Sudden cardiac death is common in patients with hypertrophic cardiomyopathy (HCM) and the risk is greatest in children and young adults with HCM in whom it is frequently associated with exercise. In adults, however, HCM is associated with arrhythmias, such as ventricular tachycardia and such patients also have a high mortality rate. Despite the lack of an association with arrhythmias, sudden cardiac death is more likely to occur in young patients than adult patients with HCM and the reason for this is unclear, although it was recently suggested that exercise-induced hypotension is related to sudden cardiac death in HCM patients. The aim of the present study was to measure the cardiac output (CO) of young patients with HCM during exercise using impedance plethysmocardiography to elucidate the hemodynamic response of these patients to exercise.

**Response of the Stroke Volume and Blood Pressure of Young Patients With Nonobstructive Hypertrophic Cardiomyopathy to Exercise**

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Stroke volume (SV), cardiac output (CO) and systolic blood pressure (SBP) were measured during maximal symptom-limited bicycle exercise testing in 13 young patients (age, 11–26 years) with nonobstructive hypertrophic cardiomyopathy (HCM). SV was measured by impedance plethysmocardiography; %SVend, %COend, and %SBPend represent the ratio of the value at termination of the exercise to the respective value at rest. In all patients of HCM-I (the Cardiac Event Group, 3 patients) and 3 of HCM-II (the Non-Cardiac Event Group, 10 patients), the %SVend was less than 100%. The %SVend of HCM-I was significantly lower than the respective values of the HCM-II and Control groups. The %COend values of the HCM-I and HCM-II groups were each significantly lower than that of the Control. The %SBPend values of the HCM-I and HCM-II groups were each significantly lower than that of the Control. Among the HCM patients, the %SVend value was positively correlated with the %SBPend value. The patients who had more severe HCM had poorer exercise-induced increases in SV and SBP. These results suggest that sudden cardiac death in young HCM patients is associated with inhibition of the increase in SV upon exercise. (Jpn Circ J 2001; 65: 300–304)

**Key Words:** Blood pressure; Exercise; Impedance plethysmocardiography; Nonobstructive hypertrophic cardiomyopathy; Stroke volume

Sudden cardiac death is common in patients with hypertrophic cardiomyopathy (HCM) and the risk is greatest in children and young adults with HCM in whom it is frequently associated with exercise! In adults, however, HCM is frequently associated with arrhythmias, such as ventricular tachycardia and such patients also have a high mortality rate. Despite the lack of an association with arrhythmias, sudden cardiac death is more likely to occur in young patients than adult patients with HCM and the reason for this is unclear, although it was recently suggested that exercise-induced hypotension is related to sudden cardiac death in HCM patients. The aim of the present study was to measure the cardiac output (CO) of young patients with HCM during exercise using impedance plethysmocardiography to elucidate the hemodynamic response of these patients to exercise.

**Methods**

**Subjects (Table 1)**

The subjects consisted of 13 consecutive patients with nonobstructive HCM who visited the Department of Pediatrics at Yokohama City University School of Medicine between November 1992 and July 1997. The diagnosis of HCM had been made based on the presence of the typical clinical and electrocardiographic findings in association with a hypertrophied, nondilated left ventricle in the absence of any other cardiac or systemic disorders that might cause left ventricular hypertrophy. In patients who had mild hypertrophy, a myocardial biopsy was performed for diagnostic purposes. A patient was diagnosed with ‘nonobstructive HCM’ if a left ventricular outflow tract gradient was not detected by echocardiography at rest or during exercise.

The patients consisted of 10 males and 3 females, and the mean age at the time of examination was 17.5 years (range, 11–26 years). The mean length of follow-up was 7.4 years (range, 2–18 years). The HCM patients were divided into 2 groups: the Cardiac Event Group (HCM-I group) consisting of 3 patients who had a history of a cardiac event (1 had a cardiac arrest and 2 had a syncopal attack), and the Non-Cardiac Event Group (HCM-II group) consisting of 10 patients who did not have a history of cardiac events. None of the 13 patients had other subjective symptoms, such as chest pain, and all 13 patients were in New York Heart Association (NYHA) functional class 1. The control group consisted of 21 young subjects (15 males, 6 females) whose mean age was 13.5 years (range, 11–17 years). Informed consent was obtained from all study subjects.

**Exercise Testing**

Each subject underwent symptom-limited exercise testing on a cycle ergometer (Nihon Koden, STB-1400, Tokyo, Japan). Exercise was started at 10W and the work rate was increased by 10W every minute.
Impedance Plethysmocardiography

Measurement of impedance in the chest was done by impedance plethysmocardiography (Nihon Koden, Al-601G) using the standard 4-band electrode arrangement fitted on the neck and chest. A constant sinusoidal current (50 KHz and 300 $\mu$A) was applied to the outer pair of electrodes, and potential changes ($\Delta Z$) reflecting impedance were picked up from the inner pair of electrodes. An electrocardiogram (ECG), impedance plethysmocardiogram, and phonocardiogram were simultaneously recorded. The heart rate (beats/min) was derived from the ECG, and the left ventricular ejection time (T) was derived from the phonocardiogram. The measurement of impedance was made during end-expiratory breath holding. The stroke volume (SV) was calculated by the following formula according to the method of Kubicek, et al.9

\[
SV = \frac{\pi}{4} (L/Z_0)^2 \frac{dZ}{dt} m \cdot T,
\]

where $\pi$ is the resistivity of blood ($\Omega \cdot cm$); L is the mean distance between the inner electrodes at the anterior and posterior midlines (cm); $Z_0$ is the basic impedance between the 2 inner electrodes ($\Omega$); $dZ/dt$ m is the maximum rate of change of impedance ($\Omega/s$); and T is the ventricular ejection time (s).

Evaluation of Ventricular Wall Thickness

Echocardiography was recorded with a Hewlett-Packard SONOS 1000 system with 3.5-MHz transducer, and the ventricular wall thickness was measured at end-diastole. For evaluation of ventricular hypertrophy, the maximal thickness of the left ventricular wall divided by the body surface area was used.

Data Analysis

SV was calculated for 5 consecutive beats, and the mean value of these 5 beats was obtained. Cardiac output was calculated as the product of SV and heart rate (HR). The systolic blood pressure (SBP) was non-invasively measured using an automatic manometer (Kyokkou-Bussan, CM-4001, Tokyo, Japan). Parameters such as SV, CO, SBP and HR were measured at every 1-min time point at rest, during exercise, and during the recovery period. The change in SV, CO and SBP upon exercise was expressed as the ratio (%) of the value during exercise to the respective value at rest while sitting. For comparison among individuals, the ratios using the value soon after termination of the exercise (30 s after termination) were used (%SVend, %COend, and %SBPend, respectively).

Statistics

Data were expressed as mean±standard deviation (SD). One-way factorial ANOVA was used to compare the hemodynamic variables such as %SVend, %COend, and %SBPend,
among the 3 groups. When a significant difference was present, Scheffe's multiple comparison test was used for intergroup comparison. A value of p<0.05 was regarded as statistically significant.

**Results**

**Changes in SV, SBP, and HR During Exercise (Figs 1, 2)**

Endurance times for the HCM-I, HCM-II and Control groups were 10.3±1.2 min, 10.4±2.8 min and 12.1±2.3 min, respectively; no significant difference. All the control subjects showed a pattern of the SV increasing during the exercise, reaching a peak value around 6 min, and then falling after termination of the exercise (Fig 1). Fig 2 shows the SV, SBP of a patient in the HCM-I group (Patient 1) in whom the SV, in contrast with the pattern of the normal subjects, remained constant for 4 min after starting the exercise, then started to decrease, and increased after termination of the exercise. All 3 patients in the HCM-I group and 1 of the 10 patients in the HCM-II group showed this pattern of SV over the course of the exercise.

**Comparison of the Exercise SV and CO Among the 3 Groups (Fig 3)**

The %SVend of the Control group was 129±16%, that of the HCM-II group was 115±18%, and that of the HCM-I group was 72±7%, the latter being significantly lower than that of the HCM-II and Control groups (p<0.01 and p<0.01, respectively). The %COend of the Control group was 265±41%, that of the HCM-II group was 200±39%, and that of the HCM-I group was 159±53%; both the HCM-I and HCM-II values were significantly lower than that of the Control group (p<0.01 and p<0.01, respectively).

**Comparison of the Exercise SBP Among the 3 Groups (Fig 3)**

The %SBPend of the Control group was 143±13%, that of the HCM-II group was 128±15%, and that of the HCM-I group was 109±3%; again the values of the HCM-I and HCM-II groups were significantly lower than that of the Control group (p<0.01 and p<0.05, respectively).

**Relationship Among SV, CO, and SBP During Exercise in the HCM Patients (Fig 4)**

There was a significant positive correlation between %SVend and %SBPend (r=0.80, p<0.01). However, %SBPend was not correlated with %COend among the HCM patients.

**Relationship Between SV and Ventricular Wall Thickness in the HCM Patients (Fig 5)**

There was a significant negative correlation between %SVend and the normalized ventricular wall thickness among the HCM patients (p<0.01).

**Discussion**

Sudden cardiac death is the most serious complication of HCM, but the mechanism of its development has not been elucidated. Adult HCM is frequently complicated with serious arrhythmias, such as ventricular tachycardia, and HCM patients with such arrhythmias have a high mortality rate. Generally, young individuals with HCM have a higher rate of sudden cardiac death than adult patients, with one study reporting that 71% of the sudden cardiac deaths in HCM patients occurred in patients younger than 30 years, and that 61% of these deaths were related to physical activity. Because arrhythmia is very rare in young HCM patients, the mechanism that leads to sudden cardiac death in young HCM patients might differ from that in adult patients. Furthermore, it has been reported that the presence of a left ventricular outflow gradient is not a major prognostic determinant for sudden cardiac death, so the mechanism of sudden cardiac death in patients with
nonobstructive HCM remains to be elucidated. Patients with HCM have characteristically abnormal responses of blood pressure to exercise. Frenneaux et al found that during exercise, the blood pressure fell in 33\% of the HCM patients, and an abnormal blood pressure response during the recovery after exercise was observed in 23\% of the patients\cite{7,8,13} and that they are frequently seen in young individuals with HCM\cite{5}. However, it seems that these pressure depressions are independent of the increase in CO\cite{5,12}. On the other hand, Lele et al\cite{14} reported that HCM patients show an insufficient increase in CO during exercise, as measured by equilibrium radionuclide ventriculography, and that the exercise capacity correlated with both the peak cardiac index\cite{14,15} and peak stroke index\cite{14}. The present study measured both the CO and SBP before, during and after exercise in HCM patients who were younger than 27 years, the age group of HCM patients that has a high risk for sudden cardiac death. To simplify the study, all of the subjects in the present study were HCM patients who did not have obstruction of the left ventricular outflow tract.

The impedance plethysmocardiography method devised by Kubicek et al\cite{16} is a clinically useful method of measuring cardiac output because it is non-invasive\cite{16}. Although the result is expressed as the absolute value (ml) of SV, the present study used the ratio (\%) of SV during exercise to that at rest, because of inter-individual variation in blood resistivity, which was used in the calculation of the absolute value of SV. It has been shown that measurement of CO by impedance plethysmocardiography is valid even during exercise and is comparable to other standard methods\cite{17,18}. However, because vigorous body movement considerably increased the noise of impedance, which would introduce error in the SV value, we used the SV value in the recovery phase soon after termination of the exercise. Therefore, the \%SV_{end} and \%CO_{end} measured in the present study might not represent the maximum value of SV and CO during exercise.

The present study clarified that patients with more severe HCM had smaller exercise-induced increases in SV and CO. In particular, all 3 patients with a history of cardiac events showed a reduction in SV at the midpoint of the exercise to a value lower than the SV at rest, and the SV gradually increased after termination of the exercise. Lele et al reported that adult patients with HCM had a poor increase in CO during exercise, although there was no patient in whom the SV decreased below the SV value at rest\cite{14}. The difference in the pattern of SV during and after exercise in the present study and that of Lele et al\cite{14} is likely because of the difference in the age of the subjects and the severity of HCM. The cardiac events in the 3 patients in the HCM-I group occurred during a physical activity: one patient was riding a bicycle up a steep hill; the second patient was running; and the third patient was walking to school in the morning. A poor increase in SV and CO during exercise may be a predictive factor for cardiac events in HCM patients. The 13 HCM patients in the present study underwent the treadmill and ergometer exercise a mean of 10.6 times (range, 3–25 times) during the follow-up period. A Holter ECG was recorded a mean of 2.8 times (range, 1–7 times). Ventricular tachycardia was not observed in any of the young patients during the exercise testing nor during daily physical activity. The low incidence of ventricular arrhythmia among young HCM patients does not mean that they are at low risk for sudden cardiac death; HCM in young patients differs from HCM in adult patients\cite{3}.

The significance of the ventricular septal thickness in the development of sudden cardiac death in HCM is controversial. In the study of Maron et al\cite{4} there was no relationship between the ventricular septal thickness and sudden cardiac death, whereas in the study of Spirito and Maron\cite{5} there was a relationship. In the present study, young HCM patients who had a thicker left ventricular wall, had a smaller exercise-induced increase in SV. Left ventricular wall thickness can be used to identify young HCM patients who are at high risk for sudden cardiac death. In this study, the left ventricular wall thickness was normalized with the patient's body surface area, because the age and body size of the patients varied.

Two mechanisms of exercise-related hypotension in HCM patients are considered. One possible mechanism is inhibition of the increase in SV and CO upon exercise, as shown in the present study, and a second possible mechanism is depression of the vascular constrictive response, although each factor would affect the other. Counihan et al proposed that the vascular constrictive response results from an inappropriate and exaggerated reduction in systemic vascular resistance at high work loads\cite{5,11}. Because the myocardium of HCM patients is reported to have abnormal perfusion\cite{20,21}, it is likely that the inhibition of the increase in CO and the reduction in systemic vascular resistance during exercise in HCM patients induce exercise-induced hypotension, which promotes further myocardial ischemia and pump failure. As a result, ventricular tachycardia and fibrillation may occur. It was concluded that inhibition of the increase in CO upon exercise is exclusively associated with sudden cardiac death in young HCM patients.

References

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