

# Relationship between cardioscopic images and histological changes in the left ventricle of patients with idiopathic myocarditis<sup>†</sup>

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## Aims

Endomyocardial biopsy is essential for definite diagnosis of idiopathic myocarditis. However, since endomyocardial biopsy is guided by fluoroscopy, whether or not the diseased myocardium is biopsied depends on chance, and this may lead to misdiagnosis. If the endocardial surface represents changes indicative of stages of myocarditis, staging of myocarditis and targeted cardioscope-guided biopsy could be used for accurate histological diagnosis.

## Methods and results

The relationship between left ventricular endocardial surface colour observed by cardioscopy and biopsy findings were examined in 78 patients with suspected idiopathic myocarditis. Of these, 59 patients were diagnosed histologically as idiopathic myocarditis. Endocardial colour was classified into red, milky white, purple, yellowish brown, or white. Biopsied specimens with red and milky white wall segments exhibited histological changes compatible with acute myocarditis; purple segments, active chronic myocarditis; and yellowish brown and white segments, inactive chronic myocarditis. The sensitivity, specificity, and predictive value of red and milky white colours for detecting acute myocarditis were 100, 100, and 100%, respectively; of purple for detecting active chronic myocarditis were 83, 92, and 78%, respectively; and yellowish brown and white for detecting inactive chronic myocarditis were 82, 74, and 53, respectively.

## Conclusion

Red and milky white endocardial surface colours predicted histological acute myocarditis, and purple predicted active chronic myocarditis. However, yellowish brown and white colours did not predict inactive chronic myocarditis.

## Keywords

Idiopathic myocarditis • Cardioscopy • Endocardial surface colour • Biopsy findings

## Introduction

Idiopathic myocarditis is an inflammatory myocardial disease, the aetiology of which is not well known.<sup>1,2</sup> The Dallas criteria<sup>3</sup> or Japanese Circulation Society criteria<sup>4</sup> have been used to diagnose this disease. With both criteria, the diagnosis is based on clinical manifestations and histology of the endomyocardial biopsy specimen.

Since endomyocardial biopsy is guided by fluoroscopy and not by direct observation, whether or not the biopsied specimens

are obtained from the inflamed areas and exhibit histological inflammatory changes is dependent on chance. This uncertainty means that myocarditis cannot be diagnosed from histological changes alone, and is the reason why clinical manifestations must also be included in the diagnostic criteria.

If endocardial surface colour can be shown to represent the stages of myocarditis, percutaneous cardioscopy, which enables observation of the cardiac chambers from inside, could be used for diagnosis and staging of myocarditis.<sup>5,6</sup> This procedure would

<sup>†</sup>This study was performed at Toho University Sakura Hospital and Funabashi-Futawa Hospital.

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also make it possible to obtain myocardial specimens from the diseased myocardium, with direct observation of where inflammation is actually occurring. A definite histological diagnosis of myocarditis could therefore be attained.<sup>7</sup>

By comparing cardioscopic images and biopsy findings, a cardioscopic diagnosis of myocarditis could therefore be established, and the interrelationships between histological changes, cardioscopic images, and clinical manifestations could be clarified more precisely.

The present study was performed to determine the relationships between cardioscopic images of the areas observed and the samples obtained by cardioscope-guided biopsy, and to clarify the relationships between cardioscopic classification, histological classification, and clinical manifestations of idiopathic myocarditis. In addition, a prospective cardioscopic follow-up study of idiopathic myocarditis was also performed.

## Methods

### Classification of idiopathic myocarditis by clinical manifestations and endomyocardial biopsy findings

There are two established criteria for the diagnosis of idiopathic myocarditis, the Dallas criteria<sup>3</sup> and the Japanese Circulation Society criteria.<sup>4</sup> Since chronic idiopathic myocarditis (CM) is not included in the Dallas criteria,<sup>3,8</sup> the Japanese Circulation Society criteria, which include both acute idiopathic myocarditis (AM) and CM, were adopted in the present study. In the Japanese Circulation Society criteria, idiopathic myocarditis is classified based on clinical manifestations, by excluding giant cell myocarditis and other secondary myocarditis, into AM and CM, and histologically into three stages, namely AM, active CM, and inactive CM (Table 1A).<sup>4</sup>

Polynuclear cell infiltration, which appears in the super-acute phase of inflammation, is included in the histological criteria. Mononuclear cell infiltration, which also indicates inflammation, was classified according to cell density into massive ( $\geq 20/f \times 400$ : number of cells per microscopic field at  $\times 400$  magnification), moderate ( $\geq 14$  to  $< 20/f \times 400$ ), and minimal ( $\geq 5$  to  $< 14/f \times 400$ ). A density below  $5/f \times 400$  was considered to indicate no infiltration and accordingly no inflammation (Table 1B).

### Patients

Between 1 April 2000 and 31 March 2007, 78 consecutive patients were identified with suspected myocarditis at Toho University Sakura Hospital (Sakura, Japan) and Funabashi-Futawa Hospital (Funabashi, Japan). Prior to cardioscopy, chest X-rays, electrocardiography, and echocardiography were performed, and serum viral titres (including hepatitis C virus)<sup>9–11</sup> serum troponin T, and C-reactive protein levels were measured.<sup>4,12,13</sup> Of these 78 patients, 21 were diagnosed as having AM and 38 as having CM according to the clinical and histological criteria. The remaining 19 patients (24%) were excluded because they were diagnosed by angiography and/or endomyocardial biopsy as having any of the following: vasospastic angina ( $n = 6$ ), unstable angina ( $n = 2$ ), idiopathic dilated cardiomyopathy (DCM;  $n = 2$ ), Takotsubo cardiomyopathy ( $n = 1$ ), microvessel angina ( $n = 2$ ), or chest pain without demonstrable angiographic and histological abnormalities ( $n = 6$ ).

**Table 1 Classification of acute and chronic idiopathic myocarditis by clinical manifestations and endomyocardial biopsy<sup>4</sup>**

A. Classification by clinical manifestations	
(1) <i>Acute idiopathic myocarditis</i>	
Within 1 month from the onset of signs and symptoms <sup>a</sup>	
Preceding common cold-like symptoms	
Signs and symptoms indicating cardiac involvement (arrhythmia, murmur, gallop rhythm, and friction rub)	
Electrocardiographic abnormality	
Ventricular contraction disturbance by echocardiography	
Elevated C-reactive protein and/or troponin T.	
Endomyocardial biopsy findings shown in B.	
(2) <i>Chronic idiopathic myocarditis</i>	
Cardiac symptoms and signs persisting for a few months or more (2 months <sup>a</sup> )	
(a) Active (persistent) type	
Elevated troponin T or C-reactive protein.	
Endomyocardial biopsy findings shown in B.	
(b) Inactive (subsided) type	
No signs of inflammation.	
No elevation of troponin T or C-reactive protein.	
With or without DCM-like appearance by ventriculography.	
Endomyocardial biopsy findings shown in B.	
B. Classification by endomyocardial biopsy findings	
(1) <i>Acute idiopathic myocarditis</i>	
Polynuclear cell infiltration.	
Mononuclear cell infiltration ( $\geq 20/f$ ) <sup>b</sup> . (massive; grouping).	
Mononuclear cell infiltration ( $\geq 5$ to $< 20/f$ ) <sup>b</sup> . (moderate to minimal).	
Cardiomyocytes: degeneration, disruption, lysis, and/or loss.	
No interstitial fibrosis.	
Interstitial and/or endocardial oedema.	
(2) <i>Chronic idiopathic myocarditis</i>	
(a) Active (persistent) type	
Mononuclear cell infiltration ( $\geq 14$ to $< 20/f$ ) <sup>a,b</sup> (moderate).	
Cardiomyocyte: degeneration, disruption, irregular size, and/or disarray.	
Interstitial oedema,	
Interstitial fibrosis ( $\geq 5\%/f$ ) <sup>c</sup> and/or fat deposition.	
(b) Inactive (subsided, or healed) type	
Mononuclear cell infiltration ( $\geq 5$ to $< 14/f$ ) <sup>a,b</sup> (minimal)	
Cardiomyocyte: degeneration, hypertrophy, irregular size, and/or disarray.	
Interstitial fibrosis ( $\geq 5\%/f$ ) <sup>c</sup> and/or fat deposition.	

<sup>a</sup>Defined by the present authors.

<sup>b</sup>Number of cells per a microscopic field at  $\times 400$  magnification.

<sup>c</sup> $\geq 5\%$  of the area of a microscopic field.

### Cardioscopy of the left ventricle

The cardioscopy system consisted of a light source (CLV-A, Olympus Corporation, Tokyo), 9 F guiding balloon catheter (Clinical Supply Co, Gifu, Japan), 4.2 F fibrescope (AF 14, Olympus), and a colour-chilled coupled device (CCD) camera (OTV-A, Olympus). Before observation, colour correction was performed by adjusting the white

balance. Details of the cardioscopy system have been described elsewhere.<sup>5,6</sup>

Cardioscopy was carried out at Toho University Sakura Hospital and Funabashi-Futawa Hospital, and all procedures were approved by the Institutional Review Boards of these hospitals. All patients provided informed, written consent for the procedures.

The patients were pre-treated with oral diazepam (10 mg) before being transferred to the catheterization laboratory. Left ventriculography was performed after administering 50 mg of intravenous lidocaine, for prevention of serious ventricular arrhythmia that might occur during the procedure, and 5000 IU of heparin. A 9 F guiding balloon was then introduced into the left ventricle and the balloon was inflated with CO<sub>2</sub>. Next, a 4.2 F fibroscope was advanced through the catheter so as to position the fibroscope tip at the tip of the catheter. The balloon was gently pushed against the targeted wall segment of the left ventricle, and 50–100 mL of saline solution (heparin 10 IU/mL, 37°C) was injected by a power injector through the catheter at 10 mL/s to displace the blood between the balloon and the ventricular endocardial surface to facilitate visual observations. The anterior, apical, inferior, and lateral walls of the left ventricle were observed (Figure 1). The guiding balloon catheter was pre-shaped so that it could be easily placed on the targeted wall segment; an 'S'- or 'crank'-configuration was used for anterior, apical, and inferior wall segments, and a 'J'-configuration for the lateral wall segment. Details of the pre-shaping and manipulation are described elsewhere.<sup>14</sup> Cardioscopy was not carried out in patients with an ejection fraction <20% to prevent the occurrence of acute congestive heart failure due to the saline infusion.

The changes in the endocardial surface were recorded using a colour CCD camera onto a DVD recorder.

### Cardioscope-guided endomyocardial biopsy

The endomyocardial biopsy system consisted of a 6 F biptome attached to a 3.3 F fibroscope.<sup>7</sup> This system was used to confirm the

endocardial colour and to prevent perforation of the ventricular wall by the biptome. After observation of the endocardial surface colour by cardioscopy, the guiding catheter was pulled back a few centimetres, and the fibroscope which was used for observation was replaced by an endomyocardial biopsy system. The biopsy procedure was then performed. The biptome cusps and the myocardium to be biopsied could be observed during the procedure by cardioscopy. Using this procedure, specimens from the observed portions or the neighbouring portions of the same wall segment could be obtained. At least three wall segments were biopsied in each patient.

### Cardioscopic follow-up study

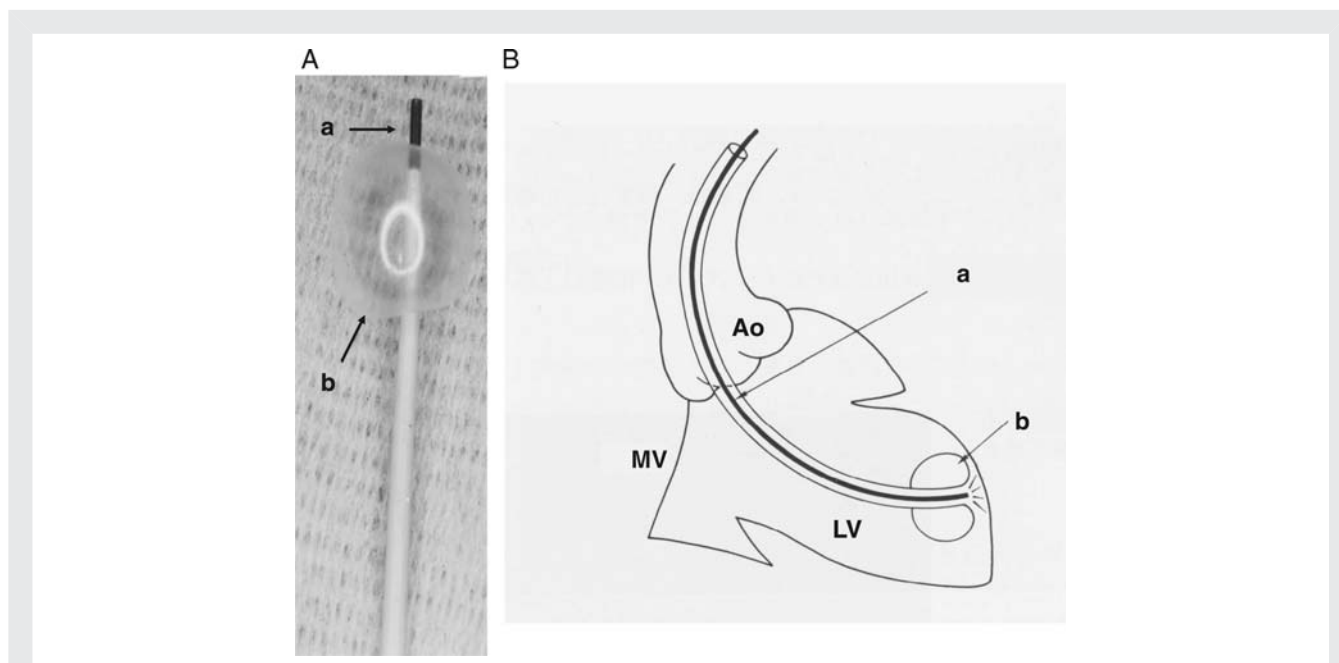
Forty-three patients, from whom informed consent was obtained, underwent repeat cardioscopy and endomyocardial biopsy 6 months later.

### Classification of endocardial colour

The colour of endocardial surface was classified as any of the following: red, milky white (oedematous and yellowish white closely resembling milk), purple, white, or yellowish brown. Intra-observer agreements for these colours were 95, 92, 100, 92, and 100%, respectively, and neutral inter-observer agreements were 95, 92, 100, 96, and 90%, respectively. Based on the histological stages of inflammation, the stages of endocardial surface colour were considered to be in the order of red, milky white, purple, yellowish brown, and white. When the endocardial surface exhibited different colours in a given patient, priority was given to the earliest stage of myocarditis.

### Histology

The biopsy specimens were fixed with 10% formaldehyde solution, cut into successive 10 µm thick slices, and stained by Azan staining. The number of inflammatory cells per microscopic field (f) at ×400



**Figure 1** Cardioscope and procedures for cardioscopy. (A) A cardioscope. A, fibroscope; B, 9 F guiding balloon catheter. Balloon diameter at maximum inflation = 2 cm. (B) Schematic representation of the cardioscopic procedure. Ao, aorta; MV, mitral valve; LV, left ventricle; a, fibroscope; b, balloon. The inflated balloon was gently pushed against the endocardial surface and saline solution was infused to displace the blood and allow visual observations.

magnification was counted and expressed as the number of cells/ $f \times 400$ . Cardiomyocyte degeneration, disruption, lysis, loss, and irregularity were examined. Interstitial oedema was defined as a translucent space between the cardiomyocytes with a diameter exceeding the diameter of the neighbouring cardiomyocytes. The fibrotic area was measured by microphotometry<sup>15</sup> using slices stained with Masson's trichrome, and a fibrotic area  $\geq 5\%$  of the microscopic field was defined as fibrosis.

When the histological stages of myocarditis differed between the biopsied specimens, priority was given to the earliest stage of myocarditis (see Table 1B). These histological diagnoses were made independently by a pathologist who had no further clinical information about the patients.

## Statistical analysis

Data are expressed as mean  $\pm$  standard deviation (SD), and were tested by the  $\chi^2$  test. A *P*-value of  $<0.05$  was considered significant.

## Results

The characteristics of the 21 patients with AM and 38 patients with CM are presented in Table 2.

### Representative cardioscopic images

As a reference, Figure 2 shows the left ventricular endocardial surface of a patient with chest pain whose biopsied specimen was proved to be normal by histology. All patients whose biopsied specimen was histologically normal exhibited a brown endocardial surface.<sup>16</sup>

Figure 3 shows a patient who was admitted 7 days after the onset of subjective symptoms. An increase in the cardiothoracic ratio

based on X-rays, electrocardiographic changes, a diffuse hypokinetic left ventricle by echocardiography, and elevated C-reactive protein and troponin T were observed. The left ventricle was diffusely hypokinetic by ventriculography, but the coronary arteries were normal. The endocardial surface of the anterior wall of the left ventricle appeared red when observed by cardioscopy. An endomyocardial biopsy specimen obtained from the same anterior wall showed polynuclear cell infiltration, massive mononuclear cell infiltration (grouping), cardiomyocyte lysis and loss, and interstitial oedema, changes which are typical of AM.

Figure 4 shows images from a 57-year-old male who was admitted 6 days after the onset of subjective symptoms. Slight lung congestion on chest X-rays, a diffuse hypokinetic left ventricle by echocardiography, electrocardiographic changes, and elevated C-reactive protein were observed. Cardioscopy of the apical segment of the left ventricle showed an oedematous and milky white endocardial surface. Biopsy specimens obtained from the same wall segment exhibited polynuclear cell infiltration, massive mononuclear cell infiltration, cardiomyocyte disruption and lysis, and marked endocardial oedema, changes which are typical of AM.

Figure 5 shows a 51-year-old female who was admitted 3 months after the onset of subjective symptoms. The apical wall segment of the left ventricle showed a purple endocardial surface. Biopsied specimens showed moderate mononuclear cell infiltration, disrupted, irregular-sized and disarrayed cardiomyocytes, and interstitial oedema and fibrosis, changes which are typical of active CM.

### Relationships between cardioscopic images and histology

The colour of the left ventricular endocardial surface was classified by cardioscopy into red, milky white, purple, white, and yellowish brown (Table 3).

**Table 2** Characteristics of patients with acute or chronic idiopathic myocarditis

	Idiopathic myocarditis	
	Acute	Chronic
<i>n</i>	21	38
Age (years)	48 $\pm$ 9	52 $\pm$ 9
Female/male	13/8	20/18
(1) Time from onset of symptoms <sup>a</sup>	5.2 $\pm$ 3 d	4.1 $\pm$ 3 m**
(2) C-reactive protein <sup>b</sup>	11	3
(3) Troponin T <sup>c</sup>	9	2
(4) Virus		
HCV	1	2
Coxsackie B	2	0
(5) Left ventriculography		
EDVI (mL/m <sup>2</sup> )	79 $\pm$ 9	91 $\pm$ 15**
EF	42 $\pm$ 9	51 $\pm$ 10*

*n*, number of patients; d, days; m, months; EDVI, end diastolic volume index; EF, ejection fraction HCV, hepatitis C virus.

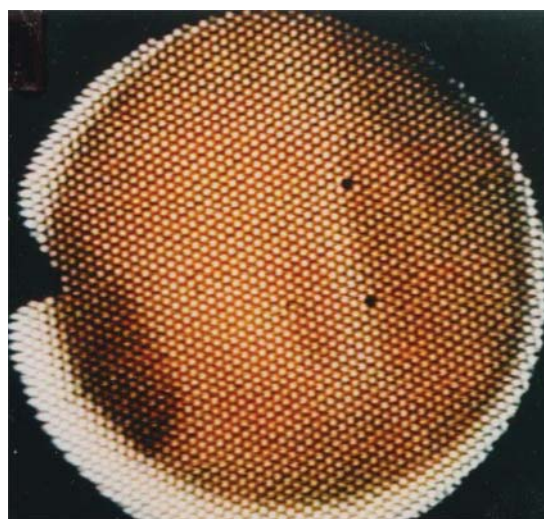
<sup>a</sup>Time from onset of symptoms or clinical diagnosis to cardioscopy.

<sup>b</sup>C-reactive protein  $\geq 0.26$  mg/dL.

<sup>c</sup>Troponin T  $\geq 0.25$  ng/mL.

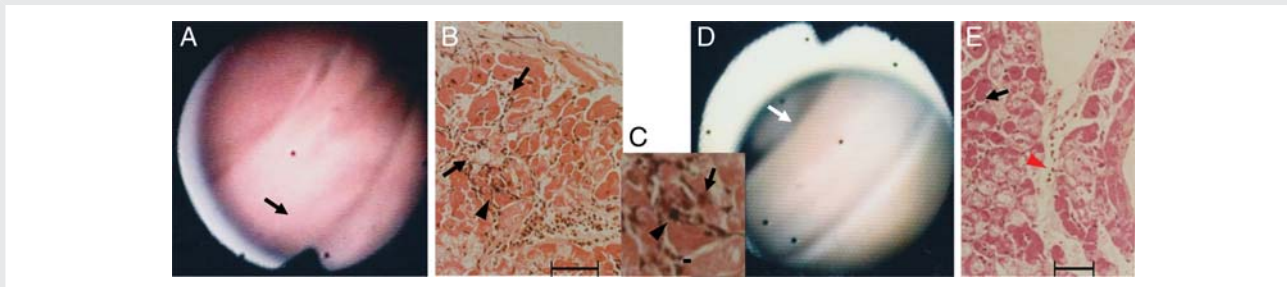
\**P* < 0.01 vs. acute.

\*\**P* < 0.001 vs. acute.

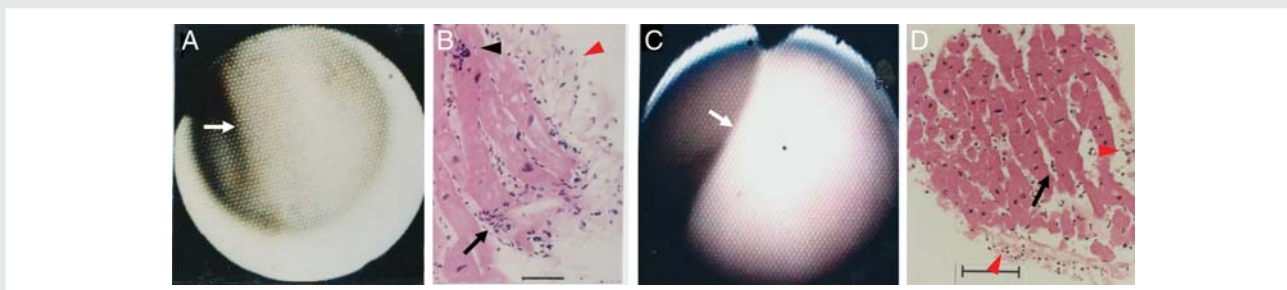


**Figure 2** Normal left ventricular endocardial surface colour in a patient with chest pain. Brown lateral wall of the left ventricle in a 49-year-old-female with chest pain without demonstrable angiographic or histological abnormalities.





**Figure 3** Cardioscopic and histological follow-up in a patient with acute idiopathic myocarditis. A patient with acute myocarditis admitted 7 days after the onset of subjective symptoms. (A) Cardioscopic image at initial observation. The endocardial surface was red (arrow), indicating acute inflammation. (B) Histology of the area observed at initial observation. Arrows, massive mononuclear cell infiltration; arrowhead, polynuclear cell. Lysis and loss of cardiomyocytes, and interstitial oedema without interstitial fibrosis were observed, indicating acute myocarditis. (C) A magnified picture of the portion indicated by the arrowhead in (B). Arrowhead, a polynuclear cell; arrow, mononuclear cells. (D) Cardioscopic image 6 months later. The endocardial surface became white (arrow). (E) Histological changes in the same wall segment 6 months later. Arrows, mononuclear cells; red arrowhead, interstitial fibrosis. Vacuolization and irregularly sized cardiomyocytes were observed. Horizontal bars in (B) and (E) 100  $\mu\text{m}$ . Horizontal bar in (C) 20  $\mu\text{m}$ .



**Figure 4** Cardioscopic and histological follow-up in a patient with acute idiopathic myocarditis. A 57-year-old-male with acute myocarditis admitted 6 days after the onset of subjective symptoms. (A) Cardioscopic image at initial observation. Milky white endocardial surface (arrow) (B) Histology of the observed portion. Arrow, massive mononuclear cell infiltration; black arrowhead, polynuclear cell infiltration; red arrowhead, marked endocardial oedema. Disruption and loss of cardiomyocytes and interstitial oedema were observed. (C) Cardioscopic image at 6 months. Purple endocardial surface (arrow). (D) Histology of the area observed. Arrow, mononuclear cell infiltration; red arrowheads, interstitial fibrosis. Irregular-sized and disarrayed cardiomyocytes were observed. Horizontal bars in (B) and (D) 100  $\mu\text{m}$ .

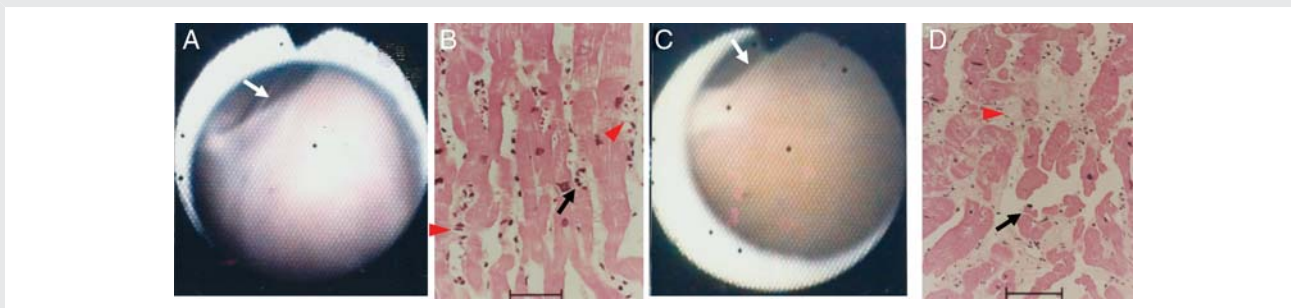
Polynuclear cell infiltration was observed in all red and milky white wall segments, indicating super-acute inflammation. It was not observed in the segments with other colours. Massive mononuclear cell infiltration, often exhibiting grouping, was observed in all red and milky white segments, indicating active inflammation, and at a lower incidence in purple segments but not in the white or yellowish brown segments. Moderate mononuclear cell infiltration was observed in the majority of purple segments, indicating active chronic inflammation, whereas white and yellowish brown segments exhibited minimal mononuclear cell infiltration, indicating inactive (subsided or healed) CM.

Cardiomyocyte degeneration (vacuolization), disruption, lysis, loss, and/or irregularity (irregular diameter) were frequently observed irrespective of the colour of the endocardial surface. Cardiomyocyte disarray was frequently observed in purple, white, and yellowish brown segments. Interstitial oedema was observed in all red and milky white segments but not in white and yellowish brown segments. Interstitial fibrosis was observed

in all purple, white, and yellowish brown segments. Lipid deposition was observed in white and yellowish brown segments (Table 3). Thus, the overall histological changes differed between Group A (red and milky white), Group B (purple), and Group C (white and yellowish brown).

### Cardioscopic images in patients diagnosed with different heart diseases

Nineteen patients were clinically suspected as having myocarditis, but this diagnosis was excluded by angiography and/or endomyocardial biopsy. In these patients, the endocardial surface colour was brown (normal colour) in two patients with chest pain; brown in one, white (partially or diffusely) in three, and yellowish brown in three patients with coronary artery disease; yellowish brown in one patient with sarcoidosis; and white in four and yellowish brown in five patients with DCM as previously reported.<sup>5-7,16</sup>



**Figure 5** Cardioscopic and histological follow-up in a patient with chronic idiopathic myocarditis. A 51-year-old-female with active chronic myocarditis 3 months after the onset of subjective symptoms. (A) Cardioscopic image. Arrow, purple endocardial colour at initial observation. (B) Histology of the area observed. Arrow, mononuclear cell infiltration; red arrowheads, interstitial fibrosis. Irregular-sized and disarrayed cardiomyocytes and interstitial oedema were observed. (C) Cardioscopic image at 6 months later. Arrow, yellowish brown endocardial surface. (D) Histology of the area observed. Arrow, minimal mononuclear cell infiltration; red arrowhead, interstitial fibrosis. Disrupted and irregular-sized cardiomyocytes were observed. Horizontal bars in (B) and (D) 100  $\mu$ m.

**Table 3** Relationship between cardioscopic images and histological changes at initial observation

Endocardial surface colour	Red	Milky white	Purple	White	Yellowish brown
<i>n</i>	13	7	20	13	5
<i>A. Histology</i>					
(a) Polynuclear cell infiltration (%)	13 (100)	7 (100)	0 (0)	0 (0)	0 (0)
(b) Mononuclear cell					
(1) Massive infiltration					
$\geq 20/f \times 400$ (%)	12 (92)	7 (100)	2 (8)	0 (0)	0 (0)
(2) Moderate infiltration					
$\geq 14$ to $< 20/f \times 400$ (%)			15 (75)	2 (15)	1 (20)
(3) Minimal infiltration					
$\geq 5$ to $< 14/f \times 400$ (%)			3 (15)	11 (84)	4 (80)
(c) Cardiomyocytes					
Disruption (%)	10 (77)	6 (85)	10 (50)	10 (76)	3 (60)
Lysis (%)	12 (92)	6 (85)	11 (55)	6 (46)	0 (0)
Loss (%)	9 (69)	6 (85)	8 (90)	10 (78)	5 (100)
Degeneration (%)	13 (100)	6 (85)	18 (90)	11 (84)	5 (100)
Irregularity (%)	7 (54)	7 (100)	17 (85)	11 (84)	5 (100)
Disarray (%)	1 (7)	1 (14)	14 (70)	9 (69)	5 (100)
(d) Oedema					
Endocardial (%)	4 (30)	7 (100)	3 (11)	0 (0)	0 (0)
Interstitial (%)	12 (92)	7 (100)	9 (34)	0 (0)	0 (0)
(e) Fibrosis ( $\geq 5\%/f$ )					
Interstitial (%)	0 (0)	0 (0)	20 (100)	13 (100)	5 (100)
Endocardial (%)	0 (0)	0 (0)	7 (26)	9 (69)	5 (100)
(f) Lipid deposition (%)	0 (0)	0 (0)	5 (25)	8 (61)	3 (60)

*n* = number of wall segments (patients).

### Sensitivity, specificity, and predictive value

Sensitivity, specificity, and predictive value were examined including the 19 patients diagnosed with other types of heart disease by histology. Polynuclear cell infiltration without interstitial fibrosis was the characteristic histological change in AM. When these two

changes were taken into consideration, the sensitivity, specificity, and predictive value of red and milky white endocardial colour for detecting AM were 100, 100, and 100%, respectively.

Moderate mononuclear cell infiltration with interstitial fibrosis was the characteristic histological change in active CM. When these changes were taken into consideration, the sensitivity,

specificity, and predictive value of purple endocardial colour for detecting active CM were 83, 92, and 75%, respectively.

Minimal mononuclear cell infiltration with interstitial fibrosis was the characteristic histological change in inactive CM. The sensitivity, specificity, and predictive value of white and yellowish brown endocardial colour for detecting inactive CM were 82, 74, and 53%, respectively.

## Relationship between cardioscopic images and clinical classifications

The majority of patients clinically diagnosed as having AM exhibited a red or milky white endocardial surface, but a small number of patients had either a purple or white endocardial surface.

The majority of patients with clinically diagnosed CM exhibited a purple, white, or yellowish brown endocardial surface. However, a

few patients exhibited a red or milky white endocardial surface (Table 4).

Thus, the patients diagnosed as having acute myocarditis based on the clinical criteria<sup>4</sup> did not necessarily exhibit endocardial surface colours that indicated histological AM. The same was also true for CM.

## Cardioscopic follow-up study

Figure 3D shows a cardioscopic white endocardial surface that was red at initial observation. Histological examination revealed minimal mononuclear cell infiltration, interstitial fibrosis, and cardiomyocyte changes (Figure 3E), indicating that AM had transformed into inactive (subsided) CM.

Figure 4C shows the purple endocardial surface of the segment that exhibited a milky white colour at initial observation (Figure 4A). Biopsy of this segment revealed moderate

**Table 4 Endocardial colour by cardioscopy**

Endocardial surface colour	n	Red	Milky white	Purple	White	Yellowish brown
<i>A. Relationship between cardioscopic images and idiopathic myocarditis classified by clinical criteria<sup>4</sup></i>						
Acute myocarditis	21	11	6	3	1	0
Chronic myocarditis	38	2	1	18	12	5
<i>B. Cardioscopic follow-up study of idiopathic myocarditis. Endocardial surface colour 6 months later</i>						
Initial endocardial surface colour						
Red	9	2	0	5	2	0
Milky white	5	1	0	3	1	0
Purple	16	0	0	8	3	5
White	9	0	0	0	9	0
Yellowish brown	4	0	0	0	0	4
Total	43	3	0	16	15	9
<i>C. Histological changes 6 months later</i>						
n		2	0	16	15	9
(a) Polynuclear cell infiltration (%)		0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
(b) Mononuclear cell						
(1) Massive infiltration $\geq 20/f \times 400$ (%)		2 (100)	0 (0)	0 (0)	0 (0)	0 (0)
(2) Moderate infiltration $\geq 14$ to $< 20/f \times 400$ (%)		1 (50)	0 (0)	15 (93)	1 (6)	1 (11)
(3) Minimal infiltration $\geq 5$ to $< 14/f \times 400$ (%)		0 (0)	0 (0)	1 (5)	14 (93)	8 (89)
(c) Cardiomyocytes						
Disruption (%)		2 (100)	0 (0)	15 (100)	14 (93)	8 (89)
Lysis (%)		2 (100)	0 (0)	3 (18)	1 (8)	0 (0)
Loss (%)		1 (50)	0 (0)	14 (93)	15 (100)	9 (100)
Degeneration (%)		2 (100)	0 (0)	14 (93)	14 (100)	9 (100)
Irregularity (%)		2 (100)	0 (0)	16 (85)	11 (84)	9 (100)
Disarray (%)		1 (10)	0 (0)	14 (77)	15 (100)	9 (100)
(d) Oedema						
Endocardial (%)		1 (50)	0 (0)	2 (12)	0 (0)	0 (0)
Interstitial (%)		2 (100)	0 (0)	9 (56)	2 (13)	0 (0)
(e) Fibrosis ( $\geq 5\%/f$ )						
Interstitial (%)		0 (0)	0 (0)	16 (100)	15 (100)	9 (100)
Endocardial (%)		0 (0)	0 (0)	7 (26)	5 (33)	6 (66)
(f) Lipid deposition (%)		0 (0)	0 (0)	5 (31)	7 (50)	3 (33)

When endocardial colour was different among the observed segments in a given patient, priority was given in the order of red, milky white, purple, yellowish brown, and white. n = number of wall segments (patients).

mononuclear cell infiltration, cardiomyocyte changes, interstitial oedema, and fibrosis (Figure 4D), indicating that acute myocarditis had been transformed into active CM.

Figure 5C shows the yellowish brown endocardial surface of the segment that was purple in colour at initial observation. Biopsy revealed minimal mononuclear cell infiltration, cardiomyocyte changes, and marked fibrosis (Figure 5D), indicating that active CM had been transformed to inactive (subsided) CM.

Repeat examinations 6 months later showed that the red and milky white endocardial surfaces had changed to purple or white. Purple endocardial surfaces remained unchanged or became white. White and yellowish brown endocardial surfaces were unchanged (Table 4B). The relationships between endocardial surface colour and histological changes were the same as those of the initial biopsy (Table 4C).

## Complications

Ventricular arrhythmias appeared transiently following placement of the balloon of the guiding balloon catheter onto the endocardial surface, but these soon subsided despite keeping the balloon on the endocardial surface during observations. The time required for cardioscopy and biopsy ranged from 10 to 15 min. The total amount of saline required for cardioscopy ranged from 300 to 500 mL. Diuretics were administered intravenously after cardioscopy. No serious complications were noted during or after cardioscopy or cardioscope-guided endomyocardial biopsy.

## Discussion

In general, endomyocardial biopsy of the right ventricle is carried out because biopsy of the left ventricle is difficult. By improving the guiding catheter and bioptome system, left ventricular biopsy was easier and safer in the present study. The left ventricle was selected for biopsy in the present study because it is the main chamber that contributes to cardiac pump function. Ventriculography is always carried out during routine catheterization; and simply replacing the angiographic catheter with a cardioscope-guided bioptome is sufficient for biopsy.

The left ventricular endocardial surface in patients with histologically normal endomyocardium is brown when observed by cardioscopy.<sup>15</sup> In contrast, the endocardial surface of the patients with idiopathic myocarditis in the present study was any of the following: red, milky white, purple, white, or yellowish brown.

All of the specimens obtained from red and milky white wall segments showed polynuclear cell infiltration which is considered to appear in the super-acute phase of inflammation, massive mononuclear cell infiltration, cardiomyocyte disruption, lysis and/or loss, and interstitial and/or endocardial oedema without fibrosis, indicating AM by histological classification.<sup>4</sup> The sensitivity, specificity, and predictive value of red and milky white endocardial colour were 100, 100, and 100%, respectively. In addition, red and milky white colours were not observed in other types of heart disease in the present and previous studies.<sup>7–10</sup> It is therefore conceivable that a red or milky white endocardial surface represents AM.

The majority of biopsied specimens obtained from purple wall segments showed, in addition to cardiomyocyte changes, moderate

mononuclear cell infiltration and interstitial fibrosis, indicating active CM.<sup>4</sup> The sensitivity, specificity, and predictive value were 83, 92, and 75%, respectively. In addition, purple endocardial colour was not observed in other types of heart disease.<sup>7–10</sup> It is therefore conceivable that a purple endocardial surface represents active CM.

The majority of specimens obtained from white and yellowish brown segments exhibited minimal mononuclear cell infiltration, cardiomyocyte changes, and interstitial fibrosis, indicating inactive (subsided or healed) CM. White or yellowish brown endocardial colour, however, was also observed in other categories of heart diseases in the present and other studies.<sup>7–10</sup> Idiopathic dilated cardiomyopathy-like cardiomyopathy with inflammatory cell infiltration by histology, indicating inactive CM, and true DCM, in which inflammatory cell infiltration is absent, are frequently observed.<sup>17,18</sup> Endocardial colour is often white or yellowish brown in both.<sup>7–10,19</sup> These endocardial colours cannot, therefore, be used for the differential diagnosis and should be limited to the follow-up study.

The time course of changes in the endocardial surface colours resembled those of furuncles of the skin. On the basis of the histological changes, the endocardial surface colours were considered as follows: red was due to inflammation-induced hyperaemia (as in acute stage furuncles); milky white, inflammatory endocardial oedema, and/or polynuclear cell infiltration; purple, subsiding inflammation; yellowish brown, subsided inflammation; and white, fibrosis.

It was revealed that the patients diagnosed with AM based on clinical criteria, although low in incidence, had histological changes compatible with CM, and those with CM, vice versa. On the other hand, cardioscopic images clearly correlated with the histological criteria for AM and CM both at the initial and follow-up biopsies. Therefore, it is conceivable that the criteria based on clinical manifestations were less accurate than cardioscopy for staging of idiopathic myocarditis.

In the present cardioscopic 6-month follow-up study, red and milky white endocardial surfaces changed to purple, indicating a transition from AM to active CM. Purple endocardial surfaces changed to white or yellowish brown, indicating transition from active CM to inactive CM, or remained unchanged, indicating persistently active CM. Thus, cardioscopy may also be useful for the follow-up of idiopathic myocarditis.

Yilmaz *et al.* compared complications and diagnostic accuracy between right and left ventricular biopsies using a conventional bioptome. Major complications occurred in 0.64% of the former and in 0.82% of the latter.<sup>20</sup> In contrast, in the present study no major complications occurred.

Yilmaz *et al.*<sup>20</sup> diagnosed myocarditis in 18.7% of patients by left ventricular biopsy, in 7.9% by right ventricular biopsy, and 73.4% by biventricular biopsy. In contrast, in the present cardioscope-guided biopsy study myocarditis was diagnosed in 75% of the study population. This value is almost compatible with the rates achieved using biventricular biopsy, in which complications are more likely,<sup>20</sup> indicating that the biopsy system used in the present study is a feasible methodology.

This study has some limitations. Cardioscopic observation of the left ventricular endocardial surface was limited to up to four wall



segments due to the limited volume (up to 500 mL) of saline solution available for displacement of the blood. It is therefore uncertain whether other segments exhibited different cardioscopic images and histological changes.

In conclusion, percutaneous cardioscopy and endomyocardial biopsy were performed in 78 patients with suspected idiopathic myocarditis, and the relationship between the endocardial colour of the left ventricle and histological changes were examined. Of these 78 patients, 59 were diagnosed histologically with idiopathic myocarditis. The colour of the left ventricular endocardial surface was classified into red, milky white, purple, white, or yellowish brown. Biopsied specimens obtained from the red and milky white wall segments showed changes associated with histologically defined AM (predictive value: 100%); those from purple wall segments, active CM (predictive value: 83%); and those from white and yellowish brown wall segments, inactive CM (predictive value 53%). It is therefore concluded that cardioscopy is feasible for the diagnosis of histologically defined AM and active CM but not for the diagnosis of inactive CM.

**Conflict of interest:** none declared.

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