Right Ventricular Endomyocardial Biopsy Findings in 25 Patients With Sick Sinus Syndrome

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SUMMARY

A variety of myocardial lesions have been demonstrated in atrial muscle in patients with sick sinus syndrome (SSS), but the right ventricular myocardium has not been studied in detail in a large series. Therefore, we performed right ventricular endomyocardial biopsies in 25 patients with SSS (SSS group), and the presence or absence of ventricular myocardial lesions was determined histologically. As a control, biopsies of corresponding sites in 12 normal autopsied hearts were obtained (N group). The mean cardiac myocyte transverse diameter was $14.2 \pm 3.6 \mu\text{m}$ in the SSS group and $11.7 \pm 3.1 \mu\text{m}$ in the N group ($P < 0.01$). In the SSS group, cardiac myocyte hypertrophy was observed in 20 of 25 subjects (80%), and myocyte size variation was more frequent. Although the difference was not significant, myocyte disorganization, myocytolysis, nuclear deformity, interstitial large mononuclear cell proliferation, and endocardial lesions, which were not seen in the N group, were observed in the SSS group. A variety of myocardial lesions, including cardiac myocyte hypertrophy, are present not only in atrial, but also in ventricular muscle in SSS. (Jpn Heart J 2004; 45: 73-80)

Key words: Sick sinus syndrome, Endomyocardial biopsy, Cardiac pathology

SICK sinus syndrome (SSS) is caused by a decrease in the number of sinus node cells, fatty degeneration of the sinus node and adjacent area, fibrosis, and injury to the internodal tract.¹⁾ In contrast, the right ventricle has been reported to show few histologic abnormalities.^{2,3)} The present study examined in detail biopsy specimens of the right ventricle obtained from patients with SSS. We noted the presence of lesions in a relatively high percentage of cases. The findings and their significance are presented here.

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Received for publication March 3, 2003.

Revised and accepted June 20, 2003.

METHODS

Subjects: Twenty-five patients with SSS (SSS group) admitted for diagnostic evaluation to either the Department of Internal Medicine, Fujita Health University School of Medicine or the Cardiovascular Center, Nagoya Dai-ni Red Cross Hospital were enrolled in this study. There were 7 men and 18 women, ranging in age from 23 to 70 years (mean $\pm$ SD, 57.2 ± 11.9 years). Patients with underlying cardiac disease, such as cardiomyopathy or valvular disease, were excluded. Fourteen patients were Rubenstein Classification⁴⁾ type II, sinus arrest or sinoatrial block with atrioventricular nodal or ventricular escape rhythm, and 11 patients were type III, bradycardia-tachycardia syndrome. For a control group, tissue specimens were obtained from 12 normal autopsied hearts (N group). Subjects in this group had no history of cardiac disease, the ante-mortem electrocardiogram (ECG) was within normal limits, and no abnormalities of either the coronary arteries or myocardium were evident on macroscopic examination at the time of autopsy. These 12 hearts were obtained from 7 men and 5 women, ranging in age from 44 to 81 years (mean $\pm$ SD: 60.6 ± 9.5). The heart weight ranged from 220 to 350 g (mean $\pm$ SD: 284 ± 35 g).

Endomyocardial biopsy: In the SSS group, 3.4 ± 1.1 endomyocardial biopsy specimens per patient were obtained from the right ventricle. Tissue specimens were prepared according to standard methods, sliced into $4\text{-}\mu\text{m}$ sections, and subjected to hematoxylin-eosin (H-E), Azan Mallory, and elastic van Gieson staining. H-E and Azan Mallory-stained tissue specimens from controls were prepared in a similar fashion. Five sites corresponding to the biopsy sites were selected at random in each normal autopsied heart.

Myocyte transverse diameter and degree of hypertrophy: A micrometer was inserted into the ocular of a light microscope, and the mean cardiac myocyte transverse diameter and variability standard deviation were determined using a longitudinal section of cardiac myocytes in which the nucleus was present. Myocytes located immediately beneath the endomyocardial layer or at sites of branching, or cells with marked swelling or degeneration were excluded from the analysis. The degree of myocyte hypertrophy was evaluated according to the criteria of Sekiguchi, *et al*⁵⁾, and the mean ($+ 1$ SD) cardiac myocyte transverse diameter in each case was classified into 4 grades: $\leq 15\text{ }\mu\text{m}$ (-), $16\text{-}20\text{ }\mu\text{m}$ (1+), $21\text{-}25\text{ }\mu\text{m}$ (2+), and $\geq 26\text{ }\mu\text{m}$ (3+). In the SSS group, 65 ± 20 sites were measured in each case.

Fibrosis area ratio: Fibrosis was evaluated using a light microscope equipped with an ocular containing a grid of 121 intersecting points. Using the point-counting method, the fibrosis area ratio was calculated on Azan-Mallory stained specimens magnified 125-fold by determining the number of fibrotic sites and

dividing this number by the total number of sites examined. In the SSS group, 670 ± 256 sites were examined in each case.

Lymphocyte count: The lymphocyte count was determined according to the method of Edwards, *et al*⁶⁾ by calculating the mean number of lymphocytes in H-E-stained specimens in a 400-fold magnified field.

Other myocardial lesions: Other myocardial lesions, including myocyte disarrangement or structural abnormalities, myocardial degeneration, nuclear deformity, and endomyocardial lesions, also were identified according to established histopathologic diagnostic criteria.⁵⁾ Lesions were semiquantitatively categorized into four grades ranging from (-) to (3+). The frequencies of these myocardial lesions also were determined.

Comparison according to Rubenstein Classification: The SSS group was divided according to the Rubenstein Classification system⁴⁾ into two groups: types II and III, and the myocyte transverse diameter, fibrosis area ratio, mean lymphocyte count, and frequency of other cardiac lesions were compared.

Comparison according to presence or absence of hypertension: Cardiac myocyte hypertrophy has been described in the hypertensive heart, not only in the left ventricle, but biventricularly as well,⁷⁾ so the myocyte transverse diameters in the four patients with SSS complicated with hypertension and the 21 normotensive patients were compared.

Statistical analysis: Values are expressed as the mean $\pm$ standard deviation. Student's unpaired *t* test and the chi-squared test were used to test for statistical differences. Differences were considered significant for $P < 0.05$.

RESULTS

Myocyte transverse diameter and degree of hypertrophy: The mean myocyte transverse diameter was $14.2 \pm 3.6 \mu\text{m}$ in the SSS group and $11.7 \pm 3.1 \mu\text{m}$ in the N group ($P < 0.01$). The degree of hypertrophy in the SSS group was (-) in 5 patients (20%), (1+) in 17 (68%), and (2+) in 3 (12%). In contrast, in the N group, it was (-) in 9 patients (75%) and (1+) in 3 (25%) (Figures 1 and 2).

Fibrosis area ratio: The fibrosis area ratio was similar in the SSS group ($5.8 \pm 2.9\%$) and N group ($5.1 \pm 2.0\%$).

Lymphocyte count: The mean lymphocyte count was similar in the SSS group (1.2 ± 0.8) and N group (1.3 ± 0.4). Neither group had five or more lymphocytes per high power field.⁶⁾

Other myocardial lesions: Myocyte size variability was more common in the SSS group than the N group ($P < 0.05$) (Figure 2). Myocyte disorganization, myocytolysis, nuclear deformity, interstitial large mononuclear cell proliferation, and endocardial lesions were observed in the SSS group (Figure 3), but not in the

Figure 1. Relationship between myocyte transverse diameter and degree of hypertrophy.

The mean myocyte transverse diameter $\pm$ SD is shown for each case. The mean myocyte transverse diameter was $14.2 \pm 3.6 \mu\text{m}$ in the SSS group compared to $11.7 \pm 3.1 \mu\text{m}$ in the N group ($P < 0.01$). N = normal; SSS = sick sinus syndrome.

Figure 2. Incidence of myocardial lesions in patients with SSS.

Myocyte hypertrophy and myocyte size variability were more common in the SSS group than the N group ($P < 0.05$). Myocyte disorganization, myocytolysis, nuclear deformity, interstitial large mononuclear cell proliferation, and endocardial lesions were observed in the SSS group, but not in the N group, although the differences in frequency were not significant. Myocyte disarrangement, abnormal branching, and fatty tissue also tended to be more common in the SSS group than in the N group. (*: $P < 0.05$ **: $P < 0.01$) N = normal; SSS = sick sinus syndrome.

Figure 3. Photomicrograph of right ventricular endomyocardial biopsy in a patient with sick sinus syndrome.

A 59-year-old Japanese woman with Rubenstein type III SSS. Cardiac biopsy specimen showed myocyte hypertrophy and size variation, myocyte disorganization, and interstitial fibrosis.

N group, although these differences did not reach statistical significance. In addition, myocyte disarrangement, abnormal branching, and fatty tissue were relatively more common in the SSS group than in the N group, though not significantly.

Comparison according to rubenstein classification: Patients with Rubenstein classification types II and III were similar in terms of myocyte transverse diameter ($14.2 \pm 3.8 \mu\text{m}$ vs $14.1 \pm 3.5 \mu\text{m}$), fibrosis area ratio ($5.7 \pm 3.2\%$ vs $5.9 \pm 2.5\%$), and mean lymphocyte count (1.3 ± 1.0 vs 1.0 ± 0.4). The frequency of other myocardial lesions also was similar.

Comparison according to presence or absence of hypertension: Myocyte transverse diameter was similar in the patients with and without hypertension ($14.4 \pm 3.4 \mu\text{m}$ vs $14.1 \pm 3.7 \mu\text{m}$).

DISCUSSION

In 1967, Lown⁸⁾ reported a group of patients with chronic atrial fibrillation in whom sinus rhythm was not restored and sinus arrest or sinoatrial block developed despite electrical defibrillation. In 1968, Ferrer⁹⁾ named the syndrome characterized by sinus node dysfunction and sinoatrial block as the “sick sinus syndrome”. Subsequently, various electrophysiologic and other studies¹⁰⁻¹²⁾ have been conducted on SSS, and numerous histopathologic studies^{1,13-15)} have focused on the sinus node and abnormalities of the atrial myocardium. Thery, *et al*¹³⁾ studied the histology of the sinus node in 111 autopsies, including 12 with acute or chronic sinoatrial block and demonstrated that the number of sinus nodal cells was $\leq 5\%$ in 8 patients with chronic sinoatrial block. These authors concluded that the cause of SSS is impaired generation of stimuli due to widespread injury to the sinus node. Sugiura and Ohkawa¹⁾ also found that the number of sinus nodal cells was decreased in a postmortem study of SSS, while concomitantly, there was a proliferation of collagen/elastic fibers, fatty infiltration, and damage to the internodal tract. However, lesions in the ventricular myocardium were not described.^{1,13)} In contrast, Hiroe, *et al*²⁾ performed endomyocardial biopsies and examined the specimens histopathologically in 24 cases, focusing not only on the right atrium but on the right ventricle as well. Right atrial fibrosis was the major finding, and although fibrotic lesions also were present in the right ventricle, they were considered minor. Nishikawa, *et al*³⁾ similarly studied 3 cases of SSS and described prominent interstitial fibrosis in the right atrium with a normal histologic picture in the right ventricle. Because such studies have led us to believe that in general ventricular myocardial involvement in sick sinus syndrome is slight, few studies have focused on the ventricular myocardium in a systematic fashion in a large number of cases.

Diphtheria is of particular interest as it has been reported in as many as 25% of SSS patients.¹⁶⁾ In diphtheric myocarditis,¹⁷⁻²¹⁾ arrhythmias, particularly conduction disturbances, such as SSS and AV block, are observed, and develop not only when the disease was contracted, but also many years later in some cases.^{20,21)} Although it is difficult to ascribe SSS to the myocarditis definitely in cases of myocarditis-induced cardiac lesions in diphtheria¹⁷⁻²¹⁾ and collagen diseases,^{22,23)} it is rather uncommon for the atrial myocardium to be affected selectively. Rather, in most cases, there is diffuse involvement extending to the ventricular myocardium, suggesting that in these patients with SSS, myocardial lesions are likely to be found on right ventricular biopsy.

In the present study, more patients in the SSS group than the N group showed myocyte hypertrophy, and many patients with SSS show morphologic abnormalities, such as myocyte disorganization, nuclear deformity, fatty tissue, and endocardial lesions. So, at least in this investigation, right ventricular lesions in SSS were more common than previously reported. However, it is not clear whether these ventricular myocardial lesions represent the same pathology that affected the sinus node and atrial myocardium or are secondary to the hemodynamic changes induced by SSS. Specifically, systolic hypertension during bradycardia is thought to be induced by volume loading secondary to an increase in the stroke volume. Accordingly, we cannot exclude an increase in pulmonary arterial pressure as the cause of right ventricular myocyte hypertrophy and degeneration. Nunoda, *et al*²⁴⁾ investigated the relationship between right ventricular myocyte transverse diameter and right ventricular pressure in 72 patients with chronic right ventricular overload, and found myocyte hypertrophy increased with increasing ventricular pressure. Among Rubenstein classification type III patients it has been shown empirically that bradycardia occurs for only a few beats after tachycardia,²⁵⁾ making it unlikely that all of the myocardial lesions can be attributed to the effect of bradycardia-induced hemodynamic changes.

Although we were not able to determine whether the myocardial lesions in the right ventricle seen in patients with SSS develop due to bradycardia-induced hemodynamic changes or accrue from the same cause that produced the myocardial lesions in the atrium that involved the sinus node, the latter explanation cannot be excluded entirely.

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