DIFFUSE MYOCARDIAL FIBROSIS IN ISCHAEMIC HEART DISEASE

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ABSTRACT

The amount of connective tissue was determined morpho-
metrically in the left ventricular myocardium of 123 autopsy
hearts. Patients with a history or signs of systemic dis-
eases (such as arterial hypertension or diabetes mellitus) or
of non-ischaemic heart disease were excluded. Three tissue
samples from the left ventricle (anterior and posterior walls,
interventricular septum) were cut at 5 μm. They were stained
with Masson trichrome stain, and the amount of connective
tissue was estimated by a point counting method in a projec-
tion microscope at a magnification of 200. A square lattice
with 36 points was used. In hearts with coronary artery
narrowing more than 10% in terms of area of the luminal
cross section, but devoid of any recent or old myocardial
infarct, the volume fraction of fibrosis +- SD was 4.1% +-
1.1% (controls 2.6% +- 0.8). Hearts with infarct scars con-
tained 6.3-6.6% diffuse connective tissue. In hearts with
acute infarcts only (no scars) the corresponding figure
was 3.2%. The results show that also limited coronary
artery narrowing is associated with diffuse myocardial
fibrosis. In fatal acute myocardial infarcts, the amount
of diffuse fibrosis remains low, whereas in hearts with
scars from earlier infarcts with or without acute infarct
diffuse fibrosis is severe.

INTRODUCTION

The capacity of the coronary circulation and the state of
the myocardium determine the development of the ischaemic

heart disease (Baroldi et al. 1974, Davies et al. 1976, Silver et al. 1980, Oliva 1981). However, the exact mechanism leading to acute myocardial infarction or to chronic myocardial damage is unknown (Oliva 1981). Several myocardial factors have been speculated as initiators of the acute myocardial infarction (Harnarayan et al. 1970, Olsen 1976, Lautsch 1979). Diffuse myocardial fibrosis of the left ventricular myocardium is already seen at the early stages of ischaemic heart disease. In an earlier study we measured morphometrically the amount of diffuse connective tissue in the myocardium of hearts with different degree of coronary narrowing (Romppanen et al. 1982). Fibrosis increased gradually with increase in coronary narrowing.

In the present study, the amount of myocardial connective tissue was measured in a series of autopsy hearts. In addition, the number of arterioles in the myocardium was estimated. There were many hearts with no visible signs of coronary or myocardial fibrotic disease. Many of the hearts had old fibrotic scars and in some acute infarction was seen. We tried to combine the results of morphometric analysis with the autopsy findings to reveal the pathogenetic relationship between coronary disease and diffuse fibrosis in different types of ischaemic heart disease.

MATERIALS AND METHODS

In a series of 342 adult autopsies (Kuopio University Hospital, Kuopio, Finland) 123 cases were selected for the study. Patients with heart disease other than ischaemic heart disease were excluded. Also cases with a clinical history of systemic disease potentially damaging to myocardium (arterial hypertension, diabetes mellitus, severe blood disorders etc.) were excluded.

The coronary arteries were cut perpendicularly at 3-5 mm intervals. Atherosclerosis was graded as follows

Grade 0: No signs of coronary narrowing.
Grade 1: Slight narrowing (less than 10% of the lumen in section replaced by plaques).
Grade 2: Moderate narrowing (10-50% of lumen replaced by plaques).
Grade 3: Severe narrowing (50-90% of lumen replaced by plaques).
Grade 4: Coronary occlusion (more than 90% of lumen replaced by plaques).

The left ventricular myocardium was inspected by cutting the muscle into slices of about 5 mm thick. The cuts were made perpendicularly to the endocardium. Three tissue samples from standard places were taken for the morphometrical study

(middle of the anterior, posterior and septal walls) (Romppa-
nen et al. 1981). The section area was 1 cm^2 or more. The
samples from anterior or posterior walls contained both endo-
cardium and epicardium. The samples were fixed in neutral
formalin and embedded in paraffin. The sections were cut at 5
um and stained with Masson trichrome stain.

In morphometrical analysis a point counting method was
used (Weibel 1979, Collan et al. 1982). We used a projection
microscope (Wild M501) equipped with a projection head and an
automatic sampling stage at a magnification of x 200. Every
fourth microscopic field was analyzed with a square lattice
containing 36 points. About 60–80 fields were analyzed per
sample. Two points at the lattice corners were used to count
the hits on the myocardial fibers and the interstitial space.
All points were counted when estimating connective tissue.
Two connective tissue compartments were separated: periar-
teriolar connective tissue and the diffuse connective tissue.
Large vascular spaces and macroscopic scars were excluded from
measurements when more than 2 mm in diameter. All areas with
signs of myocardial necrosis were excluded. Subpericardial
fat and connective tissue were excluded. The volume fractions
(V_{Vi}) were determined according to the equation: $V_{Vi} = P_i / P_T$,
where P_i = number of point hits on tissue component i and P_T =
number of point hits on the reference area. The numerical
density of intramural arterioles was computed by recording the
number of their profiles in each microscopical field and
dividing it by the corresponding area. In statistics two-
tailed Student's t-test was used.

RESULTS

The main results are summarized in Table 1. In control
hearts (grade 0 or 1) the amount of diffuse connective tissue
was 2.05%. In hearts with coronary narrowing (grade 2 or
higher) and in hearts with acute myocardial infarction without
scars, the amount of connective tissue was 3.52% and 2.79%,
respectively. In hearts with scars and acute infarction the
amount of connective tissue was 5.69%, and in hearts with
scars only, 6.10%. The highest values were seen in hearts with
left ventricular aneyrysm (9.75%).

The perivascular connective tissue showed no significant
differences between the different groups (Table 1). No
definite changes in the numerical density of arterioles
were recorded, either. The posterior wall was more fibrotic
than other wall segments (Table 2).

DISCUSSION

The results show that heart's suffering from ischaemic
heart disease increased the amounts of diffuse fibrosis in

TABLE 1.
Summary of the morphometrical parameters.

Study group	V_{Vmy}[1]	V_{Vint}	V_{Vcttot}	$V_{Vctdiff}$	$V_{Vctperiv}$	N_{Aart}
Controls (n=26)	76.0+-5.0[2]	24.0+-5.0	2.6+-0.8	2.1+-0.8	0.5+-0.2	0.7+-0.2
Coronary narrowing (n=29)	73.8+-5.4	26.2+-5.4	4.1+-1.1***	3.5+-1.0***	0.6+-0.2	0.7+-0.2
Acute myocardial infarction (n=10)	73.9+-5.2	26.1+-5.2	3.2+-1.6	2.8+-1.4*	0.5+-0.1	0.6+-0.2
Myocardial scars (n=24)	73.8+-5.1	26.2+-5.1	6.3+-2.5***	5.7+-2.4***	0.6+-0.2	0.7+-0.2
Acute myocardial infarct and scars (n=30)	70.2+-5.1***	29.8+-5.1***	6.7+-2.6***	6.1+-2.6***	0.6+-0.2	0.6+-0.2
Left ventricular aneurysm (n=4)	67.0+-6.8**	33.0+-6.8**	10.1+-7.0***	9.8+-7.0***	0.4+-0.1*	0.6+-0.2

[1] Volume fractions in per cent.
   V_{Vmy} : Volume fraction, myocardial fibers
   V_{Vint} : Volume fraction, interstitial space (including connective tissue)
   V_{Vcttot} : Volume fraction, connective tissue, total
   $V_{Vctdiff}$: Volume fraction, connective tissue, diffuse
   $V_{Vctperiv}$: Volume fraction, connective tissue, perivascular
   N_{Aart} : Number of arterioles (1/mm^{-2})
[2] Standard deviation   Significance of findings: * $p < 0.05$
                                                         ** $p < 0.01$
                                                         *** $p < 0.001$

TABLE 2.
Amount of total connective tissue in different left ventricular walls.[1]

Study group	Anterior wall	Interventricular septum	Posterior wall
Controls (n=26)	2.7+-1.6	2.3+-0.9	2.8+-0.9
Coronary narrowing (n=29)	4.5+-1.6***	3.4+-1.0***	4.5+-1.7***
Myocardial infarction, all groups (n=68)	5.2+-3.4***	5.8+-4.8***	7.5+-5.9***

[1] Values in per cent +- standard deviation.
* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$, in relation to controls.

all developmental stages of the disease. The result supports
the finding that the degree of coronary narrowing is asso-
ciated with the amount of diffuse myocardial fibrosis in the
absence of myocardial infarction (Østergaard 1978, Romppanen
et al. 1982).

Unaffected myocardium in hearts with myocardial infarction and visible scars contained more fibrosis than unaffected hearts with acute infarction only. In hearts with visible scars the amount of diffuse connective tissue was increased reflecting the severe and long lasting derangement in coronary circulation. On the other hand, in hearts with acute infarction connective tissue was only slightly increased in respect to controls. In these cases ischaemia is probably of sudden onset possibly due to coronary thrombosis. If these cases had shown increased diffuse fibrosis, this would have indicated coronary narrowing of longer duration.

Our results showed that the left posterior ventricular wall is more susceptible to myocardial fibrosis than other parts of the wall. The study by Rafflenbeul et al. (1980) suggested that muscle dysfunction is caused by slighter stenotic changes in the right coronary artery than in the left coronary artery. Because the right coronary artery also supplies the posterior wall, these findings can be expressions of the same process.

The number of myocardial arterioles showed no significant changes between different heart groups studied. In animal studies, it has been shown that intercoronary collaterals, which usually are arterioles, can protect the myocardium from ischaemia (Flameng et al. 1979). These collaterals have been shown in man by coronary angiography (Williams et al. 1976, Fuster et al 1977, Schwarz et al. 1981, Horwitz et al. 1982, Rousseau et al. 1982). More studies are, however, needed to evaluate the real significance of these collaterals in different stages of ischaemic heart disease.

On the basis of this study it is difficult to say if the increased myocardial fibrosis has any clinical significance, i.e. whether it causes functional derangement of the myocardium or whetherit may in one way or other predispose to acute myocardial infarction. It is, however, postulated that myocardial fibrosis may decrease the compliance of left ventricle during diastole. Especially this may be true when diffuse myocardial fibrosis is associated with macroscopic scarring and possibly with ischaemic dyskinetic regions. It is also possible that myocardial fibrosis may protect the myocardium from infarction, because it may be a compensatory and adaptive phenomenon of the myocardium in ischaemic heart disease.

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