Narrowing of the Left Ventricular Cavity Associated With Transient Ventricular Wall Thickening Reduces Stroke Volume in Patients With Acute Myocarditis

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It has been reported that some patients with acute myocarditis have transient ventricular thickening associated with narrowing of the left ventricular cavity caused by interstitial edema. The present study investigated this phenomenon in 20 patients with acute myocarditis. Based on the sum of the interventricular septal wall thickness and left ventricular posterior wall thickness (IVST + PWT), measured by M-mode echocardiography, patients were divided into group A (IVST + PWT ≥ 25 mm, n=12) and group B (IVST + PWT < 25 mm, n=8). The IVST + PWT was 31.8±3.5 mm in group A and 21.9±2.7 mm in group B (p<0.0001). The left ventricular end-diastolic dimension (LVDd) was 42.3±6.0 mm in group A and 49.4±6.7 mm in group B (p<0.05). The stroke volume (SV) was 41.1±20.5 ml and 73.0±32.3 ml in groups A and B, respectively (p<0.05). The left ventricular ejection fraction (LVEF) was similar in group A (47.9±13.0%) and group B (56.9±9.0%). The SV correlated inversely with IVST + PWT (r=–0.62, p<0.01), and directly with both the LVDd (r=0.95, p<0.0001) and LVEF (r=0.64, p<0.01). The LVDd correlated inversely with IVST + PWT (r=–0.62, p<0.01). In conclusion, the reduction in SV that occurs during the acute phase of myocarditis is not only the result of systolic dysfunction, but also of the concentric left ventricular wall thickening associated with myocardial interstitial edema, which results in narrowing of the left ventricular cavity at end diastole. (Circ J 2003; 67: 490–494)

Key Words: Echocardiography; Edema; Myocarditis; Stroke volume; Wall thickness

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weeks after onset) and convalescent (≥1 month after onset) phases in 29 of the patients. Of these, 9 patients with second or third degree atrioventricular block were excluded, and the remaining 20 patients comprised the current study group (12 men, 8 women; mean age, 36.5±16.1 years) (Table 1). In addition to the conventional pharmacological therapies, steroids, catecholamines, and diuretics were being taken by 5, 13, and 16 patients, respectively. Percutaneous cardiopulmonary support and intraaortic balloon pumping were used in 2 patients each.

Endomyocardial Biopsies
Right ventricular endomyocardial biopsies were performed, and at least 3 tissue fragments were obtained in each patient. The samples were fixed immediately in 10% buffered formalin, and multiple sections were stained with hematoxylin-eosin, Azan-Mallory, and elastica van Gieson stains for light microscopic examination. The histologic sections were analyzed by 3 observers, and a diagnosis of myocarditis was reached by consensus. The final diagnosis of lymphocytic myocarditis was based on the Dallas criteria. Only patients with histologic evidence of “active” myocarditis were included.

Eosinophilic myocarditis was defined as the development of cardiac symptoms in the presence of peripheral blood eosinophilia and endomyocardial biopsy evidence of eosinophilic infiltration, degranulation, and myocyte necrosis. Using the Azan-Mallory-stained specimens, myocardial
Hemodynamic Deterioration in Acute Myocarditis

interstitial edema was semi-quantitatively graded as (−), (1+) or (2+)1

Echocardiography

Standard 2-dimensional (2-D) and M-mode echocardiography images were obtained during both the acute and convalescent phases (Fig 1). Using the M-mode echocardiograms, the left ventricular dimensions and left ventricular wall thickness were measured in 3 consecutive beats and averaged. If the appropriate M-mode beam alignment was not available, these measurements were performed on 2-D parasternal long axis images with off line software. Left ventricular volume was calculated according to the method of Teichholz et al.25 The sum of the interventricular septal wall thickness (IVST) and left ventricular posterior wall thickness (PWT) was calculated. The mean value and standard deviation of the sum of IVST and PWT in the convalescent phase in all patients was 19.6±2.7 mm, the mean +2SD being 25.0 mm, and was assumed to be abnormally thickened. Thus, the 20 patients were stratified

Table 1 Demographics and Clinical Characteristics of the Patients With Myocarditis

<table>
<thead>
<tr>
<th>patient no.</th>
<th>Age (years)</th>
<th>Gender</th>
<th>IVST + PWT (mm)</th>
<th>LVDd (mm)</th>
<th>SV (ml)</th>
<th>LVEF (%)</th>
<th>Int. edema</th>
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<tbody>
<tr>
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<td>29</td>
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<td>5</td>
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<td>M</td>
<td>31</td>
<td>22</td>
<td>36</td>
<td>36</td>
<td>18</td>
</tr>
</tbody>
</table>

Eosinophilic

| Group A | Lymphocytic | 1  | 25 | M  | 33 | 20 | 38 | 46 | 19 | 78 | 35 | 50 | + | − |
|         | Eosinophilic | 6  | 25 | M  | 33 | 20 | 38 | 46 | 19 | 78 | 35 | 50 | + | − |

Group B

| Group B | Lymphocytic | 13  | 50 | M  | 24 | 22 | 51 | 41 | 73 | 53 | 55 | 69 | + | − |
|         | Eosinophilic | 20  | 47 | M  | 22 | 20 | 38 | 38 | 22 | 39 | 40 | 70 | − | − |

Mean±SD 37±15

<table>
<thead>
<tr>
<th>IVST + PWT (mm)</th>
<th>LVDd (mm)</th>
<th>SV (ml)</th>
<th>LVEF (%)</th>
<th>Int. edema</th>
</tr>
</thead>
</table>

*p<0.05; **p<0.01. Group A (IVST + PWT ≥25 mm); Group B (<25 mm); Conv, convalescent; Int. edema, interstitial edema; IVST, interventricular septal wall thickness; LVDd, left ventricular end-diastolic dimension; LVEF, left ventricular ejection fraction; PWT, posterior wall thickness; SV, stroke volume.

Fig 1. Representative sequential echocardiographic changes in a patient with eosinophilic myocarditis. (A) Hospital day 2: the thickness of the left ventricular wall is increased (IVST: 16 mm; PWT: 16 mm), and the left ventricular end-diastolic dimension (LVDd) is decreased to 35 mm. The left ventricular ejection fraction (LVEF) is 32% and the stroke volume (SV) is decreased to 18 ml. (B) Hospital day 6: the thickness of the left ventricular wall is less (IVST: 11 mm, PWT: 8 mm) than it was 4 days earlier. The LVDd is normal (35 mm). The LVEF and SV have improved to 51% and 41 ml, respectively. (C) Hospital day 9: improvement in all parameters. IVST: 10 mm; PWT: 12 mm; LVDd: 42 mm; LVEF: 66%; SV: 50 ml. (D) Hospital day 16: all parameters have normalized. IVST: 8 mm; PWT: 9 mm; LVDd: 46 mm; LVEF: 74%; SV: 71 ml. IVST, interventricular septal wall thickness; PWT, posterior wall thickness.
according to the sum of the IVST and PWT in the acute phase into group A (n=12) with IVST + PWT ≥ 25 mm and group B (n=8) with IVST + PWT < 25 mm. The left ventricular end-diastolic dimension, stroke volume, and left ventricular ejection fraction in the acute and convalescent phases were studied. In addition, the correlations between IVST + PWT, left ventricular end-diastolic dimension, stroke volume, and left ventricular ejection fraction in the acute phase were determined.

**Statistics**

Values are reported as the mean ± standard deviation. Comparisons of frequencies were performed using the chi-square test. Changes in the values of the echocardiographic parameters between the acute and convalescent phases were evaluated by a paired Student’s t test. Comparisons of the values of echocardiographic parameters between groups A and B were performed using an unpaired Student’s t test. Correlations between 2 variables were determined by linear regression. Statistical significance was defined as p<0.05.

**Results**

**Interstitial Edema**

The degree of interstitial edema in each patient is listed in Table 1. Edema was present in 16 patients (80%) during the acute phase, with (2+) edema observed in 7 patients, and (1+) edema in 9 patients. The incidence of edema during the convalescent phase was lower, with only 3 patients (15%) having (1+) edema (p<0.01).

**Echocardiographic Findings**

By definition, the IVST + PWT was greater in group A (31.8±3.5 mm) than in group B (21.9±2.7 mm) in the acute phase (p<0.0001, Table 1). However, in the convalescent phase, the wall thickness had normalized and was similar in both groups (20.3±2.0 mm in group A and 18.5±3.4 mm in group B).

The left ventricular end-diastolic dimension was smaller in group A (42.3±6.0 mm) than in group B (49.4±6.7 mm) in the acute phase (p<0.05, Table 1). In the convalescent phase, the left ventricular end-diastolic dimension increased to 47.3±5.3 mm in group A (p<0.05), but was unchanged in group B (46.0±7.5 mm) (Table 1). No significant difference was noted between the 2 groups in the convalescent phase.

The stroke volume was smaller in group A (41.1±20.5 ml) than in group B (73.0±32.3 ml) in the acute phase (p<0.05, Table 1). In the convalescent phase, it increased to 70.3±22.2 ml in group A (p<0.01), and was unchanged in group B (77.9±39.7 ml, Table 1). The stroke volume was similar in the 2 groups in the convalescent phase.

The left ventricular ejection fraction in the acute phase was similar in the 2 groups (47.9±13.0% in group A vs. 56.9±9.0% in group B, Table 1). In the convalescent phase, the left ventricular ejection fraction increased in both groups (67.7±14.9% in group A, p<0.01; and 73.9±6.2% in group B, p<0.001), but the intergroup difference was not significant.

The relationships between these parameters are shown in Fig 2–5. The stroke volume correlated inversely with the...
IVST + PWT (r = –0.62, p < 0.01; Fig 2), and correlated directly with the left ventricular end-diastolic dimension (r = 0.95, p < 0.0001; Fig 3) and the left ventricular ejection fraction (r = 0.64, p < 0.01; Fig 4). The left ventricular end-diastolic dimension correlated inversely with the IVST + PWT (r = –0.62, p < 0.01; Fig 5).

### Discussion

We have previously demonstrated that some patients with acute myocarditis develop thickening of the left ventricular wall because of interstitial edema and this change can obliterate the left ventricular cavity, with consequent decrease in stroke volume even when the ejection fraction remains unchanged. However, the present study demonstrates that the left ventricular ejection fraction also decreases, and therefore the stroke volume is reduced beyond that which would result from systolic dysfunction alone.

Felker et al reported echocardiographic findings similar to ours in 43 cases of acute myocarditis and 11 cases of fulminant myocarditis. At presentation, the thickness of the interventricular septum was normal (1.0±0.1 cm), but the left ventricular end-diastolic dimension was increased (6.1±0.8 cm) in patients with acute myocarditis, whereas in patients with fulminant myocarditis, the thickness of the interventricular septum was increased (1.2±0.2 cm), but the left ventricular end-diastolic dimension was relatively normal (5.3±0.9 cm). In both groups, the fractional shortening was compromised. By 6 months, patients with fulminant myocarditis demonstrated a dramatic improvement in left ventricular systolic function, as compared with no improvement in patients with acute myocarditis. The initial echocardiographic findings and their subsequent improvement in patients with fulminant myocarditis as reported by Felker et al are consistent with our findings. Although myocardial biopsies were performed, the presence or absence of interstitial edema was not reported. Pinamonti et al also studied 41 patients with myocarditis, and analyzed left ventricular morphology and cardiac function using echocardiography. They reported that, although 4 of their patients showed impaired systolic function, the left ventricular end-diastolic dimension was not increased overall. Transient left ventricular wall thickening was observed in 6 patients in that series. However, it was not specified whether the 4 patients with impaired systolic function were included in the group. In addition to those studies, several case reports have described patients in whom left ventricular wall thickening resulted in narrowing of the left ventricular cavity during the acute phase of myocarditis (Table 2). The left ventricular ejection fraction in those cases was not necessarily low (48–95%), despite the fact that all the patients developed cardiac failure in the acute phase. It is likely that the narrowing of the cavity influenced the development of cardiac failure in those patients.

Thus, our results and those of several previous reports suggest that there is a group of patients with acute myocarditis in whom transient ventricular wall thickening is associated with narrowing rather than dilation of the left ventricular cavity as usually occurs with normal or depressed systolic left ventricular function; these patients usually improve during the convalescent phase of the disease. In the present study, the stroke volume in the acute phase was significantly less in group A than in group B, though the ejection fraction was decreased similarly in the 2 groups. That relationship indicates that the decrease in stroke volume in group A can be ascribed to the left ventricular narrowing.

Impaired diastolic function, although not studied, may also have played a role in reducing the stroke volume in group A. Ito et al described a 2-year-old child with idiopathic hypereosinophilic syndrome with left ventricular diastolic dysfunction. Although the left ventricular systolic function was good in their patient, marked thickening of the ventricular walls was present (the interventricular septum was 10 mm and the left ventricular posterior wall was 7 mm). In addition, the ratio of the peak velocity of the diastolic (D) to the systolic (S) wave (peak D/S) for the pulsed Doppler pulmonary venous flow patterns was markedly elevated. The authors hypothesized that the diastolic dysfunction was caused by an increase in the left ventricular wall thickness, resulting in congestive heart failure. After 3 days of prednisolone therapy, the eosinophil count normalized and the symptoms of heart failure improved. The pulmonary venous flow pattern also had normalized within 2 weeks after the initiation of steroid therapy. By 1 month, the left ventricular wall thickness had returned to normal.

After heart transplantation, diastolic dysfunction sometimes occurs during acute rejection with lymphocytic infiltration and interstitial edema. These histologic changes are closely correlated with abnormal echocardiographic findings.

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Table 2 Nine Patients With Myocarditis and Narrowing of Left Ventricular Cavity: Case Reports From the Previous 20 Years

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Age (years)</th>
<th>Gender</th>
<th>Myocarditis</th>
<th>IVST (mm)</th>
<th>PWT (mm)</th>
<th>LVDd (mm)</th>
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Mean ± SD: 16.6±2.8, 10.4±1.5, 14.0±1.7, 9.3±1.8, 37.1±7.4, 46.6±3.1, 52.0±16.8, 68.7±12.0

† The values were not noted in the original reports, but were measured by us using data from the respective reports. The mean ± SD was determined, excluding the two infants (17 days and 11 months). *p < 0.05, **p < 0.01

Conv., convalescent; d, days; IVST, interventricular septal wall thickness; LVDd, left ventricular end-diastolic dimension; LVEF, left ventricular ejection fraction; m, months; PWT, posterior wall thickness.
graphic parameters of ventricular filling and relaxation. Further studies are needed to determine whether diastolic dysfunction occurs in addition to the decreased ejection fraction and left ventricular narrowing related to an increase in wall thickness in lymphocytic or eosinophilic myocarditis.

Study Limitations

The majority of the present cases showed diffuse wall motion abnormalities, with localized asynergy limited to only a few cases. Therefore, on M-mode echocardiography, errors in determining the left ventricular volume might occur in the presence of localized asynergy. Even though, as a rule, this has little influence as the degree of asynergy becomes less marked in the study cases, it should be addressed in further studies.

Conclusion

Some patients with acute lymphocytic or eosinophilic myocarditis have ventricular wall thickening caused by myocardial interstitial edema, which results in narrowing of the left ventricular cavity. We found that the reduced stroke volume that occurs in acute myocarditis is attributable not only to left ventricular systolic dysfunction, but also to a smaller end-diastolic volume. This hemodynamic change improves as the myocardial edema resolves.

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References