical COCM are not pathognomonic for this condition, as similar morphological changes may be seen in a variety of other conditions, such as ischaemic disease or valvar lesions with heart failure. "Ordinary" hypertrophy could apply to an early stage of clinical COCM, the morphological signs of dilatation having not yet developed, or to other conditions.

With these reservations, agreement between histological descriptions and clinical diagnosis was
Critical analysis of endomyocardial biopsies from patients suspected of having cardiomyopathy

present in 86 per cent of cases (Table 6). In four of the remaining patients the clinical diagnosis was not yet firmly established. Five of nine patients in whom a clinical diagnosis of hypertrophic obstructive cardiomyopathy (HOCM) was not histologically confirmed had no obstruction. Of three cases with "Löffler-endomyocardial fibrosis" only one had been histologically verified: in one patient the right ventricular biopsy showed ordinary hypertrophy, but subsequent operation showed endomyocardial fibrosis limited to the left ventricle. In the third patient the diagnosis is suspected on clinical grounds only.

On examination of the clinical notes it was found that the histological report had caused a change of the clinical diagnosis in 15 of 111 patients (Table 7).

In about 10 to 20 per cent of patients with typical anginal chest pain the selective coronary angiograms are normal. Twenty-nine patients of that category were included in this study (Table 6). The morphological changes in these patients varied; only in two were the biopsies normal.

Discussion

The haemodynamic variables—ejection fraction and left ventricular end-diastolic pressure—showed a few significant differences when analysed with respect to the subsequent clinical course; but these were ambiguous. Patients with "ordinary" hypertrophy and showing clinical deterioration differed from the rest, and so did patients with COCM and a stable clinical course.

No correlation could be established between morphological quantification, and clinical information (length of history, subsequent course) and haemodynamic variables (ejection fraction, left ventricular end-diastolic pressure) in the two groups, "ordinary" hypertrophy and COCM. Thus, prognosis or the severity of disease cannot be assessed from histological changes. Davies et al.11 agree, but Kunkel et al.12 do not.

The reasons for this discrepancy could be because of differences in the selection of patients, different definitions of tissue structures; or inadequate endomyocardial biopsies. Quantitative investigations have shown that pronounced topographic variations may be found within the myocardium and only with five or more biopsies is accuracy likely.19 With fewer biopsies the changes observed may well be fortuitous and thus a further study on a larger scale using five or more biopsies is needed to settle this point. Such a study might benefit methods of study other than the morphological, for representative sampling is equally important in, for instance, biochemical studies which have been used in the study of heart muscle biopsies.

The myocardium can react only in a limited way

<table>
<thead>
<tr>
<th>From</th>
<th>To</th>
<th>No. of patients</th>
<th>Op/ necropsy</th>
</tr>
</thead>
<tbody>
<tr>
<td>COCM</td>
<td>HOCM</td>
<td>2</td>
<td>+</td>
</tr>
<tr>
<td>Aortic stenosis?</td>
<td>HOCM</td>
<td>1</td>
<td>+</td>
</tr>
<tr>
<td>HOCM?</td>
<td>No HOCM (hypertension)</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>COCM</td>
<td>Sarcoidosis</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>COCM</td>
<td>No COCM (constrictive pericarditis)</td>
<td>1</td>
<td>+</td>
</tr>
<tr>
<td>CAD + COCM</td>
<td>+ Myocarditis</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>COCM</td>
<td>+ Myocarditis</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>NCA</td>
<td>Myocarditis</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Myocarditis?</td>
<td>No inflammation</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>COCM? rheumatic fever</td>
<td>Rheumatic fever</td>
<td>1</td>
<td>+</td>
</tr>
</tbody>
</table>

CAD, coronary arterial disease; NCA, normal coronary arteries, anginal chest pain.

<p>| | | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HY</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HA</td>
<td>15</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HS</td>
<td>COCM 1</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>HAS</td>
<td>33</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HOCM</td>
<td>8</td>
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<td></td>
</tr>
<tr>
<td>Myocarditis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Interstitial fibrosis</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>68</td>
<td>17</td>
<td>8</td>
</tr>
<tr>
<td>Failed</td>
<td>17</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>201</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

HY, hypertrophy; HA, hypertrophy with attenuation; HS, hypertrophy with smooth muscle cell hypertrophy of the endocardium; HAS, hypertrophy with attenuation and smooth muscle cell hypertrophy of the endocardium; CAD, coronary arterial disease; NCA, normal coronary arteries, anginal chest pain, no study of lactate production; + Lact, abnormal lactate production in NCA patients; − Lact, normal lactate production in NCA patients.
to a variety of stimuli, most commonly with hypertrophy. Morphological descriptions cannot, therefore, always be expressed in terms of clinical diagnoses but the attempt to establish a correlation between morphology and either myocardial function or prognosis with two groups of patients reclassified on clinical grounds as having or as not having COCM was unsuccessful.

In 86 per cent of patients there was a crude correlation between the morphological description and the clinical diagnosis. Similar results—but maybe more optimistically interpreted—have been reported by others. A "crude correlation", however, is not adequate.

The biopsies from patients with normal coronary arteries and anginal chest pain showed an abnormal morphology. Though the histological changes were not uniform, this finding strongly supports the view that these patients are suffering from a myocardial disorder. No evidence of small vessel disease was found, a confirmation of the findings by Richardson et al.

In 13.5 per cent of patients morphological and morphometric examination altered the clinical diagnosis and thus treatment and prognosis. This alone in our opinion justifies the continued use of myocardial biopsy of these patients.

To establish the value of histological examination of endomyocardial tissue the diagnostic sensitivity and specificity of the procedure should be known but this will need a prospective study in which the morphological descriptions are first defined precisely, and are related to specific clinical diagnoses.

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References

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