Prevalence of Short Stature and Growth Hormone Deficiency and Factors Associated With Short Stature After Fontan Surgery

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Background: Fontan circulation is characterized by many features commonly observed in heart failure that may affect physical growth regardless of pituitary gland dysfunction status. The aims of the present study were to investigate the prevalence of short stature and growth hormone deficiency (GHD) and determine the factors associated with short stature after Fontan surgery.

Methods and Results: On retrospective evaluation of 47 patients after Fontan surgery, a very high prevalence of short stature was observed (38.3%). In the short stature group, 5 patients were diagnosed with GHD (10.6% of patients after Fontan Surgery), which is much higher than the frequency of 1/10,000 in the general population. Central venous pressure (CVP) was significantly higher (14.6±4.5 vs. 12.2±1.9 mmHg, P<0.05) and the blood pressure and arterial oxygen saturation were significantly lower in the short stature group. Laboratory data also indicated volume retention and congestion in the short stature group. Mean change in stature from catheterization 1 year after Fontan surgery to the most recent visit was significantly lower in the short stature group (−1.1±1.1 SD vs. 0.0±0.8 SD, P<0.05) and significantly negatively correlated with CVP (r=−0.42, P<0.05).

Conclusions: Volume retention and congestion, the prominent features of Fontan circulation, affect physical growth partly due to pituitary gland dysfunction, highlighting the need for the screening for and treatment of this condition after Fontan surgery.

Key Words: Fontan circulation; Growth hormone deficiency; Short stature

Fontan surgery has contributed to prognostic improvement in patients with single ventricular circulation,1 but it has been increasingly recognized that a long-lasting high central venous pressure (CVP), which is inevitable in Fontan circulation,2,3 causes end-organ congestion and damage in the mid/long term. Such end-organ damage includes dysfunction of the brain,4,6 thyroid,7 liver,8 kidney,9 and lymphatic system.10 Fontan patients may also have growth disorders and short stature due to heart failure hemodynamics.11,12 In addition, high CVP and congestion may affect pituitary gland function, thereby causing short stature due to growth hormone deficiency (GHD). However, no reports have examined the relationship between short stature and the circulatory characteristics of patients with Fontan circulation. Also, it remains unknown whether Fontan circulation affects pituitary function and whether its dysfunction is involved in the onset of GHD-induced short stature after Fontan surgery. Here, we examined the prevalence of short stature and GHD after Fontan surgery, their relationship with Fontan hemodynamics, and factors that trigger short stature.

Methods

From 52 consecutive pediatric patients (aged <18 years) with Fontan circulation who had been followed up at Saitama Medical Center, Saitama Medical University, we excluded 3 patients <6 years of age; 1 patient who was born small for gestational age; and 1 patient with chromosomal abnormality. Finally, we retrospectively examined the remaining 47 patients. Each underwent cardiac catheterization as a routine checkup 1 year after Fontan surgery according to institution protocol and general practice in Japan. Demographic data, body height and weight, and hemodynamic and laboratory data obtained during cardiac catheterization were retrospectively analyzed using medical records. Body height measured just before the Fontan surgery, at the time of the catheter examination, and at the most recent outpatient visit were analyzed and are expressed as standard deviation (SD) of the reference value of Japanese
To identify factors associated with short stature in patients with Fontan circulation, data of short stature patients were compared with those of the remaining Fontan patients (normal stature: control group). We also examined the potential effects of the status of Fontan circulation on the short stature by examining the relationship between short stature and hemodynamic and laboratory cardiac catheter data. Furthermore, the relationship between $\Delta SD$ and Fontan hemodynamics was examined to clarify the effects of Fontan circulation on somatic growth.

The study was approved by the institutional review board of Saitama Medical Center, Saitama Medical University (no. 2120) and Kitasato University Hospital (no. C19-130) and followed the Declaration of Helsinki.

Statistical Analysis
Comparison of data between the short stature and control groups was done using unpaired t-test. Short stature with or without GHD was compared using unpaired t-test as well. Change in height following Fontan surgery was tested using paired t-test. The correlations between $\Delta SD$ and Fontan hemodynamics were evaluated on linear regression.

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Table 1. Fontan Patient Characteristics vs. Short Stature Status

|                          | Control (n=29) | Short stature (n=18) | P-value |
|--------------------------|---------------|---------------------|---------|
| Male                     |               |                     |         |
|                          | 21 (72.4)     | 10 (55.6)           | 0.238   |
| GHD                      | 0 (0)         | 5 (27.8)            |         |
| Age (years)              |               |                     |         |
| Before Fontan            | 2.2±0.6       | 2.4±0.5             | 0.424   |
| 1 year after Fontan      | 3.6±1.2       | 3.7±0.9             | 0.719   |
| Most recent              | 10.9±3.3      | 10.9±2.7            | 0.974   |
| Height (SD†)             |               |                     |         |
| Before Fontan            | −1.3±1.3      | −1.9±1.2            | 0.159   |
| 1 year after Fontan      | −0.8±0.9      | −1.9±1.0            | <0.001  |
| Most recent              | −0.8±0.8      | −3.0±1.0            | <0.001  |
| Height extension         |               |                     |         |
| Before Fontan to 1 year after Fontan | 0.4±1.2   | −0.1±0.9            | 0.159   |
| From 1 year after Fontan to the most recent follow-up ($\Delta SD$) | 0.0±0.8 | −1.1±1.1 | 0.001 |
| Weight (SD†)             |               |                     |         |
| Before Fontan            | −0.7±1.0      | −1.4±1.0            | 0.022   |
| 1 year after Fontan      | −0.5±0.9      | −1.3±0.7            | 0.004   |
| Most recent              | −0.7±0.5      | −1.6±0.6            | <0.001  |
| Cardiac index (L/min/m²) | 3.9±1.0       | 4.3±2.1             | 0.384   |
| CVP (mmHg)               | 12.2±1.9      | 14.6±4.5            | 0.025   |
| SBP (mmHg)               | 98±16         | 85±19               | 0.024   |
| SpO₂ (%)                 | 92±2.8        | 88±7.6              | 0.047   |
| $\gamma$-GTP (IU/L)      | 25.6±7.5      | 70.8±28.4           | 0.009   |
| Na (mEq/L)               | 140±2         | 138±2               | 0.004   |
| Renin activity (ng/mL/h) | 17.5±15.1     | 32.5±28.1           | 0.047   |
| ACE (IU/L)               | 17.9±4.9      | 13.6±5.4            | 0.045   |
| Angiotensin II (pg/mL)   | 34.8±29.3     | 34.7±24.2           | 0.992   |
| Aldosterone (pg/mL)      | 719±699       | 805±1,139           | 0.785   |
| Diuretics                | 15 (51.7)     | 14 (77.8)           | 0.074   |
| $\beta$-blocker          | 11 (37.9)     | 8 (44.4)            | 0.658   |
| ACEI or ARB              | 27 (93.1)     | 16 (88.9)           | 0.615   |

Data given as n (%) or mean±SD. †SD of the reference value of Japanese children of the same age and sex.13 ACE, angiotensin-converting enzyme; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor antagonist; CVP, central venous pressure; $\gamma$-GTP, $\gamma$-glutamyl transpeptidase; GHD, growth hormone deficiency; SBP, systolic blood pressure; SpO₂, oxygen saturation.

children of the same age and sex.13 We compared the prevalence of short stature in patients with Fontan circulation with that in the general population of Japanese children. We also compared the prevalence of short stature with that after repair of tetralogy of Fallot (TOF) as a disease control. The TOF group consisted of 24 patients who were selected from a total of 62 patients using the same exclusion criteria as the Fontan patients (i.e., age, small for gestational age, and chromosomal abnormalities).

Change in height from the time of catheter examination to the most recent visit ($\Delta SD$) was also calculated to check the increase in height after Fontan surgery and examine the association between somatic growth and Fontan circulation. We defined short stature as −2 SD or lower than the reference value. The short stature patients were then referred to pediatric endocrinologists and a GH secretion stimulation test was performed to check for GHD as a cause of the short stature. The GH secretion stimulation test was performed using any 2 of the following: insulin, arginine, clonidine, glucagon, and l-dopa, and the patients whose peak GH with stimulation was <6 ng/mL were diagnosed with GHD.
Short Stature in Fontan Patients

### Results

None of the studied patients had familial short stature, intracranial tumor, poor family environment such as child abuse or neglect, or chronic diseases other than heart disease. The demographic, hemodynamic, laboratory, and medication data of the Fontan patients according to short stature status are listed in Table 1. Short stature was observed in 18 patients (38.3%), a much higher frequency than that in the general population of Japanese children (2.3%).\(^\text{13}\) Height was significantly lower in Fontan patients than in TOF patients (P=0.004; Table 2), and the prevalence of short stature in TOF (16.7%) was lower than that in Fontan patients (38.3%, P=0.057) with borderline statistical significance. Five Fontan patients (10.6%) were diagnosed with GHD. Even in the Fontan control group, the average height was less than the reference for normal children at any stage (before Fontan, $-1.3\pm1.3$ SD; 1 year after Fontan, $-0.8\pm0.9$ SD; most recent visit, $-0.8\pm0.8$ SD). Interestingly, body height tended to catch up during the first year after the Fontan operation in the control group but not in the short stature group, as indicated by the significant difference in the height 1 year after Fontan surgery (P<0.05). In addition, although the SD of the control group showed no significant change thereafter, the SD of the short stature group showed progressive decline after surgery (1 year after surgery vs. most recent visit, P=0.001, paired t-test). Body weight was significantly lower in each stage in the short stature group. Compared with control Fontan patients, those with short stature had worse hemodynamic characteristics 1 year after Fontan operation as reflected by the significantly higher CVP, lower systolic blood pressure, and lower oxygen saturation (SpO₂; Table 1). Mean γ-glutamyl transpeptidase, a marker of hepatic congestion,\(^\text{14}\) was significantly higher (70.8±28.4 IU/L vs. 25.6±7.51 IU/L, P<0.05) and

| Table 2. Characteristics of TOF vs. Fontan Patients |
| TOF (n=24) | Fontan (n=47) | P-value |
|---|---|---|
| Male | 13 (54.2) | 31 (66.0) | 0.333 |
| Age (years) | 12.1±3.4 | 10.9±3.1 | 0.135 |
| Short stature | 4 (16.7) | 18 (38.3) | 0.057 |
| Height (SD) | $-0.6\pm1.3$ | $-1.6\pm1.4$ | 0.004 |
| Weight (SD) | $-1.0\pm1.4$ | $-1.0\pm0.7$ | 0.939 |

Data given as n (%) or mean±SD. \(^*\)SD of the reference value of Japanese children of the same age and sex.\(^\text{13}\) TOF, tetralogy of Fallot.

| Table 3. Multivariate Indicators of ΔSD After Fontan Surgery |
| P-value |
|---|
| CVP | 0.002 |
| Height (before Fontan) | 0.707 |
| CVP | 0.006 |
| Height (1 year after Fontan) | 0.063 |

ΔSD, height extension; CVP, central venous pressure.
mean serum Na concentration was significantly lower in the short stature group than in the control group. Mean angiotensin-converting enzyme (ACE) was significantly lower, while mean renin activity was significantly higher (32.5±28.1 ng/mL/h vs. 17.5±15.1 ng/mL/h, P<0.05). These data suggest that short stature is more prevalent in Fontan patients with more congestive hemodynamics. In fact, ΔSD had a significant negative correlation with CVP (r=−0.42, P=0.006, Figure). This was also confirmed on multivariate analysis when adjusted for height before or 1 year after the surgery (Table 3).

In the short stature group, 5 patients were diagnosed with GHD. This frequency (10.6% of patients after Fontan Surgery) was much higher than that of the general population (0.01%) according to the Japanese Ministry of Health and Welfare. There were no significant differences in hemodynamic or laboratory data between short stature with and without GHD (Table 4), but patients with GHD had shorter stature than those without GHD (P<0.05).

### Discussion

In the present study, the prevalence of short stature, defined as −2 SD or lower (38.3%), and GHD diagnosed on GH stimulation test (10.6%), was much higher in Fontan patients than in the general population and the TOF patients. Although Fontan surgery by itself appeared to contribute to ameliorating preoperative growth retardation, worse Fontan hemodynamics with more congestive laboratory findings were associated with continuing short stature after Fontan surgery. This tendency was enhanced by GHD. Increased CVP, a key hemodynamic parameter of Fontan circulation, negatively affected the postoperative increase in height.

Fontan circulation shares pathophysiologic features with heart failure, including hemodynamic derangement, manifested as increased CVP and decreased CO, neurohormone activation, inflammation, endothelial activation, and increased oxidative stress. These features of heart failure can result in an important catabolic drive that is capable of contributing to growth retardation and ultimately to sarcopenia and/or cachexia, which are often observed in failed Fontan patients. Heart failure is also associated with malnutrition, which can be another cause of short stature in Fontan patients. The etiology of malnutrition can be multifactorial and involve hypermetabolism, decreased intake, increased nutrient losses, inefficient utilization of nutrients, and malabsorption. The present results indicating

| Table 4. Short Stature Fontan Patient Characteristics vs. GHD Status |
|-------------------|-------------------|-------------------|-------------------|
|                   | Short stature     |                   |                   |
|                   | Non-GHD (n=13)    | GHD (n=5)         | P-value           |
| Male sex          | 6 (46)            | 4 (80)            | 0.182             |
| Age (years)       |                   |                   |                   |
| Before Fontan     | 2.3±0.6           | 2.5±0.5           | 0.502             |
| 1 year after Fontan | 3.8±1.0          | 3.5±0.6           | 0.510             |
| Most recent       | 10.7±2.9          | 11.5±2.3          | 0.599             |
| Height (SD)       |                   |                   |                   |
| Before Fontan     | −1.8±1.3          | −2.1±0.9          | 0.743             |
| 1 year after Fontan | −2.0±0.9         | −1.6±1.1          | 0.387             |
| Most recent       | −2.6±0.4          | −3.8±1.6          | 0.019             |
| Height extension  |                   |                   |                   |
| Before Fontan to 1 year after Fontan | −0.1±1.0 | 0.1±0.5          | 0.682             |
| 1 year after Fontan to most recent (ΔSD) | −0.6±0.9 | −2.3±0.7 | 0.002             |
| Weight (SD)       |                   |                   |                   |
| Before Fontan     | −1.3±1.0          | −1.8±1.0          | 0.454             |
| 1 year after Fontan | −1.3±0.8         | −1.2±0.8          | 0.888             |
| Most recent       | −1.5±0.3          | −1.6±0.5          | 0.868             |
| Cardiac index (L/min/m²) | 4.0±1.8 | 5.4±3.1          | 0.265             |
| CVP (mmHg)        | 13.7±4.3          | 16.8±4.7          | 0.195             |
| SBP (mmHg)        | 86±20             | 83±19             | 0.796             |
| SpO₂ (%)          | 88±8.4            | 90±5.5            | 0.612             |
| γ-GTP (IU/L)      | 80.7±33.9         | 56.0±14.1         | 0.418             |
| Na (mEq/L)        | 138±2             | 136±3             | 0.151             |
| Renin activity (ng/mL/h) | 24.9±24.6 | 49.7±31.0       | 0.147             |
| ACE (IU/L)        | 14.0±6.4          | 12.6±2.7          | 0.736             |
| Angiotensin II (pg/mL) | 27.3±24.1 | 49.3±20.3       | 0.220             |
| Aldosterone (pg/mL) | 527±628         | 1,499±1,881       | 0.156             |
| Diuretics         | 9 (69.2)          | 5 (100)           | 0.160             |
| β-blocker         | 6 (46.2)          | 2 (40.0)          | 0.814             |
| ACEI or ARB       | 12 (92.3)         | 4 (80.0)          | 0.615             |

Data given as n (%) or mean±SD. 1 SD of the reference value of Japanese children of the same age and sex. Abbreviations as in Table 1.
that short stature in Fontan patients is associated with worse hemodynamics with renin activation and perhaps endothelial dysfunction (low ACE) support the notion that the heart failure condition of Fontan circulation by itself contributes to short stature after Fontan operation. The notion is consistent with a previous report by François et al, who examined serum anthropometric parameters recorded from birth to the latest follow-up after Fontan surgery (mean, 12.5±6.1 years) and reported that the need for heart failure treatment after Fontan completion is independently associated with decreased late somatic development. In addition to the heart failure condition of Fontan patients, the present study has shown for the first time that GHD can contribute to short stature after Fontan surgery. Similar to other organs in Fontan circulation, it is possible that venous congestion may cause pituitary gland dysfunction and result in impaired GH synthesis and/or secretion. Muneuchi et al reported that pituitary gland volume measured on magnetic resonance imaging significantly increased after Fontan surgery compared with that in age-matched control children, and that increased pituitary volume is related to increased CVP. We also previously reported that cerebral circulation in patients with Fontan circulation was impaired and that it might affect neurological development. This suggests that volume retention and congestion, the prominent features of Fontan circulation, affect physical growth partly due to pituitary gland dysfunction, highlighting the need for the screening and treatment of this condition after Fontan surgery. Whether the GHD in Fontan patients is due primarily to pituitary gland dysfunction induced by Fontan hemodynamics or to pre-existing factors before Fontan completion requires future study.

Study Limitations

This study had several limitations. First, it is very important to recognize that growth impairment is affected by many factors other than heart failure condition and GHD, such as socioeconomic and nutritional, as well as lifestyle factors. Future studies should be conducted to clarify such effects on short stature in Fontan children. Second, the subjects consisted of Fontan children both before and during puberty. Short stature may be improved in some patients after puberty, but there were no significant differences in gender or age between the 2 groups; and, importantly, height was compared using SD. Therefore, puberty would not have considerable effects on the key findings of the present study. Last, although height was significantly lower after puberty, but there were no significant differences in gender or age between the 2 groups; and, importantly, height was compared using SD. Therefore, puberty would not have considerable effects on the key findings of the present study. Last, although height was significantly lower after puberty than in TOF patients after Fontan surgery, the prevalence of short stature in Fontan patients was still higher than in the general population, further studies are needed to determine whether the present results are specific to Fontan patients and to clarify the determinants of short stature in congenital heart disease, including after Fontan surgery.

Conclusions

In addition to well-known long-term complications after Fontan surgery, short stature and GHD should be considered as post-Fontan complications.

Acknowledgment

The authors thank the pediatric endocrinologists Hiroshi Arakawa and Shoyo Tanikawa, Saitama Medical Center, Saitama Medical University who performed the GH secretion stimulation test and treated these patients.

IRB Information

The present study was approved by the institutional review board of Saitama Medical Center, Saitama Medical University (no. 2120) and Kitasato University Hospital (no. C19-130).

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