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Small Heart as a Constitutive Factor Predisposing to Chronic Fatigue Syndrome

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1. Introduction

The chronic fatigue syndrome (CFS), which affects many young people in modern, stressful society, is an important health problem, characterized by persistent and relapsing, severe disabling fatigue, not resolved by rest, causing a marked reduction of working activity. [1-4] Despite the public health burden imposed by CFS, effective diagnostic, treatment and prevention strategies are not available because the etiology, risk factors and pathophysiology remain unclarified. Various factors have been implicated in the genesis of CFS, including abnormal immune activation, chronic viral infection, impairment of central nervous system, exaggerated oxidative stress and current emotional disorders.[1-8] Diagnosis of CFS can be made only after alternative known medical and psychiatric causes of chronic fatiguing illness have been excluded.[1,3]

2. Chronic Fatigue Syndrome (CFS) and cardiac dysfunction or low cardiac output

Cardiovascular dysfunction such as chronic heart failure, can be a main cause of disabling chronic fatigue and many symptoms seen in CFS patients are common in patients with low cardiac output syndrome. Indeed, accumulating evidence points to a possible problem with circulation in CFS. [9-14] The reported findings included autonomic dysfunction,[15,16] lower plasma volume and/or red cell mass,[17,18] and abnormalities in neurohumoral systems of circulatory control.[19,20] In 2003 Peckerman et al.[10] provided a preliminary indication of reduced cardiac output in patients with severe CFS.

2.1 Small heart syndrome

The concept that a heart small in relation to the body is inadequate for work was first stated by Laennec[21] in 1826. Later Master[22] reported several, so-called "neurocirculatory asthenia" cases with weakness or fatigue even after ordinary exertion, tachycardia, palpitation and dyspnea, who had a small heart shadow on chest radiography. The most frequent complaints are fatigue or weakness, rapid heart, precordial or chest pain, shortness of

breath, nervousness, trembling, sweating and fainting, many of them resembling those in CFS patients. Master hypothesized that these symptoms were caused by diminished venous return, diminished cardiac output, anoxemic heart muscle and decreased oxygen saturation of the blood due to congenital or constitutionally small heart. Similarly DaCosta[23] described "irritable heart" in 1871, a peculiar form of functional disorder of the heart seen in the military population during the American Civil War. The disorder frequently presented either after an episode of diarrhea and persisted after the digestive disturbances had diminished, or originated suddenly without previous digestive disorder. Fatigue was an almost universal complaint in DaCosta's syndrome, although symptoms includes palpitation, cardiac pain, headache, dimness of vision and giddiness.[23,24] Diarrhea may lead to dehydration and reduce venous return or preload, resulting in further decreases in stroke volume and cardiac output in subjects with small heart.

The apparent heart size or cardiothoracic ratio (CTR) is influenced by the position of the heart in the thoracic cage. A small heart may be due to a standing or dropped heart resulting from a low diaphragm and a narrow chest in association with a thin physique and low fat content in epicardial and pericardial spaces. Consequently, the pathognomonic significance of small heart has not been established and is now being overlooked or even ignored.[25]

In order to clarify the pathophysiological significance of small heart syndrome as a cardiovascular disease, we studied 47 patients (16 men and 31 women, mean age: 29±6 years) with a small heart shadow (CTR ≤42% on a chest roentgenogram) and without significant systemic disease who consecutively visited our clinic with possible cardiovascular symptoms, as well as 24 controls (C). These patients with small heart syndrome were divided into 2 groups, 25 patients with severe symptoms (S) and 22 patients with mild ones (M), according to the presence or absence of cardiovascular symptoms including general malaise, easy fatigability, fainting, dizziness, weakness, chest pain, dyspnea and palpitations that were sufficiently severe to significantly disturb their occupational, educational, social or personal activities. Figures 1 and 2 show the chest X roentgenograms of typical cases of group S.

All individuals underwent standard M-mode and two-dimensional echocardiography. The left ventricular (LV) dimensions were measured according to the recommendations of the American Society of Echocardiography.[26] LV volume was calculated by the Teichholz' formura,[27] and an ejection feaction was obtained by the conventional method.

Results are summarized in Tables 1 and 2 and Figures 3-6. As shown in Table 1, the symptom of general malaise and/or easy fatigability was significantly more frequent in S than in M (88% vs. 50%, $p<0.05$). In addition, symptoms including orthostatic dizziness, shortness of breath, dyspnea on effort, palpitations, fainting and chest pain were more frequent in S than in M, although no significant difference was found. In addition, physical findings including narrow chest, foot coldness, pretibial pitting edema, bimanual right kidney palpability, epigastric splash sound, mid-systolic click, late systolic murmur and hypotension were more frequently noted in S than in M, although no significant difference was found.

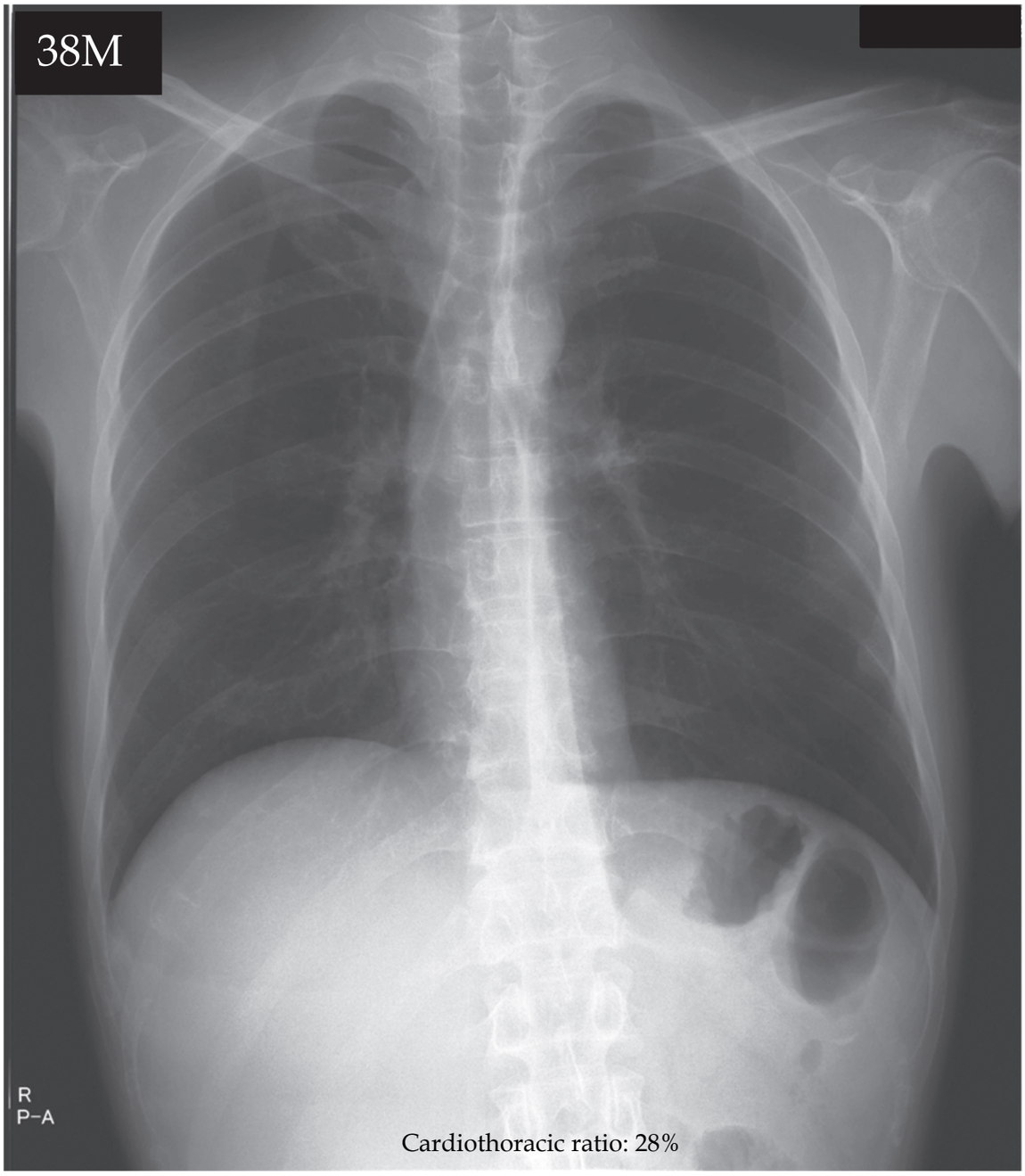


Fig. 1. Chest roentgenogram of a 38-year-old male patient with small heart syndrome (cardiothoracic ratio: 28%) in which vertebral scoliosis was also noted. From about 15 years ago, the patient suffered from severe general malaise, easy fatigability, dyspnea on effort, palpitations and chest pain. He also occasionally developed severe dyspnea with hyperventilation, trembling, sweating and sleep disturbance. He found that upon obtaining employment, he could not work as expected. Upon consulting a psychiatrist 10 years ago, he was diagnosed with anxiety neurosis and treated with medication. He subsequently developed alcoholism. He frequently visited emergency outclinics due to severe dyspnea and anxiety.

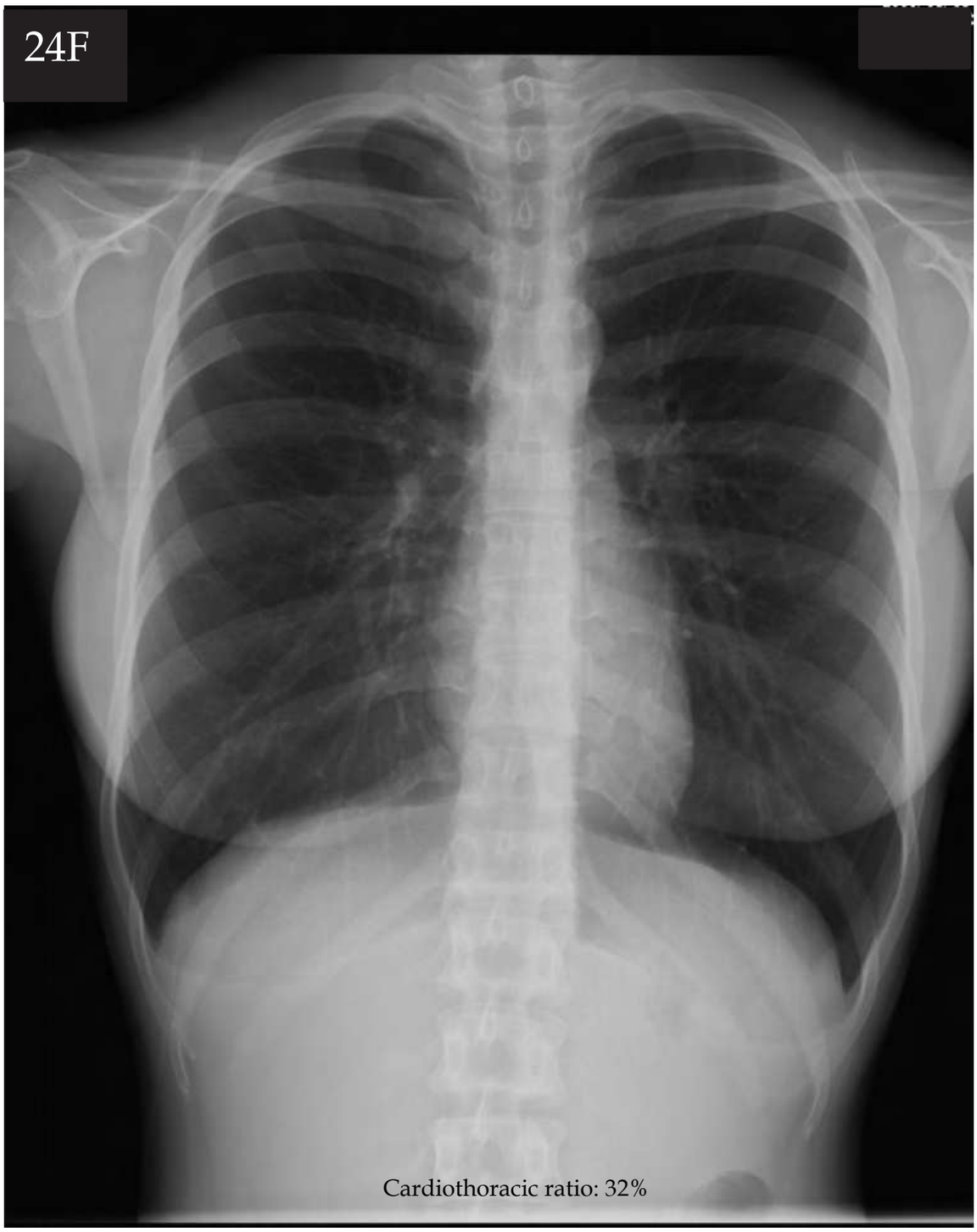


Fig. 2. Chest roentgenogram of a 24-year-old female patient with small heart syndrome (cardiothoracic ratio: 32%). For about 7 years, the patient suffered from severe general fatigue, fainting and orthostatic dizziness. She also frequently developed a headache, chest pain and a sore throat. She was frequently unable to work as a dietician due to increasingly impaired short-term memory and concentration.

	Small heart syndrome		
	Mild (M)	p value	Severe (S)
Number of patients	22		25
Sex (male/female)	7/15		8/17
Age (years)	30±7	NS	28±6
Symptoms			
General malaise	10 (45%)	NS	18 (72%)
Easy fatigability	7 (32%)	NS	14 (56%)
General malaise and/or easy fatigability	11 (50%)	<0.05	22 (88%)
Orthostatic dizziness	8 (36%)	NS	11 (44%)
Shortness of breath	4 (18%)	NS	7 (28%)
Dyspnea on effort	5 (23%)	NS	9 (36%)
Palpitations	5 (23%)	NS	7 (28%)
Faintng	5 (23%)	NS	9 (36%)
Chest pain	7 (32%)	NS	10 (40%)
Physical findings			
Narrow chest	11 (50%)	NS	18 (72%)
Foot coldness	8 (36%)	NS	16 (64%)
Pretibial pitting edema	5 (23%)	NS	9 (36%)
Right kidney palpability	9 (41%)	NS	14 (56%)
Epigastric splash sound	3 (14%)	NS	6 (24%)
Mid-systolic click	2 (9%)	NS	3 (12%)
Late systolic murmur	4 (18%)	NS	5 (20%)
Hypotension (SBP <100 mmHg)	5 (23%)	NS	8 (32%)

M: patients with small heart syndrome and mild symptoms, S: patients with small heart syndrome and severe symptoms, NS: not significant, SBP: systolic blood pressure

Table 1. Comparison of the prevalence of symptoms and physical findings between the study groups with mild or severe symptoms

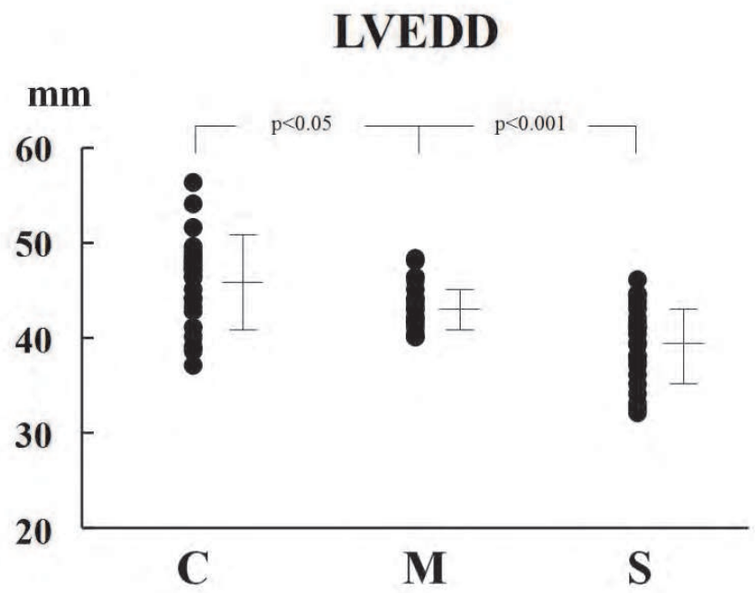


Fig. 3. Comparison of the left ventricular end-diastolic dimension (LVEDD) among the study groups. The mean LVEDD was significantly smaller in S (patients with small heart syndrome and severe symptoms) than in M (patients with small heart syndrome and mild symptoms) and C (control subjects). It was also significantly smaller in M than in C.

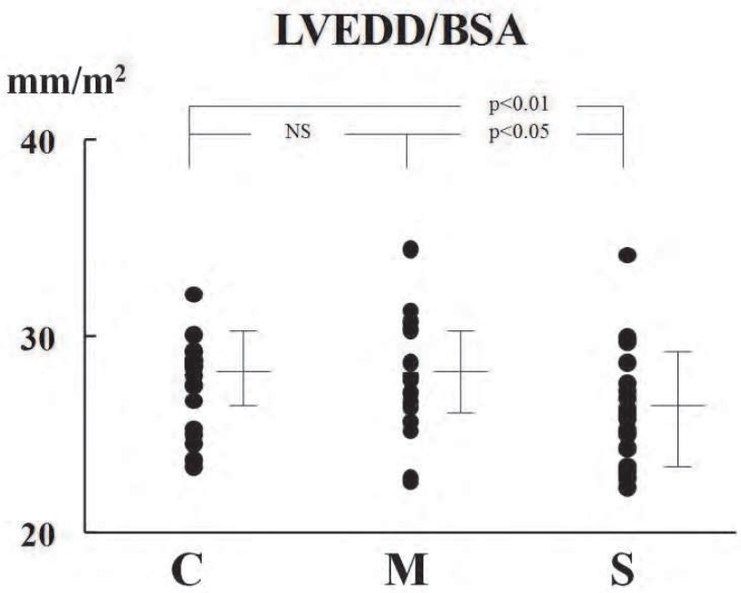


Fig. 4. Comparison of the left ventricular end-diastolic dimension/body surface area (LVEDD/BSA) among the study groups. The mean LVEDD/BSA was significantly lower in S (patients with small heart syndrome and severe symptoms) than in M (patients with small heart syndrome and mild symptoms) and C (control subjects). No significant difference was found between M and C.

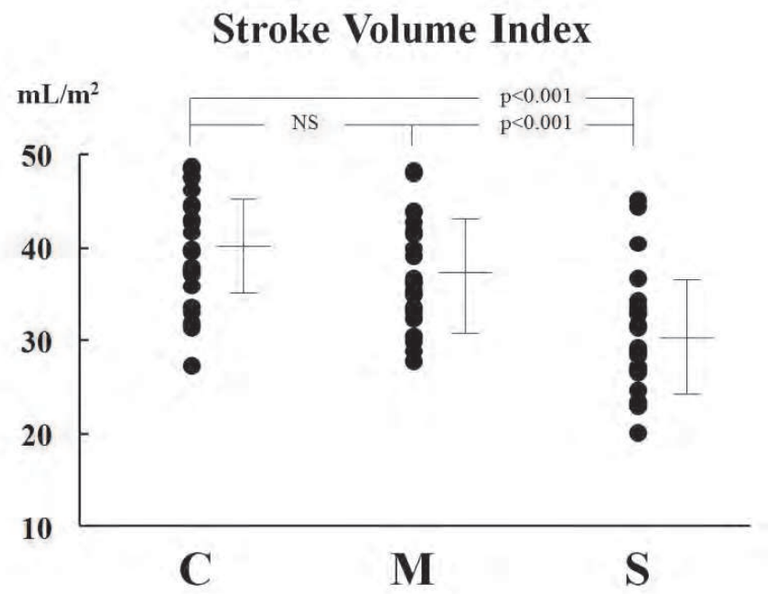


Fig. 5. Comparison of the stroke volume index among the study groups. The mean stroke volume index was significantly lower in S (patients with small heart syndrome and severe symptoms) than in M (patients with small heart syndrome and mild symptoms) and C (control subjects). No significant difference was found between M and C.

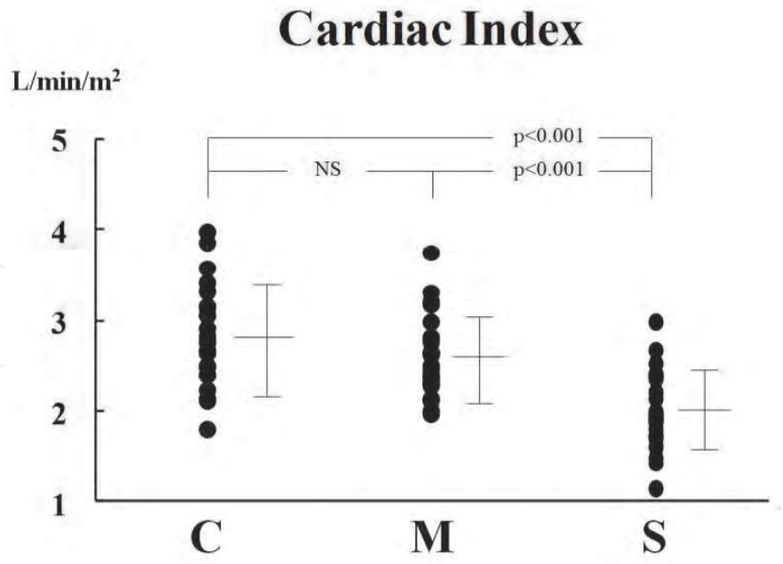


Fig. 6. Comparison of the cardiac index among the study groups. The mean cardiac index was significantly lower in S (patients with small heart syndrome and severe symptoms) than in M (patients with small heart syndrome and mild symptoms) and C (control subjects). No significant difference was found between M and C.

	Control (C)		Small heart syndrome		
			Mild (M)		Severe (S)
		p value		p value	
Number of patients	24		22		25
Sex (male/female)	8/16		7/15		8/17
Age (years)	32±8	NS	30±7	NS	28±6
Body height (cm)	161±9	NS	163±8	NS	163±9
Body weight (kg)	63±17	<0.01	52±10	NS	50±10*
Body mass index (kg/m^2)	24±5	<0.001	19±2	NS	18±2†
Body surface area (m^2)	1.67±0.24	NS	1.56±0.17	NS	1.53±0.17‡
Cardiothoracic ratio (%)	45±2	<0.001	40±3	NS	38±4†
Heart rate (beats/min)	70±11	NS	71±12	NS	68±11
IVST (mm)	8.8±1.2	NS	8.4±0.9	NS	8.3±1.4
LVPWT (mm)	9.0±1.0	<0.01	8.2±1.1	NS	7.9±1.3*
LVEDD (mm)	46±5	<0.05	43±2	<0.001	39±4†
LVEDD/BSA (mm/m^2)	28±2	NS	28±3	<0.05	26±3*
LVESD (mm)	28±3	NS	26±3	NS	25±4†
LVESD/BSA (mm/m^2)	17±2	NS	17±2	NS	16±3
LAD (mm)	28±5	NS	25±3	NS	25±4
AoD (mm)	27±4	NS	25±3	NS	25±3
RVD (mm)	15±4	NS	16±3	NS	16±4
Stroke volume (mL)	68±16	<0.001	58±9	<0.001	46±12†
Stroke volume index (mL/m^2)	40±6	NS	37±6	<0.001	30±7†
Cardiac output (L/min)	4.7±1.2	<0.05	4.0±0.6	<0.001	3.1±0.8†
Cardiac index (L/min/m^2)	2.8±0.6	NS	2.6±0.5	<0.001	2.0±0.4†
Cardiac index <2 L/min/m^2	1 (4%)	NS	2 (9%)	<0.01	15 (60%)*
Fractional shortening (%)	39±3	NS	38±5	NS	37±5
Ejection fraction (%)	69±4	NS	69±6	NS	68±6
Mitral valve prolapse	0 (0%)	NS	3 (14%)	NS	4 (16%)

M: patients with small heart syndrome and mild symptoms, S: patients with small heart syndrome and severe symptoms, IVST: interventricular septum thickness, LVPWT: left ventricular posterior wall thickness, LVEDD: left ventricular end-diastolic dimension, LVESD: left ventricular end-systolic dimension, LAD: left atrial dimension, AoD: aortic root diameter, RVD: right ventricular dimension, NS: not significant, *: $p<0.01$ vs. C, †: $p<0.001$ vs. C, ‡: $p<0.05$ vs. C

Table 2. Comparison of the echocardiographic findings among study groups

As shown in Table 2, both the mean body weight and body mass index were significantly lower in both S and M than in C, although the mean body height was not significantly different among the study groups. The mean body surface area was also significantly ($p<0.05$) smaller in S than in C, although the difference was not significant between M and C. The mean CTR (%) values were in the order of S (38±4) < M (40±3) < C (45±2). CTR was significantly ($p<0.001$) lower in S and M than in C, although no significant difference was noted between S and M.

The results of the echocardiographic examination are shown in Table 2 and Figures 3-6. The LV posterior wall (mm) was significantly ($p<0.01$) thinner in S (7.9±1.3) and M (8.2±1.1) than in C (9.0±1.0), although interventricular septum thickness was not significantly different among the groups. The mean LV end-diastolic dimension (LVEDD) (mm) values were in the order of S (39±4) < M (43±2) < C (46±5) (Figure 3). LVEDD was significantly smaller in S ($p<0.001$) and larger in C ($p<0.05$) than in M. The mean LVEDD/body surface area (mm/m^2) was significantly smaller in S (26±3) than in M (28±3, $p<0.05$) and C (28±2, $p<0.01$) (Figure 4). No significant difference was noted in the mean value of LVEDD/body surface area between M and C. In addition, the mean LV end-systolic dimension (LVESD) (mm) values were in the order of S (25±4) < M (26±3) < C (28±3). LVESD was significantly ($p<0.001$) smaller in S than in C. The mean LVESD/body surface area (mm/m^2) was not significantly different among S (16±3), M (17±2) and C (17±2).

Both mean stroke volume and cardiac output values were in the order of S < M < C. Both values were significantly smaller in S and larger in C than in M. The mean stroke volume index (mL/m^2) was significantly ($p<0.001$) smaller in S (30±7) than in M (37±6) and C (40±6) (Figure 5). The mean cardiac index ($L/min/m^2$) was significantly ($p<0.001$) smaller in S (2.0±0.4) than in M (2.6±0.5) and in C (2.8±0.6) (Figure 6). No significant difference was noted in the mean value of stroke volume index or cardiac index between M and C. The prevalence of low cardiac index (<2 $L/min/m^2$) was significantly ($p<0.01$) higher in S (60%) than in M (9%) and C (4%). LV ejection fraction (%) was quite comparable among S (68±6), M (69±6) and C (69±4). Mitral valve prolapse was diagnosed in some of the subjects in S (16%) and M (14%).

Thus, we concluded that in patients with a small heart shadow on a chest roentgenogram, a small LV size was generally associated with low cardiac output, which was particularly

Small heart syndrome

postulated by Master in 1944

1) Small heart shadow on chest roentgenogram
2) Hypotension and/or orthostatic dysregulation
3) General malaise, easy fatigability, dizziness, palpitation, dyspnea, chest pain, headedness and cold feet
4) No organic heart disease or systemic disease
5) Thin physiques, asthenia, visceroptosis and wandering kidney
6) Straight back and flat chest
7) Often complicated with mitral valve prolapse syndrome
8) Young female dominant
9) Naïve, delicate and serious character

Fig. 7. Characterization of the patients with small heart syndrome.

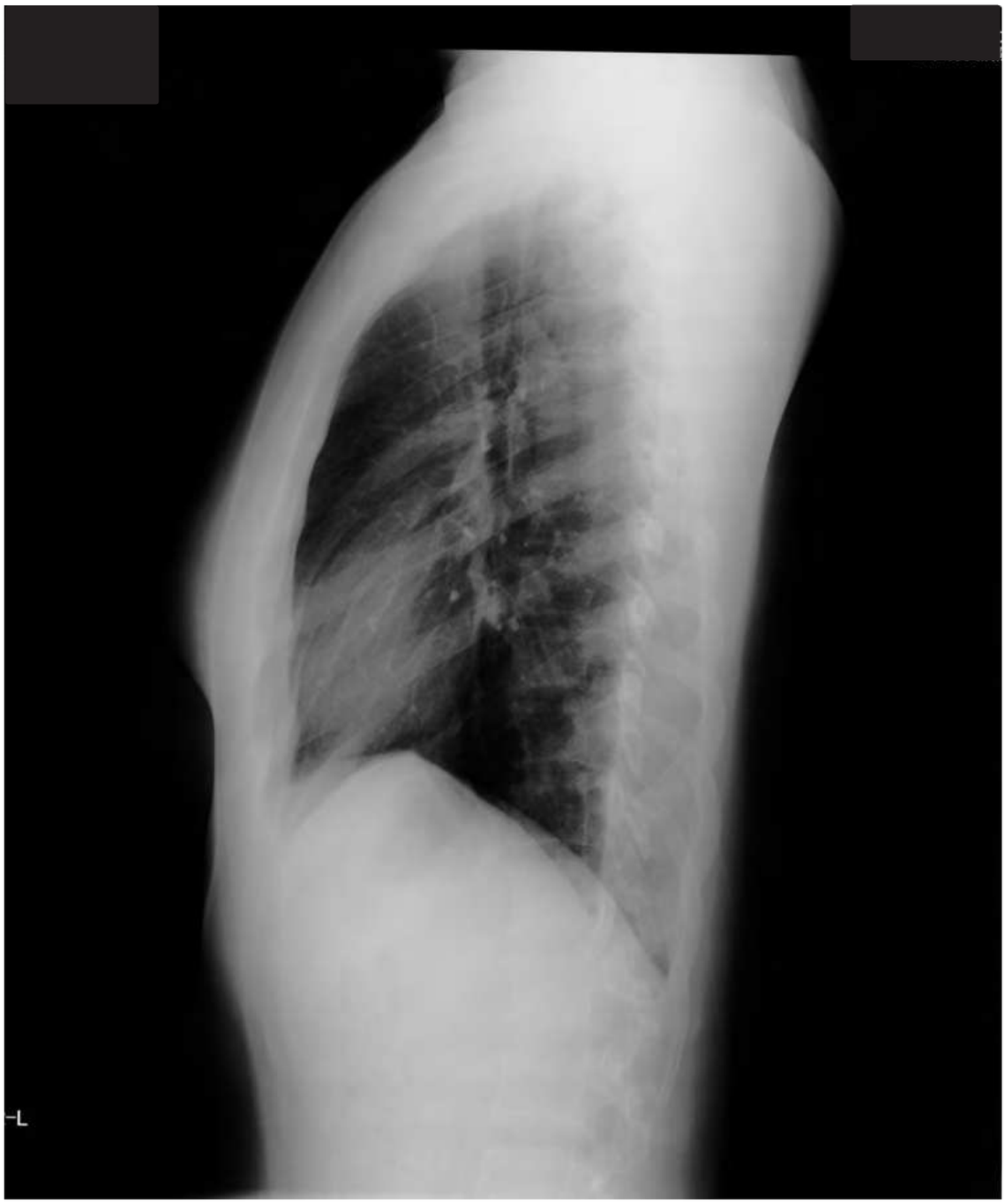


Fig. 8. A typical "straight back" observed in a lateral view chest roentgenogram obtained from a 18-year-old female patient with small heart syndrome.

marked in the patients with severe symptoms and therefore, the pathognomonic significance of a small heart should be recognized as a constitutional factor that predisposes individuals to low output syndrome.[28]

Patients with small heart syndrome are known to have slender structures with low body mass indexes, frequently visceral ptosis with wandering kidney, asthenia, nervousness as well as foot coldness, suggesting physical, autonomic nervous and psychological irritability or lack of relaxation (Figure 7).[11,22,28,29] Thoracic skeletal abnormalities such as shallow chest, straight thoracic spine or loss of the physiologic thoracic kyphosis (Figure 8), and scoliosis are frequently noted in the patients.[11,22,30-32] Mitral valve prolapse[33,34] associated with symptoms such as chest pain, palpitation and dyspnea is a frequent complication of patients with small heart syndrome.[11,22,24,30-32] Many of the small heart subjects appeared to be emotionally sensitive, often delicate and nervous. These conditions may be genetically determined, although several other factors may also be involved in the constitution.[22]

In order to work and perform other duties without excessive exhaustion patients with small heart syndrome need to have enough rest and both physical and emotional relaxation.[11,12] Various triggers including loss of appetite, diarrhea and summer sweating can cause dehydration resulting in preload reduction. It is possible that further reductions in cardiac performance due to preload reduction play an important role in predisposing subjects with small hearts to symptoms including general malaise, fatigue, dizziness, orthostatic dysregulation, dyspnea on effort and palpitations. Autonomic nervous dysfunction with possible accentuated basal parasympathetic tone may be associated with these symptoms through the inhibition of sympathetic activation, which is required to preserve proper cardiac function.[13] Habitual exercise, which can facilitate autonomic nervous adaptation and induce pulmonary and cardiovascular conditioning, may improve the functional work capacity and fatigue by increasing cardiac output. Diarrhea, sweating and loss of appetite as triggering factors for exacerbation should be avoided or treated properly. Constitutional change or conversion is not easy. They may need to take holidays occasionally. And people in their work place and society should understand their specific needs.

2.2 Small heart syndrome as an unrecognized cause of CFS

Recently it has been reported that chest roentgenographic, electrocardiographic and, echocardiographic examinations revealed several distinct findings in CFS patients.[11-13] Specifically, a small heart shadow was often observed on the chest roentgenogram in these patients. In 2008 we first reported that "small heart" with low cardiac output demonstrated by both roentgenographically and echocardiography is prevalent in CFS patients.[11] In this report. small heart syndrome (CTR ≤42%) was significantly more prevalent in the CFS group (n=56) (61%) than in the control group (n=38) (24%) (Table 3). In CFS patients with a small heart (n=34), narrow chest (88%), orthostatic dizziness (44%), foot coldness (41%), pretibial pitting edema (32%), r-kidney palpability (47%), and mitral valve prorapse (29%) were all significantly more prevalent than in the control group, and also in the CFS patients without small heart syndrome (Table 4). Echocardiographic examination demonstrated significantly smaller values of both LV end-diastolic and end-systolic dimensions, and stroke volume and cardiac indexes in CFS with a small heart as compared with control subjects with a normal heart size (42%< CTR <50%) (Table 5). Thus, a considerable number of CFS patients have a small heart and cardiac performance is actually impaired with low cardiac output due to a small LV chamber size and poor cardiac function with low stroke volume and cardiac indexes in many of CFS patients.[11] In addition, both the reduced cardiac size and performance during the exacerbation phase was improved during the remission phase in

CFS patients with "small heart", suggesting that small heart syndrome with impaired cardiac function may play an important role in the genesis of CFS (Table 6).[12] Also cardiothoracic ratios increased significantly during the remission phase as compared with exacerbation phase (Table 6).[12] Reduced LV ejection fraction was not observed in any patients, suggesting no myocardial systolic dysfunction. Many CFS patients have low cardiac output and the resulting low flow circulatory state may make it difficult for patients to meet the demands of everyday activity, and it may also lead to fatigue and other conditions. Small heart syndrome may contribute to the development of CFS as a constitutional factor predisposing to fatigue, and may be included in the genesis of CFS.

	Control	CFS	p
n	38	56	
Gender (male/female)	19/19	26/30	NS
Age (year)	36±8	33±8	NS
Body mass index	22±3	21±5	NS
CTR (%)			
≤42	9 (24%)	34 (61%)	p<0.01
≤40	6 (16%)	25 (45%)	p<0.01
Narrow chest	7 (18%)	33 (59%)	p<0.01

CFS: Chronic fatigue syndrome; CTR: cardiothoracic ratio; NS: not significant

Table 3. Comparison of chest roentgenographic and physical examination findings in study patients

	Control	CFS		
		Small heart		
		(-)	(+)	p value
n	38	22	34	
Male/female	19/19	13/9	13/21	
Age (year)	36±8	34±8	31±8	<0.05*
Body mass index	22±3	25±6	19±3	<0.001*
Narrow chest	7 (18%)	4 (18%)	30 (88%)	<0.01*
Orthostatic dizziness	5 (13%)	3 (14%)	15 (44%)	<0.05*
Foot coldness	4 (11%)	2 (9%)	14 (41%)	<0.05*
Pretibial pitting edema	3 (8%)	1 (5%)	11 (32%)	<0.05*
r-kidney palpability	4 (11%)	1(5%)	1 (47%)	<0.01*
Mitral valve prolapse	3 (8%)	0 (0%)	10 (29%)	<0.05*

*: vs. Control and Small heart (-)
CFS: Chronic fatigue syndrome

Table 4. Comparison of physical examination findings in control and CFS, with and without a small heart

Indeed, CFS patients had a variety of possible cardiovascular complaints, including chest pain, palpitation, dyspnea or shortness of breath, coldness of feet, dizziness and fainting,

although all of these symptoms are not necessarily attributable to cardiovascular dysfunction.[13] Frequently noted physical examination findings such as epigastric splash sound, right kidney palpability, cold feet and pretibial pitting edema, may be related to visceral ptosis with slender build, and peripheral circulatory impairment.[13] Weakness, rapid heartbeat and orthostatic dizziness may be related to hypotension and orthostatic dysregulation. Auscultatory findings including a late systolic murmur and a mid-systolic click suggested typical mitral valve prolapse in some of the patients. In addition, electrocardiograms showed severe sinus arrhythmia and vertical or right axis deviation in a considerable number of the patients, suggesting parasympathetic predominance and vertical heart position.[13] Following our reports Hurwitz et al.[14] reported that severe CFS patients had lower cardiac output associated with lower cardiac volume indicated echocardiographically and lower total blood volume, plasma volume and red blood cell volume indicated by dual tag blood volume assessments as compared with controls, suggesting a co-morbid hypovolemic condition.

	Control	CFS with small heart	
	50%>CTR>42%	CTR≤42%	p value
n	30	34	
Male/female	11/19	13/21	NS
Age (y)	34±13	31±8	0.219
Body height (cm)	163±7	164±10	0.451
Body weight (kg)	60±16	53±11	0.040*
Body surface area (m^2)	1.6±0.2	1.6±0.2	0.146
Heart rate (beats/min)	69±12	72±13	0.363
IVS (mm)	9±1	9±1	0.574
PW (mm)	9±1	8±1	0.709
LVEDD (mm)	45±4	41±5	0.002*
LVESD (mm)	28±3	25±5	0.038*
LAD (mm)	27±5	25±4	0.229
AoD (mm)	27±5	26±4	0.261
RAD (mm)	15±3	16±4	0.361
Stroke volume (ml)	65±14	52±14	0.001*
Stroke volume index (ml/m^2)	39±7	33±8	0.001*
Cardiac output (l/min)	4.4±1.2	3.7±1.0	0.005*
Cardiac index (l/min/m^2)	2.7±0.6	2.3±0.6	0.012*
Fractional shortening (%)	39±4	37±4	0.188
Ejection fraction (%)	69±4	68±5	0.313

*: significant
IVS: interventrricular septum thickness; PW: LV posterior wall thickness; EDD: end-diastolic dimension; ESD: end-systolic dimension; LAD: left atrial dimension; AoD: aortic root diameter; RVD; right ventricular dimension
CFS: chronic fatigue syndrome

Table 5. Comparison of echocardiographic findings in control with a normal heart size and CFS with a small heart

	Exacerbatioin	Remission	p value
Heart rate (beats/min)	71±9	63±6	0.014*
LVEDD (mm)	38±4	43±3	<0.001*
LVESD (mm)	24±2	27±2	0.015*
Stroke volume (ml)	41±10	56±11	<0.001*
Stroke volume index (ml/m^2)	28±7	39±6	<0.001*
Cardiac output (l/min)	2.8±0.6	3.6±0.9	0.017*
Cardiac index (l/min/ m^2)	2.0±0.4	2.5±0.5	0.014*
Ejection Fraction (%)	66±3	68±6	0.443
CTR (%)	38±2	40±2	<0.001*

LV: left ventricular; EDD: end-diastolic dimension; ESD: end-systolic dimension; CTR: cardiothoracic ratio
*: statistically significant

Table 6. Comparison of echocardiographic findings of 10 CFS patients with a small heart between the exacerbation and remission phases

3. Orthostatic Intolerance (OI)

Patients with orthostatic intolerance have been clinically recognized.[35-37] The patients predictably develop symptoms of disabling fatigue, dizziness, diminished concentration, tremulousness, and nausea while standing (Table 7). Simple activities such as eating, showering, or low intensity exercise may profoundly exacerbate these symptoms. Reduced cerebral blood flow with impaired cerebral oxygenation during an upright posture is considered as major mechanism for orthostatic intolerance,[17,38] although compensatory sympathetic activation also seems to play an important role in the development of the

Symptoms While Standing in Patients with Orthostatic Intolerance
Disabling fatigue
General malaise
Diminished concentration
Dizziness
Fainting
Pallolr
Weakness
Tremulousness
Sweating
Light headedness
Visual disturbance
Palpitations
Dyspnea
Nausea
Nervousness

Table 7. Symptoms while standing in patients with orthostatic intolerance

various symptoms in cases it is exaggerated.[36-41] Assuming an upright posture causes translocation of approximately 800 ml of blood from the intrathoracic venous compartment to veins of the buttocks, pelvis and legs.[42] The normal compensatory cardiovascular response to this orthostatic stress is a neurogenically mediated increase in heart rate and in systemic vascular resistance.[42] Not all vascular beds contribute equally to the reflex increase in vascular resistance.[42] Splanchnic vasoconstriction accounts for one third, and skin and muscle vasoconstriction, approximately 40% of the increased vascular resistance during normal levels orthostatic stress.[42] Symptoms of orthostatic intolerance develop as these reflexes approach the limit of compensation.

3.1 Similarities and overlaps between CFS and OI

Many of the primary symptoms of orthostatic intolerance are often seen in patients with disabling CFS.[17,42,43] Both CFS and orthostatic intolerance affects many young people, predominantly women. Many symptoms of OI appear to be related to reduced cerebral blood flow. Symptoms are associated with inadequate systemic venous return to the right heart or thoracic hypovolemia,[35,36] although precise mechanisms remain to be clarified. Also excessive lower body venous pooling with delayed orthostatic hypotension, by reducing cerebral perfusion, has been suggested to be involved in the orthostatic component of fatigue in CFS patients.[44]

3.2 Pathopysiology of OI

Potential pathophysiological mechanisms in chronic orthostatic intolerance include a β-adrenergic hypersensitivity,[45] decreased plasma volume,[46] an inappropriate venous pooling,[44] and possible dysautonomia.[36-41,47] Several disorders including delayed orthostatic hypotension,[17] neurally mediated hypotension[48] and postural orthostatic tachycardia syndrome[35-38] underlies or promotes orthostatic intolerance. Delayed orthostatic hypotension can be caused by excessive gravitational venous pooling.[17,44] Impaired vasoconstrictor function with relative bradycardia is often seen in neurally mediated hypotension.[48] In 1995 Rowe et al.[48] described the cases with an overlap in the symptoms of CFS and neurally mediated hypotension, suggesting that neurally mediated hypotension should be considered as a treatable cause of CFS. Exaggerated tachycardia and vasoconstriction without hypotension of postural orthostatic tachycardia syndrome (POTS) during standing can cause orthostatic intolerance,[35-38] although pathophysiology of POTS remains unclear. In 1982 Rosen and Cryer were the first to describe a woman with a 7-year history of disabling postural tachycardia and palpitations in association with an idiopathic reduction in plasma volume.[35] In 1993 Schondorf and Low[36] reviewed the patients who exhibited exaggerated tachycardia at rest or during head-up tilt and named "idiopathic postural orthostatic tachycardia syndrome" which may be a manifestation of a mild form of acute autonomic neuropathy. Studies suggest that POTS is accompanied with a range of autonomic nervous system abnormalities including vagal withdrawal and enhanced sympathetic modulation, associated with findings consistent with pooling in the lower limbs.[36-41,44,47] Also studies in adolescents suggest that POTS physiology underlies OI in the majority of CFS patients.[41-44] POTS is a frequent finding in patients with CFS.[41-44] Clinical evaluation of CFS patients should include response to standing. POTS may be an under-recognized condition in CFS as Hoad et al.[49] recently suggested.

3.3 OI and small heart

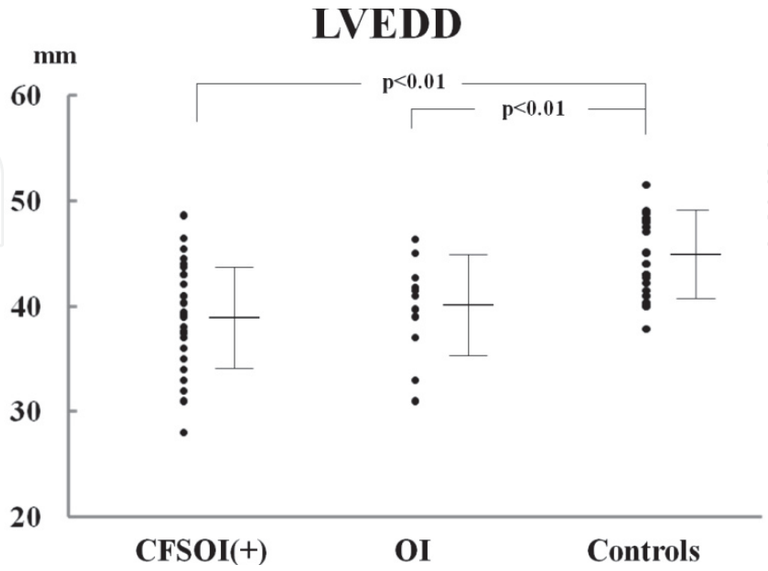
Recently it has been reported that patients with postural orthostatic tachycardia, which is often noted in patients with chronic orthostatic intolerance, had a smaller heart coupled with reduced blood volume compared with healthy controls.[50] By using a cardiac magnetic resonance imaging technique, Fu et al.[50] assessed precisely the heart size and mass in POTS patients and found that cardiac size and mass and blood volume were much smaller in the patients compared with healthy sedentary controls. The marked orthostatic tachycardia in these patients seemed to be a physiologic compensatory response to a smaller stroke volume and exercise training improved this syndrome in most patients.[50] Fu et al.[50] offered POTS a new name based on its underlying pathophysiology, the "Grinch syndrome", because in this famous children's book by Dr Seuss, the main character had a heart that was "two sizes too small". In their assessment of both sympathetic baroreflex sensitivity and cardiovagal baroreflex sensitivity, the function of autonomic nervous system was intact in the patients,[50] although other researchers have postulated autonomic nervous dysfunction with exaggerated sympathetic nervous activation over compensatory levels during standing as a major mechanism for the symptoms.[35,36,40,41,47]

Although some dysautonomia cause orthostatic instability accompanied with abnormal changes in heart rate and blood pressure, whether disorders of the autonomic nervous system is responsible for OI and also OI in CFS patients is controversial.[38,39,43,44,50] Recently, Jones et al.[51] reported that orthostatic instability was similar in persons with CFS and nonfatigued control subjects recruited from the general Wichita population. Interestingly persons with higher serum osmolarity levels had significantly higher abnormal tilt rates than those with lower serum osmolarity levels, suggesting that delayed responses to head-up tilt tests may reflect hydration status.[51] Reappraisal of primary dysautomia as a factor in the pathogenesis of CFS and also OI may be needed. In the meanwhile Ewan et al.[52] reported that use of the sinus node blocker ivabradine led to dramatic improvements in subjective and objective symptomatology in line with a reduction in heart rate on standing in a 21 year-old female patient with POTS. Use of this medication appears to not only improve tachycardia but also symptomatology, including fatigue, suggesting that tachycardia is not only unnecessary for maintaining cerebral perfusion while standing as a compensatory mechanism but also triggers many symptoms possibly through disturbances in autonomic nervous system.

3.4 Pronounced small heart in CFS with OI

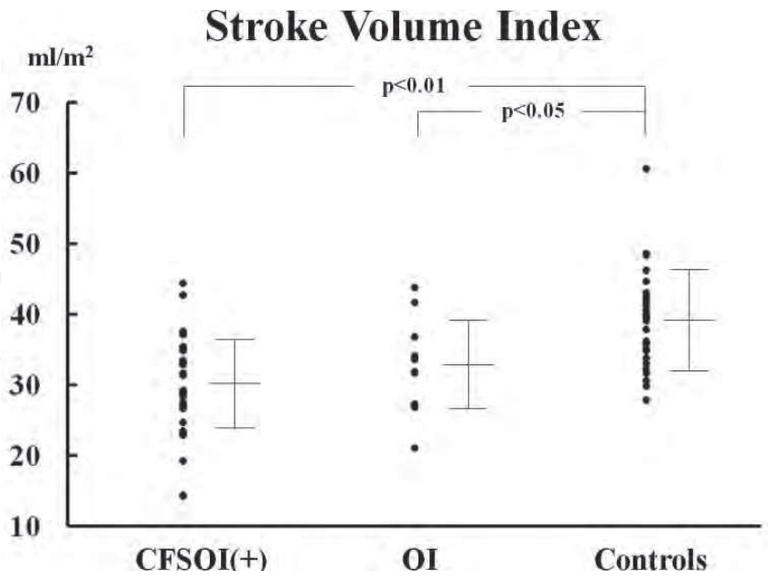
We aimed to test a hypothesis that small heart is associated with OI in patients with CFS. Among the 46 study CFS patients, 26 (57%) were classified as CFSOI according to the presence of OI. In addition, 11 OI patients and 27 age- and sex-matched control subjects (Controls) were studied. Left ventricular (LV) dimensions and function were determined echocardiographically. As shown in Table 8 and Figures 9-11, the mean values of cardiothoracic ratio, systemic systolic and diastolic pressures, LV end-diastolic dimensions, LV end-systolic dimensions, stroke volume indexes, cardiac indexes and LV mass indexes were all significantly smaller in CFSOI and OI than in Controls. A smaller LV end-diastolic dimension (< 40 mm) was significantly more prevalently noted in CFSOI (54%) and OI (45%) than in Controls (4%). A lower cardiac index (< 2 l/min/mm^2) was more prevalent in CFSOI (65%) than in OI (27%) and Controls (11%). The mean values of both LV fractional shortening and ejection fraction were comparable among the groups (Table 8). In conclusion, a small size of

LV with low cardiac output was noted in OI and marked in CFSOI. A small heart appears to be related to the genesis of OI and CFS via both cerebral and systemic hypoperfusion. CFSOI seems to constitute a well-defined and predominant subgroup of CFS.



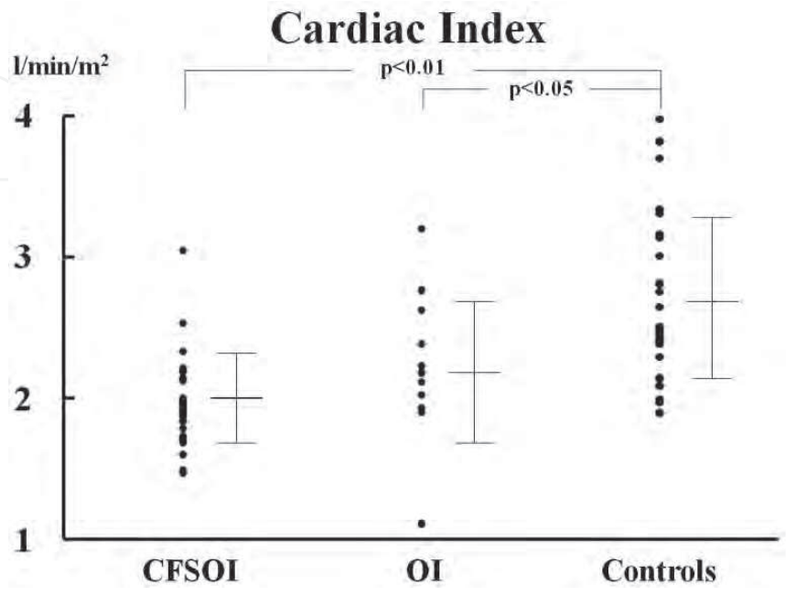
CFSOI: patients with chronic fatigue syndrome and orthostatic intolerance
OI: patients with orthostatic intolerance but without chronic fatigue syndrome
Controls: healthy control subjects

Fig. 9. Comparison of the left ventricular end-diastolic dimensions (LVEDD) among the study groups.



CFSOI: patients with chronic fatigue syndrome and orthostatic intolerance
OI: patients with orthostatic intolerance but without chronic fatigue syndrome
Controls: healthy control subjects

Fig. 10. Comparison of the stroke volume indexes among the study groups.



CFSOI: patients with chronic fatigue syndrome and orthostatic intolerance
OI: patients with orthostatic intolerance but without chronic fatigue syndrome
Controls: healthy control subjects

Fig. 11. Comparison of the cardiac indexes among the study groups.

Elucidation of the pathophysiology of CFS and OI may lead to better therapeutic strategies. Recently, xenon-computed tomography blood flow studies demonstrated that CFS patients have global cerebral hypoperfusion with reduced absolute cortical blood flow in broad areas, especially in bilateral middle cerebral artery territories, compared with healthy controls.[53] Impaired cerebral oxygenation due to reduced cerebral hemodynamics in young CFS with OI during an active standing test was suggested from the findings of continuous measurement of cerebral oxygenated hemoglobin using near-infrared spectroscopy.[54] In the present study, low systolic and diastolic blood pressures were noted in OI patients with and without CFS compared with those in control subjects. Newton et al.[55] have consolidated the evidence using 24-hour ambulatory blood pressure monitoring that lower blood pressure occurs in CFS patients and lower nighttime blood pressure seems to be a significant problem that may lead to the enhanced diurnal variation. The putative mechanism by which OI and CFS are triggered or caused in patients with a small heart is shown in Figure 12.

	CFSOI	OI	Controls
Number of patients	26	11	27
Male/Female	7/19	2/9	10/17
Age (years)	28±8	31±7	32±7
Cardiothoracic ratio (%)	38±5†	42±3‡	44±4
Heart rate (beats/min)	69±15	68±11	70±12
Systolic blood pressure (mmHg)	109±11*	112±14†	121±11
Diastolic blood pressure (mmHg)	66±12*	68±13†	75±12
IVS (mm)	8±1	8±1	9±1
PW (mm)	8±1	8±1	9±1
LVEDD (mm)	39±5*	40±5*	45±4
<40	14 (54%)*	5 (45%)*	1 (4%)
LVESD (mm)	25±5*	24±5*	27±2
LAD (mm)	25±5	24±4	27±4
AoD (mm)	26±4	25±3	27±5
RVD (mm)	15±4	15±2	15±3
Stroke volume (ml)	45±13*	49±11*	63±13
Stroke volume index (ml/m^2)	30±7*	33±7†	39±7
Cardiac output (l/min)	3.0±0.7*	3.3±1.0*	4.4±1.0
Cardiac index (l/min/m^2)	2.0±0.3*†	2.2±0.5†	2.7±0.6
< 2	17 (65%)*	3 (27%)	3 (11%)
Fractional shortening (%)	37±4	40±7	39±3
LV Ejection fraction (%)	67±5	71±8	69±4
LV mass index (g/m^2)	62±16†	64±13‡	77±16

IVS: interventricular septum thickness; PW: left ventricular (LV) posterior wall thickness; LVEDD: LV end-diastolic dimension; LVESD: LV end-systolic dimension; LAD: left atrial dimension; AoD: aortic root diameter; RVD: right ventricular dimension

*: p <0.01 vs. Controls †: p <0.05 vs. Controls

Comparisons of values between the study groups were performed with ANOVA followed by Student's unpaired t-test. Proportional data were analyzed by the chi-square test, with Yates' correction.

Table 8. Comparative echocardiographic data among the study groups

Reasonable potentiation of cerebrovascular flow without exaggerated activation or perturbation of autonomic nervous system may be needed for effective treatment. However, administration of nonselective vasoconstrictive agents may cause a simple reduction of cerebral blood flow via elevation of cerebrovascular resistance, although intravenous infusion of phenylephrine, a sympathetic nerve α_1 stimulator, has been reported to improve OI, as a result of producing significant peripheral vasoconstriction and venoconstriction in some OI patients.[56] Volume repletion by increasing sodium intake or by treatment with fludrocortisones may theoretically improve OI and also symptoms of CFS by replenishing intravascular volume.[17,35,38,42,46] Military anti-shock trousers as well as elastic stockings which compress lower extremities may also be effective via potentiation of venous return, resulting in increased cardiac output.[44] Although CFS patients are limited by the discomfort of an increased perception of exertion, there are some data to support the notion that an appropriately designed exercise program is beneficial.[50,57-59] Various triggers including loss

of appetite, diarrhea and sweating can cause dehydration accompanied by preload reduction, leading to further decreases in stroke volume and cardiac output, thereby impairing both systemic and cerebral circulation and exacerbating symptoms, and therefore should be avoided or treated appropriately.

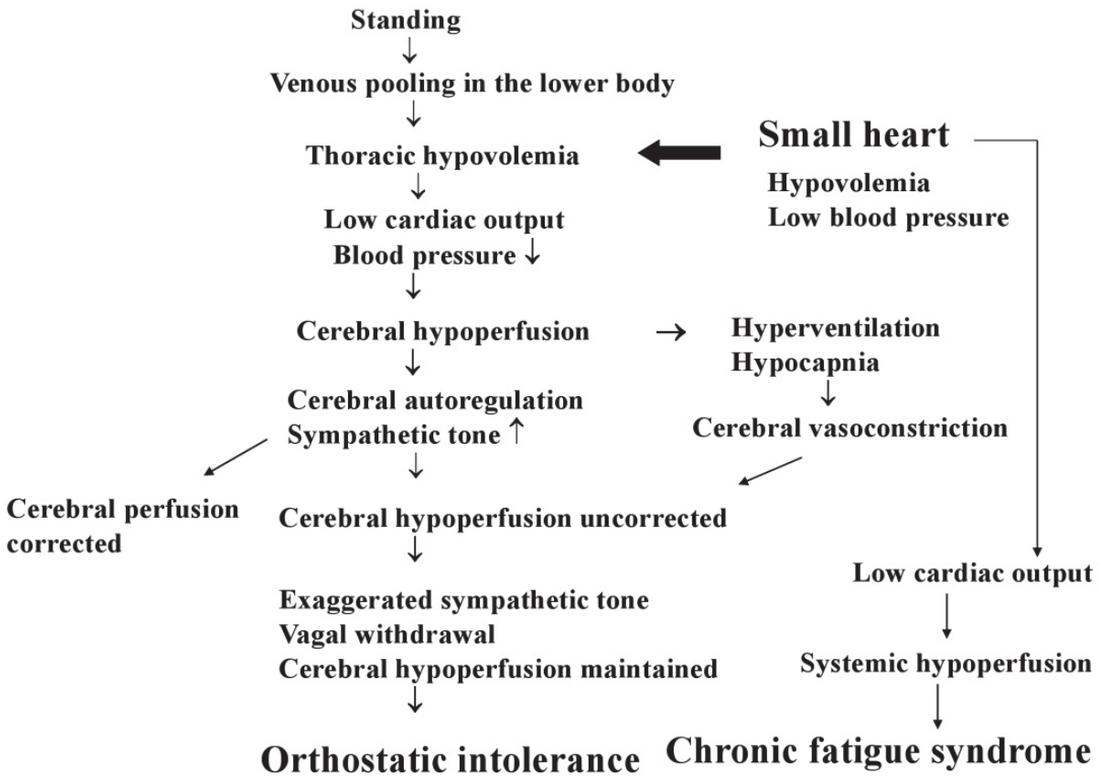


Fig. 12. The putative mechanism by which orthostatic intolerance and chronic fatigue syndrome are triggered in patients with a small heart.

4. Conclusions

Cardiac dysfunction with low cardiac output due to a small LV chamber may contribute to the development of chronic fatigue as a constitutional factor in a considerable number of CFS patients and its degree appears to be more pronounced in CFS patients with OI.[60] CFS with OI seems to constitute a well-defined and predominant subgroup of CFS. Small heart with reduced cardiac performance due to decreased preload may be an important target for the treatment of CFS.

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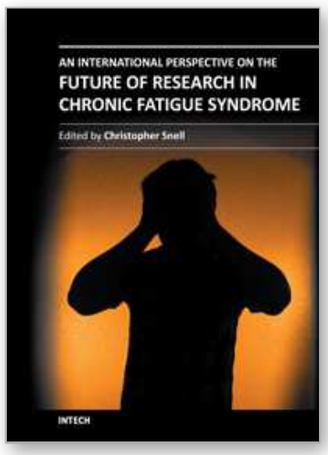

An International Perspective on the Future of Research in Chronic Fatigue Syndrome

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While the chapters in this book are a long way from solving the enigma that is CFS, they do represent important attempts to understand this complex and perplexing disease. A common theme in them all is CFS as a multisystem disease with the possibility of more than one cause and influenced by a variety of interacting factors. Further, they acknowledge the reality of CFS for persons with this disease and the importance of finding causes, treatments and ultimately a cure. As advanced biomedical research techniques are increasingly applied to the study of CFS, it is surely only a matter of time before biomarkers are identified, etiologies understood, and remedies devised.

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