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ORIGINAL ARTICLE

# Development of suction force during early diastole from the left atrium to the left ventricle in infants, children, and adolescents

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## Abstract

Although the suction force that moves blood into the left ventricle during early diastole is thought to play an important role in diastolic function, there have been a few studies of this phenomenon in normal children. Suction force is measured as the intraventricular pressure difference (IVPD) and intraventricular pressure gradient (IVPG), which is calculated as IVPD divided by left ventricular length. The purpose of this study was to determine the suction force in infants, children, and adolescents using IVPD and IVPG. We included 120 normal children categorized into five groups based on age: G1 (0–2 years), G2 (3–5 years), G3 (6–8 years), G4 (9–11 years), and G5 (12–16 years). The total, basal, and mid–apical IVPD and IVPG were calculated using color M-mode Doppler imaging of the mitral valve inflow using the Euler equation. The total IVPD increased with age from G1 to G5 (1.75 + 0.51 vs. 2.95 + 0.72 mmHg, respectively; $p < 0.001$), due to an increase in mid–apical IVPD with constant basal IVPD. Although total IVPG was constant, mid–apical IVPG was larger in G5 than in G1 (0.21 + 0.06 vs. 0.16 + 0.07 mmHg/cm, respectively; $p = 0.006$). Total, basal, and mid–apical IVPDs were significantly correlated with age and the parameters of heart size and mitral annular $e'$. Mid–apical IVPG correlated with age and $e'$ positively, but basal IVPG did with age negatively and did not with $e'$. The suction force increased at the mid–apical segment, correlating with increasing heart size and developing left ventricular relaxation, even after adjustment for left ventricular length.

**Keywords** Diastolic function · Intraventricular pressure difference · Intraventricular pressure gradient · Echocardiography

## Introduction

Assessment of diastolic dysfunction is thought to be important as it predicts reduced left ventricular (LV) systolic dysfunction, a clinical symptom of both acquired [1, 2] and

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congenital heart diseases [3, 4], in infants, children, and adolescents. However, methods for assessing diastolic function using conventional echocardiography, such as mitral inflow E-wave ($E$) velocity using pulsed-wave Doppler (PWD) and mitral annular early diastolic velocity ($e'$) using tissue Doppler imaging (TDI), have limitations due to the dependence on loading conditions and the limited accuracy in patients with regional myocardial dysfunction [5]. In congenital heart disease, abnormal cardiac muscular structure and artificial patches used to close defects in the LV can cause abnormal LV wall motion, which, in turn, can cause inaccurate estimation of diastolic function [3, 5, 6].

The suction force during early diastole from the left atrium (LA) to the LV apex has been thought to play an important role in diastolic function [6–15], with the mid–apical intraventricular pressure difference (IVPD) being important for the creation of active suction [6–8, 14]. Additionally, the intraventricular pressure gradient (IVPG) is also considered important, and is calculated as IVPD divided by LV length to overcome differences in LV size [6, 7, 11, 12]. IVPG is believed to be useful to assess suction force in pediatric populations [6, 11] and fetuses [7], as the length of the LV increases with growth. Moreover, IVPD has an excellent correlation with the Tau Index, which is the gold standard for evaluating diastolic function, and can only be measured through invasive techniques [10]. Therefore, IVPD is considered as an useful and important method for assessing diastolic function in various diseases [6–10, 13, 14].

Despite its importance, there have been few studies of IVPD in normal children because the measurement of IVPD was initially invasive, requiring cardiac catheterization. However, a new noninvasive method using echocardiography has recently been proposed for measuring regional pressure differences within the heart [9, 15], allowing IVPD to be measured noninvasively in normal patients.

It is known that advancing age is associated with characteristic changes in myocardial properties that are related to diastolic function, especially in infants and children [16–18], and IVPD and IVPG are also expected to be affected by those changes. When these measures are used to evaluate diastolic function in children, the child's typical development with respect to growth should be elucidated. Therefore, the aim of this study was to elucidate the suction force in normal infants, children, and adolescents using IVPD and IVPG as indicators of diastolic function.

## Materials and methods

### Study population

One hundred and twenty-eight healthy children who were undergoing echocardiography for the evaluation of innocent murmurs, and who had no history of cardiovascular disease, were prospectively recruited. Parents or legal guardians of all participants provided informed consent, as established by the Research Ethics Board at Juntendo University and Shizuoka Children's Hospital. The inclusion criteria were as follows: age between 1 month and 16 years; with normal blood pressure; and with normal electrocardiographic and transthoracic echocardiographic findings. For a clearer understanding of potential differences due to age, we categorized the study population into five representative groups: G1 (0–2 years), G2 (3–5 years), G3 (6–8 years), G4 (9–11 years), and G5 (12–16 years).

### Echocardiography

Echocardiography was performed using GE Vivid E9 (GE Healthcare, Milwaukee, WI, USA) with a 6S or M5S probe by two experienced cardiologists (KT and MY) at Juntendo University or Shizuoka Children's Hospital. Basic data analysis was performed using EchoPAC version 108.1.4 (GE Healthcare, Milwaukee, WI, USA). All participants underwent a complete transthoracic echocardiogram. Measurements of basic two-dimensional echocardiogram, PWD, and TDI were conducted using standard procedures. LV mass was assessed as previously described [19]. The timing of the onset of the Q-wave on the electrocardiogram, aortic valve closure, and mitral valve opening was also measured using PWD. To overcome differences in heart rate, the timing of all parameters was normalized to the duration of systole (i.e., at the onset of the QRS-wave [$t = 0\%$] and at end-systole [$t = 100\%$]) [20].

### Intraventricular pressure difference and intraventricular pressure gradient measurements

IVPD was estimated using color M-mode images to integrate the one-dimensional Euler equation, as previously described [6, 7]. The median sampling rate of Color M-mode was 292 (ranging from 194 to 456), which was considered to be high enough to calculate IVPD accurately. This method has been validated through comparison to direct measurements using micromanometers [9, 15]. Peak IVPD values were measured over at least three beats, and the mean values were used for the final analysis. Furthermore, to overcome the difference in sizes of the LV, we calculated IVPG as follows [6, 7, 11, 12]:

$$\text{IVPG} = \text{IVPD}/\text{LV length}$$

Total IVPD was further separated into basal and mid–apical segments, as previously described [6] (Fig. 1). The basal segment was defined as one-third of the total LV length from the mitral valve, whereas the mid–apical segment was defined as the remaining two-thirds. Previous

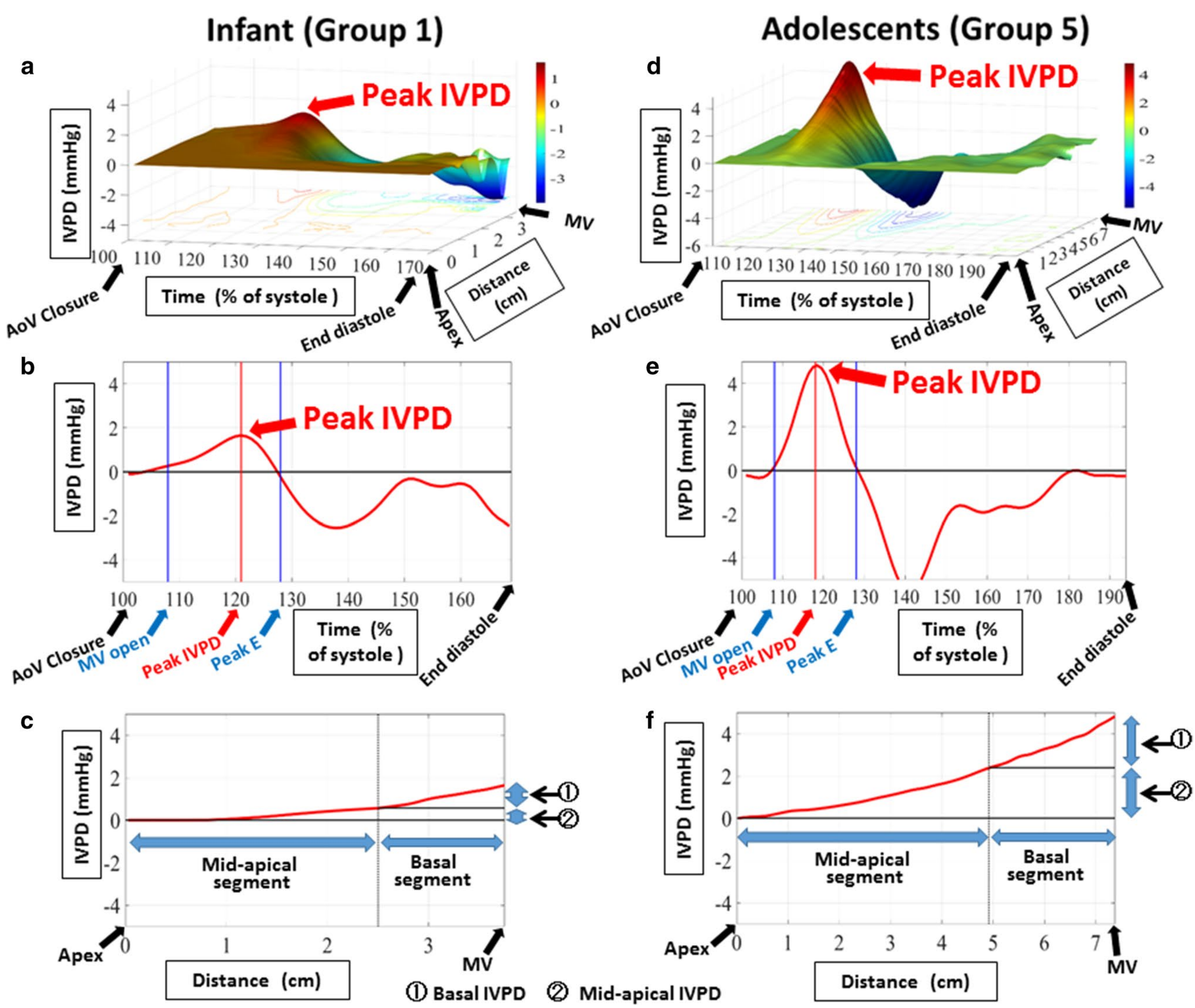


**Fig. 1** Examples of intraventricular pressure difference in (**a**–**c**) **a** 1-month-old infant and (**d**–**f**) **a** 14-year-old adolescent **a** and **d** Three-dimensional temporal and spatial profiles of intraventricular pressure difference (IVPD) over percent of time of systolic duration from 100% (at aortic valve closure) to end diastole. The *z*-axis represents the distance (cm) from the apex to the mitral valve. Peak IVPD in early diastole is identified in the three-dimensional array. **b** and **e** Temporal profile of IVPD over percent of time of systolic duration from aortic closure. The thick solid and thin red dash lines in the two-dimensional graph shows the temporal profile at peak total IVPD and mid–apical IVPD, respectively. **c** and **f** Spatial profile of IVPD based on the location from the apex to the mitral valve. The red line in the two-dimensional graph shows the spatial profile at peak IVPD, which usually occurs at the mitral valve level. The basal and mid–apical segments of IVPD were calculated based on the left ventricle segmentation rule of one-third for basal and two-thirds for mid–apical. The infant has lower total IVPD with relatively larger basal IVPD and smaller mid–apical IVPD compared to the adolescent spatial IVPD profile

studies in adults separated the LV into two segments (2 cm from the mitral valve and the remaining segments) [9, 15]; however, the length of the LV is more than twice as large in adults as in children. Therefore, we made adjustments to account for small children [6, 11]. The timing of peak total IVPD and mid–apical IVPD from the onset of the Q-wave was also measured and normalized to the duration of systole as described above [20].

## Statistical analysis

Data with normal distributions are expressed as means ± standard deviations, whereas data with non-normal distributions are expressed as median (25$^{th}$ and 75$^{th}$ percentiles). After evaluating the data for normality, correlations between IVPD and each variable were evaluated using the Pearson's correlation coefficient (*r*) for data with normal distributions, or the Spearman's correlation coefficient ($\rho$) for data with non-normal distributions.

All group differences were assessed using a one-factor analysis of variance with a post hoc comparison using the Tukey–Kramer method for data with normal distribution or the Steel–Dwass test for data with non-normal distribution in each age group.

To assess intra-observer agreement for total IVPD, basal IVPD, mid–apical IVPD, total IVPG, basal IVPG, and mid–apical IVPG, 10 participants in each age group were similarly examined. Two independent observers analyzed the same images, and one blinded observer repeated the analysis on a separate day. Intraobserver and interobserver agreements were calculated using the Bland–Altman approach, including the calculation of mean bias (average difference between measurements), and the lower and upper limits of agreement (95% limits of agreement of mean bias) in 10 randomly selected patients in each age group at more than 2 months apart. In addition, the coefficient of variation was determined (i.e., the SD of the difference of paired samples divided by the average of the paired samples).

Statistical significance was set at $p < 0.05$. Analyses were performed using the commercially available statistical software JMP (version 9.0; SAS Institute Inc., Cary, NC, USA).

## Results

### Feasibility

Of the 128 recruited patients, four children (two with arrhythmia and two with inadequate image quality from the echocardiogram) did not meet the inclusion criteria and were excluded. Additionally, four infants who could not remain settled during the echocardiography were also excluded. Therefore, 120 subjects were analyzed. The age ranges and demographic data of the five groups are shown in Table 1. Significant growth in body size and a corresponding decrease in heart rate with relatively constant blood pressure were observed with advancing age. LV volumes and masses increased with age, whereas LV ejection fractions were not different among the five groups. *E*, A-wave, *E*/*A* ratio (*E*/*A*), and *e′* were relatively constant in groups G2–G5; only those in G1 were significantly different compared to those in all other groups (Table 2).

### Total and segmental intraventricular pressure differences and gradients

The scatter plots between IVPDs and IVPGs and age are shown in Fig. 2. Age showed a significantly positive correlation with total, basal, and mid–apical IVPDs. Mid–apical IVPG positively correlated with age, and basal IVPG showed a significantly negative correlation with age. As they offset each other, the total IVPG was constant among the different age groups in this study. IVPDs and IVPGs in each age group are shown in Table 3. Peak IVPD occurred during early diastole in all age groups around the timing of 120% of systole. Total IVPDs in G3–G5 were significantly larger than that in G1, and total IVPD in G5 was also significantly larger than that in G2. Basal IVPDs in G3– G5 were significantly larger than that in G1. Mid–apical IVPD was significantly smaller in G1 than in any other group. Importantly, mid–apical IVPD tended to increase with age, and was significantly larger in G5 than in all other groups. Despite the obvious difference in total IVPD with aging, total IVPG was relatively constant across all age groups, with no significant group differences. However, basal IVPG in G5 was significantly smaller than that in G2 and G3. Furthermore, mid–apical IVPG in G5 was significantly larger than that in G1.

**Table 1** Basic subject profile

| | Group 1 | Group 2 | Group 3 | Group 4 | Group 5 |
|---|---|---|---|---|---|
| Number (male) | 19 [11] | 28 [15] | 26 [14] | 20 [11] | 27 [13] |
| Age range (years) | 0–2 | 3–5 | 6–8 | 9–11 | 12–16 |
| Age (years) | 0.4 (0.1–0.7) | 4.5 (3.8–6.4)** | 8.0 (7.2–8.5)**,†† | 9.9 (9.5–10.7)**,††,‡‡ | 13.2 (12.5–14.2)**,††,‡‡,§§ |
| Body weight (kg) | 7.4 (4.7–8.7) | 17.8 (14.7–20.2)** | 26.4 (23.7–30.0)**,†† | 34.1 (30.0–40.4)**,††,‡‡ | 44.7 (38.2–50.0)**,††,‡‡,§§ |
| Body height (cm) | 63 ± 9 | 107 ± 8** | 124 ± 8**,†† | 136 ± 9**,††,‡‡ | 153 ± 6.9**,††, ‡‡, §§ |
| Body surface area ($m^2$) | 0.34 ± 0.08 | 0.73 ± 0.09** | 0.98 ± 0.15**, †† | 1.15 ± 0.16**, ††, ‡‡ | 1.39 ± 0.13**, ††, ‡‡, §§ |
| Heart rate (bpm) | 138 ± 15 | 87 ± 12** | 74 ± 11**, †† | 76 ± 13**, ††, ‡‡ | 68 ± 10**, ††, ‡‡, §§ |
| Systolic blood pressure (mmHg) | 85.7 ± 8.0 | 99.0 ± 9.8** | 99.5 ± 9.5** | 98.9 ± 7.2** | 108.5 ± 8.9**, †, ‡, § |
| Diastolic blood pressure (mmHg) | 50.0 ± 8.5 | 56.3 ± 7.6 | 54.2 ± 10.9 | 56.8 ± 8.8 | 60.9 ± 11.0* |

*$p < 0.05$ G1 versus other groups; **$p < 0.001$ G1 versus other groups, †$p < 0.05$ G2 versus G3, G4, or G5; ††$p < 0.001$ G2 versus G3, G4, or G5; ‡$p < 0.05$ G3 versus G4 or G5; ‡‡$p < 0.001$ G3 versus G4 or G5, §$p < 0.05$ G4 versus G5; §§$p < 0.001$ G4 versus G5

**Table 2** Conventional echocardiographic measurements

| | Group 1 | Group 2 | Group 3 | Group 4 | Group 5 |
|---|---|---|---|---|---|
| *2-dimensional echocardiography* | | | | | |
| LV end-diastolic volume (ml) | 13.9 (8.9–18.4) | 31.9 (27.1–40.1)** | 45.3 (35.5–53.2)**, † | 57.1 (48.6–60.3)**, †† | 69.3 (54.1–84.3)**, ††, ‡‡ |
| LV end-systolic volume (ml) | 4.1 (2.4–5.2) | 10.0 (9.1–13.3)** | 14.1 (11.5–17.8)**, † | 18.1 (13.9–20.4)**, †† | 23.3 (16.2–29.4)**, ††, ‡‡ |
| LV ejection fraction (%) | 69.1 ± 4.3 | 67.5 ± 4.0 | 67.0 ± 3.7 | 68.1 ± 3.9 | 66.3 ± 4.1 |
| LV end-diastolic volume (ml/body surface area) | 40.6 ± 12.4 | 46.1 ± 10.6 | 48.6 ± 12.1 | 49.2 ± 12.2 | 50.8 ± 13.4 * |
| LV end-systolic volume (ml/body surface area) | 12.5 ± 4.2 | 14.9 ± 3.9 | 15.9 ± 4.7 | 16.0 ± 5.4 | 17.2 ± 5.6 * |
| LV length (cm) | 4.26 ± 0.52 | 5.40 ± 0.48** | 6.01 ± 0.60**, † | 6.37 ± 0.66**, †† | 7.31 ± 0.73**, ††, ‡‡, §§ |
| LV diameter (cm) | 2.59 ± 0.38 | 3.60 ± 0.34** | 3.97 ± 0.33**, †† | 4.23 ± 0.39**, †† | 4.52 ± 0.37**, ††, ‡‡ |
| LV mass (g) | 16.3 (11.2–24.0) | 45.9 (41.5–57.0)** | 63.1 (55.0–70.1)**, †† | 76.1 (68.5–90.8)**, ††, ‡ | 98.0 (90.4–123.7)**, ††, ‡‡, §§ |
| LV mass index ($g/m^2$) | 53.4 ± 15.9 | 67.6 ± 12.9* | 66.2 ± 13.8* | 67.9 ± 8.6* | 75.6 ± 13.8** |
| Diameter/Length ratio | 0.61 ± 0.11 | 0.67 ± 0.06 | 0.66 ± 0.07 | 0.67 ± 0.06 | 0.62 ± 0.08 |
| *Pulse wave Doppler and tissue Doppler imaging measurements* | | | | | |
| Duration between Q-wave and aortic valve closure (ms) | 166 ± 27 | 354 ± 81** | 456 ± 117**, † | 427 ± 118** | 514 ± 119**, ††, ‡‡, § |
| Isovolumic relaxation time (ms) | 36.4 ± 13.7 | 38.7 ± 17.6 | 47.8 ± 18.9 | 52.8 ± 17.2**, † | 46.7 ± 15.6 |
| *E* (m/s) | 0.92 ± 0.15 | 1.07 ± 0.12 * | 1.03 ± 0.17 | 1.05 ± 0.14 | 1.04 ± 0.17 |
| A (m/s) | 0.85 (0.73–0.97) | 0.45 (0.411–0.59)** | 0.42 (0.37–0.45)** | 0.47 (0.35–0.52)** | 0.46 (0.38–0.59)** |
| *E*/*A* ratio | 1.14 (0.95–1.26) | 2.26 (1.83–2.47)** | 2.59 (2.08–2.79)** | 2.11 (1.95–3.04)** | 2.29 (1.76–2.84)** |
| *e*′ (cm/s) | 10.3 ± 2.5 | 15.7 ± 2.8** | 16.7 ± 2.5** | 17.4 ± 2.6** | 16.8 ± 5.5** |
| *E*/*e*′ ratio | 9.43 (6.8–11.0) | 6.82 (5.9–7.6) * | 6.28 (5.4–7.1)** | 6.18 (5.1–6.8)** | 6.11 (5.5–7.2)** |

*BSA* body surface area

*$p < 0.05$ G1 versus other groups;**$p < 0.001$ G1 versus other groups, †$p < 0.05$ G2 versus G3, G4, or G5; ††$p < 0.001$ G2 versus G3, G4, or G5; ‡$p < 0.05$ G3 versus G4 or G5; ‡‡$p < 0.001$ G3 versus G4 or G5, §$p < 0.05$ G4 versus G5; §§$p < 0.001$ G4 versus G5

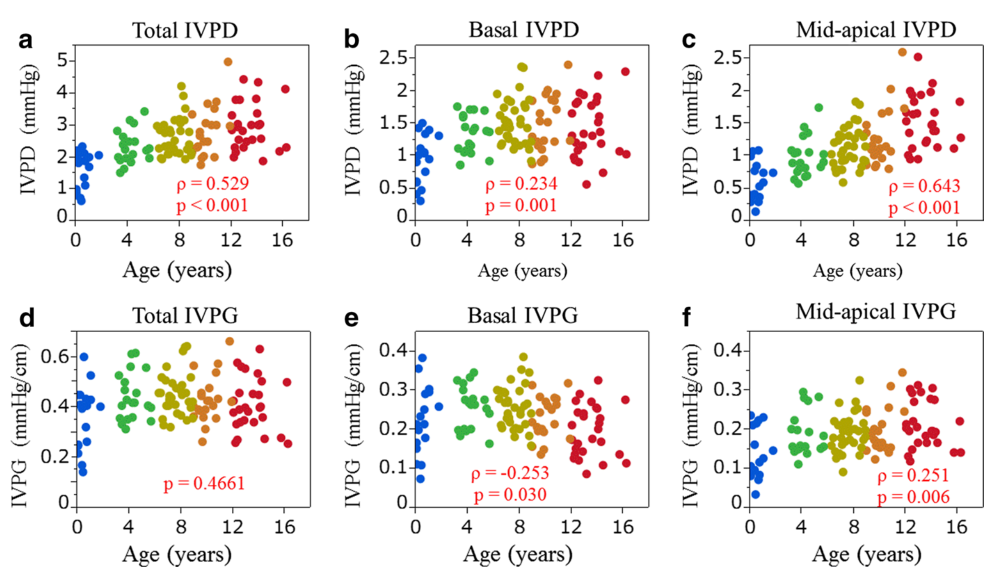


**Fig. 2** Relation between total, basal, and mid–apical IVPDs and IVPG s and age. Blue, green, yellow, orange, and red dots represent the following age groups: G1, G2, G3, G4, and G5, respectively

**Table 3** Total and segmental IVPDs and IVPGs

| | Group 1 | Group 2 | Group 3 | Group 4 | Group 5 |
|---|---|---|---|---|---|
| Total IVPD (mmHg) | 1.75 ± 0.51 | 2.35 ± 0.50 | 2.70 ± 0.58** | 2.78 ± 0.77** | 2.96 ± 0.72**, † |
| Basal IVPD (mmHg) | 1.07 ± 0.34 | 1.37 ± 0.30 | 1.51 ± 0.38 * | 1.49 ± 0.42 * | 1.42 ± 0.46 * |
| Mid–apical IVPD (mmHg) | 0.68 ± 0.28 | 0.98 ± 0.28 * | 1.19 ± 0.30** | 1.28 ± 0.45** | 1.53 ± 0.40**, †, ‡, § |
| Total IVPG (mmHg/cm) | 0.41 ± 0.12 | 0.44 ± 0.09 | 0.45 ± 0.08 | 0.43 ± 0.09 | 0.41 ± 0.10 |
| Basal IVPG (mmHg/cm) | 0.25 ± 0.08 | 0.26 ± 0.05 | 0.25 ± 0.06 | 0.23 ± 0.05 | 0.20 ± 0.06 †, ‡ |
| Mid–apical IVPG (mmHg/cm) | 0.16 ± 0.07 | 0.18 ± 0.05 | 0.20 ± 0.04 | 0.20 ± 0.06 | 0.21 ± 0.06 * |

*$p < 0.05$ G1 versus other groups; **$p < 0.001$ G1 versus other groups, †$p < 0.05$ G2 versus G3, G4, or G5; ‡$p < 0.05$ G3 versus G4 or G5; §$p < 0.05$ G4 versus G5

## Correlation between intraventricular pressure difference and HR, body parameters, and echocardiographic measurements

The correlations between IVPDs and parameters are shown in Table 4 and Online Resource 1. All IVPDs showed significant correlations with LV length, LV mass, LV end-diastolic volume, LV end-systolic volume, and body surface area. Importantly, mid–apical IVPD tended to show a stronger correlation with the above values than basal IVPD. Total, basal, and mid–apical IVPDs correlated with $e'$, $E$, and $E/A$ positively, and with $E/e'$ ratio ($E/e'$) and heart rate negatively, with the exception of the correlation between $E/e'$ and basal IVPD.

## Correlations between intraventricular pressure gradient and HR, body parameters, and echocardiographic measurements

The correlations between IVPGs and parameters are shown in Table 5 and Online Resource 2. In contrast to IVPDs, basal IVPG correlated with LV and body size parameters negatively and mid–apical correlated only with LV mass and BSA positively. Importantly, only total and mid–apical IVPGs correlated with $e'$, but basal IVPG did not.

## The timing of events

Both the absolute value of the timing of events and the relative (%) timing of events, adjusted for systolic duration, are shown in Table 6. The events occurred in the following order: mitral valve opening, peak total IVPD, peak mid–apical IVPD, peak $e'$, and peak $E$. The order of those events was

**Table 4** Correlation between IVPDs, body size, heart rate and LV parameters

| | Total IVPD | | Basal IVPD | | Mid–apical IVPD | |
|---|---|---|---|---|---|---|
| | $\rho$ or $r$ | $p$ | $\rho$ or $r$ | $p$ | $\rho$ or $r$ | $p$ |
| *Parameters for age and HR* | | | | | | |
| Age | $\rho = 0.529$ | < 0.001 | $\rho = 0.234$ | 0.007 | $\rho = 0.643$ | < 0.001 |
| HR | $\rho = -0.467$ | < 0.001 | $\rho = -0.240$ | 0.008 | $\rho = -0.531$ | < 0.001 |
| *Parameters for the LV and body size* | | | | | | |
| LV length | $\rho = 0.608$ | < 0.001 | $r = 0.376$ | < 0.001 | $\rho = 0.674$ | < 0.001 |
| LV mass | $\rho = 0.556$ | < 0.001 | $\rho = 0.308$ | < 0.001 | $\rho = 0.622$ | < 0.001 |
| LVEDV | $\rho = 0.537$ | < 0.001 | $\rho = 0.290$ | 0.001 | $\rho = 0.612$ | < 0.001 |
| LVESV | $\rho = 0.547$ | < 0.001 | $\rho = 0.295$ | < 0.001 | $\rho = 0.630$ | < 0.001 |
| BSA | $\rho = 0.578$ | < 0.001 | $\rho = 0.302$ | < 0.001 | $\rho = 0.668$ | < 0.001 |
| *Parameters for TDI, PWD measurements* | | | | | | |
| $e'$ | $\rho = 0.600$ | < 0.001 | $\rho = 0.425$ | < 0.001 | $\rho = 0.568$ | < 0.001 |
| E | $\rho = 0.359$ | < 0.001 | $r = 0.347$ | <0.001 | $\rho = 0.232$ | 0.011 |
| $E/A$ | $\rho = 0.409$ | < 0.001 | $\rho = 0.295$ | 0.001 | $\rho = 0.368$ | < 0.001 |
| $E/e'$ | $\rho = -0.337$ | < 0.001 | – | 0.073 | $\rho = -0.389$ | < 0.001 |

*IVPD* intraventricular pressure difference, *LV* left ventricle, *LVEDV* left ventricular end-diastolic volume, *LVESV* left ventricular end-systolic volume, *BSA* body surface area, *TDI* tissue Doppler imaging, *PWD* pulse-waved Doppler

**Table 5** Correlation between IVPGs, body size, heart rate and LV parameters

| | Total IVPG | | Basal IVPG | | Mid–apical IVPG | |
|---|---|---|---|---|---|---|
| | $\rho$ or $r$ | $p$ | $\rho$ or $r$ | $p$ | $\rho$ or $r$ | $p$ |
| *Parameters for age and HR* | | | | | | |
| Age | – | 0.4661 | $\rho = -0.253$ | 0.030 | $\rho = 0.251$ | 0.006 |
| HR | – | 0.853 | – | 0.123 | $\rho = -0.197$ | 0.031 |
| *Parameters for the LV and Body size* | | | | | | |
| LV length | – | 0.253 | $r = -0.268$ | 0.002 | – | 0.098 |
| LV mass | – | 0.608 | $\rho = -0.209$ | 0.021 | $\rho = 0.181$ | 0.048 |
| LVEDV | – | 0.278 | $\rho = -0.244$ | 0.040 | – | 0.557 |
| LVESV | – | 0.191 | $\rho = -0.262$ | 0.027 | – | 0.553 |
| BSA | – | 0.722 | $\rho = -0.220$ | 0.016 | $\rho = 0.227$ | 0.013 |
| *Parameters for TDI, PWD measurements* | | | | | | |
| *e′* | $\rho = 0.024$ | 0.008 | – | 0.263 | $\rho = 0.316$ | < 0.001 |
| E | $\rho = 0.336$ | < 0.001 | $r = -0.251$ | 0.006 | $\rho = 0.268$ | 0.002 |
| *E*/*A* | – | 0.153 | – | 0.755 | – | 0.076 |
| E/*e′* | – | 0.924 | – | 0.221 | – | 0.107 |

*IVPG* intraventricular pressure gradient, *LV* left ventricle, *LVEDV* left ventricular end-diastolic volume, *LVESV* left ventricular end-systolic volume, *BSA* body surface area, *TDI* tissue Doppler imaging, *PWD* pulse-waved Doppler

**Table 6** Timing of the early diastolic events

| | Group 1 | Group 2 | Group 3 | Group 4 | Group 5 |
|---|---|---|---|---|---|
| Time to AVC (ms) | 271.5 ± 29.6 | 332.2 ± .27.0** †† | 374.5 ± 17.7** †† | 379.8 ± 19.9** †† | 392.1 ± 25.3** †† ‡ |
| Time to MVO (ms) | 307.9 ± 29.2 | 369.6 ± 20.1** †† | 421.0 ± 18.4** †† | 432.6 ± 25.5** †† | 440.5 ± 29.7** †† ‡ |
| Time to peak total IVPD (ms) | 330.1 ± 38.4 | 414.5 ± 47.7** †† | 445.9 ± 24.6** †† | 458.8 ± 39.2** †† | 476.9 ± 38.2** †† ‡ |
| Time to peak mid–apical IVPD (ms) | 334.3 ± 37.4 | 427.5 ± 44.3** †† | 456.1 ± 26.7** †† | 466.9 ± 42.0** †† | 481.6 ± 44.5** †† ‡ |
| Time to Peak *e′*(ms) | 346.2 ± 32.3 | 430.9 ± 21.6** †† | 470.6 ± 19.8** †† | 480.3 ± 27.2** †† | 495.8 ± 35.8** †† ‡ |
| Time to Peak E (ms) | 351.3 ± 32.6 | 435.4 ± 15.7** †† | 481.1 ± 24.4** †† | 488.3 ± 32.6** †† | 515.3 ± 35.8** †† ‡‡ § |
| % time to MVO | 113.6 ± 5.4 | 111.5 ± .6.5 | 112.8 ± 5.6 | 113.9 ± 4.6 | 112.4 ± 4.7 |
| % Time to peak total IVPD | 121.7 ± 8.1 | 122.6 ± 12.2 | 120.1 ± 7.4 | 120.8 ± 8.8 | 121.7 ± 6.7 |
| % Time to peak mid–apical IVPD | 122.9 ± 8.3 | 124.3 ± 12.1 | 122.3 ± 8.1 | 123.1 ± 9.4 | 122.3 ± 8.3 |
| % Time to Peak *e′* | 128.1 ± 10.3 | 128.4 ± 9.7 | 126.5 ± 6.5 | 126.5 ± 4.5 | 126.6 ± 6.7 |
| % Time to Peak E | 129.8 ± 8.9 | 130.0 ± 9.7 | 129.5 ± 7.1 | 128.6 ± 5.7 | 131.5 ± 7.5 |

*AVC* aortic valve closure, *MVO* mitral valve open, *IVPD* intraventricular pressure difference

*$p < 0.05$ G1 versus other groups;**: $p < 0.001$ G1 versus other groups, †: $p < 0.05$ G2 versus G3, G4, or G5; ††: $p < 0.001$ G2 versus G3, G4, or G5; ‡: $p < 0.05$ G3 versus G4 or G5; ‡‡: $p < 0.001$ G3 versus G4 or G5, §: $p < 0.05$ G4 versus G5

constant. Although the absolute values of the timing of peak IVPD tended to be larger in the groups with older age, there were no significant differences in the timing of those events among age groups, when adjusted for systolic duration.

### Reproducibility

The Bland–Altman analyses of intra-observer and inter-observer agreements for total, basal, and mid–apical IVPDs in each age group are shown in Table 7. Although younger age groups and segmental IVPDs tended to show larger CV, most of them were less than 10. Therefore, intra-observer and inter-observer agreements were thought to be reasonable.

## Discussion

### The relationship between left ventricle size and mid–apical intraventricular pressure differences and gradients

Age has a significant effect on diastolic function during childhood [21, 22]. Importantly, the changes in basal and

**Table 7** Intraobserver and interobserver variabilities of IVPDs

| Valuable | Bias | LLA | ULA | CV |
|---|---|---|---|---|
| *Intraobserver variability for total IVPD* | | | | |
| Group 1 | 0.031 | − 0.221 | 0.284 | 6.78 |
| Group 2 | − 0.054 | − 0.272 | 0.165 | 4.86 |
| Group 3 | 0.002 | − 0.294 | 0.300 | 5.87 |
| Group 4 | − 0.014 | − 0.216 | 0.189 | 3.40 |
| Group 5 | 0.020 | − 0.283 | 0.323 | 5.10 |
| *Intraobserver variability for basal IVPD* | | | | |
| Group 1 | 0.031 | − 0.190 | 0.252 | 10.24 |
| Group 2 | − 0.038 | − 0.181 | 0.106 | 5.61 |
| Group 3 | 0.004 | − 0.301 | 0.309 | 10.09 |
| Group 4 | 0.001 | − 0.316 | 0.336 | 9.90 |
| Group 5 | 0.011 | − 0.247 | 0.271 | 8.41 |
| *Intraobserver variability for mid–apical IVPD* | | | | |
| Group 1 | 0.001 | − 0.171 | 0.171 | 10.92 |
| Group 2 | − 0.016 | − 0.166 | 0.135 | 7.82 |
| Group 3 | − 0.001 | − 0.189 | 0.186 | 9.18 |
| Group 4 | − 0.023 | − 0.247 | 0.200 | 8.39 |
| Group 5 | 0.001 | − 0.175 | 0.191 | 6.39 |
| *Interobserver variability for total IVPD* | | | | |
| Group 1 | 0.024 | − 0.170 | 0.218 | 5.21 |
| Group 2 | − 0.051 | − 0.301 | 0.198 | 5.55 |
| Group 3 | − 0.024 | − 0.305 | 0.258 | 5.59 |
| Group 4 | − 0.027 | − 0.259 | 0.204 | 3.89 |
| Group 5 | − 0.006 | − 0.241 | 0.230 | 3.99 |
| *Interobserver variability for basal IVPD* | | | | |
| Group 1 | − 0.001 | − 0.219 | 0.200 | 9.84 |
| Group 2 | − 0.035 | − 0.278 | 0.208 | 9.48 |
| Group 3 | − 0.000 | − 0.302 | 0.329 | 10.87 |
| Group 4 | 0.011 | − 0.250 | 0.274 | 7.94 |
| Group 5 | − 0.006 | − 0.261 | 0.250 | 8.35 |
| *Interobserver variability for mid–apical IVPD* | | | | |
| Group 1 | 0.033 | − 0.192 | 0.259 | 14.1 |
| Group 2 | − 0.016 | − 0.152 | 0.120 | 7.04 |
| Group 3 | − 0.023 | − 0.217 | 0.170 | 9.58 |
| Group 4 | − 0.039 | − 0.278 | 0.200 | 9.03 |
| Group 5 | 0.001 | − 0.254 | 0.254 | 8.91 |

*CV* coefficient of variation, *LLA* 95% lower limit of agreement, *ULA* 95% upper limit of agreement

mid–apical IVPDs with age were different. Mid–apical IVPD showed a stronger correlation with age compared to basal IVPD. Although mid–apical IVPD continued to increase and was larger in the oldest age group than in all other groups, basal IVPD was relatively constant after 3 years of age. The difference in age-related changes between basal and mid–apical IVPDs is likely due to the differences in the size of the heart. Popovic et al. [11] reported that a greater IVPD was associated with larger LV length and volume, resulting in more spaces to create greater pressure differences from the valves to the apex. Importantly, mid–apical IVPD showed a stronger correlation with all LV size parameters compared to basal IVPD in the present study. This finding is understandable, as the mid–apical segment is believed to be the segment that is responsible for generating active suction [8, 14]. In contrast, basal IVPD was thought to be primarily affected by LA pressure rather than active suction [8, 14]. Those mechanisms would explain the differences in the observed correlations between LV size and basal and mid–apical IVPDs. As IVPGs were adjusted by the LV length, it seems reasonable that most of the relationships between total and mid–apical IVPGs and LV size parameters were canceled.

## The relationship between *e*′ and left ventricular suction and mid–apical intraventricular pressure differences and gradients

Development of active relaxation of the LV from infancy to adolescence is another reason for the change in IVPD with aging. Measured *e*′ values reflect the rate of myocardial long-axis expansion during early diastole in the normal heart [23] and may contribute to the generation of early diastolic IVPD [8, 14]. Given that *e*′ is influenced by not only LV relaxation, but also preload, systolic function, and LV minimal pressure [23], a significant association between *e*′ and LV relaxation has been observed in both animals [24] and humans [25]. As preload, systolic function, and LV minimal pressure were thought to be within normal limits in our participants, *e*′ likely reflected LV relaxation. Myocardial relaxation is initiated by transient intracellular calcium, and the release of potential energy starts when the actin–myosin bridges begin to deactivate. However, younger children have immature active transport of calcium into the sarcoplasmic reticulum [16] and experience alterations in connective tissue [17] and titin [18] from fetal life to adulthood. Thus, ventricular recoil should increase throughout the postnatal development, which is consistent with the increase in LV *e*′. Since active suction primarily occurs at the mid–apical segment [8, 14], it is reasonable that *e*′ showed a stronger correlation with mid–apical IVPD than with basal IVPD. Therefore, those alterations may be caused by the development of active relaxation created at mid–apical segment with growth. Even after adjusting for LV length, mid–apical IVPG correlated with age and *e*′ positively, suggesting that mid–apical IVPG increased with the increasing active relaxation in this age group.

## Mid–apical intraventricular pressure differences and gradients in infants

Eidem et al. [21] demonstrated that systolic and early diastolic TDI velocities at the mitral annulus were lower in infants than in older groups, similar to the results in this study. First, in this study, most conventional parameters for diastolic function and all IVPDs in children younger than 3 years old were significantly lower compared to those in children aged 3 years or older. Furthermore, mid–apical IVPG in children younger than 3 years old, even after adjusting for LV length, was also smaller compared to that in adolescents.

### Basal intraventricular pressure differences and gradients

Importantly, basal IVPG correlated with age and LV length negatively, without no significant correlation with *e′*. As the basal IVPD was relatively constant after 3 years of age, basal IVPG decreased with increasing LV length as results of aging. Basal IVPD was thought to be primarily affected by LA pressure rather than active suction [8, 14]. On the other hand, the *E*/*e′* ratio has been reported to correlate well with invasive measurements of LV filling pressure in adults with normal diastolic function [5]. However, basal IVPD/IVPG did not correlate with *E*/*e′* in our study, which could be due to the following reasons: [1] *E*/*e′* is not useful in detecting increases in LA pressure in normal adults; [26] and [2] the precise nature and etiology of diastolic function in infants are different compared to adults as reflected by the prohibition against using the adult criteria of diastolic dysfunction for children aged younger than 3 years [27]. Although the *E*/*e′* ratio is high during the first year of life, decreasing with increasing age, heart rate, and LV diameter and mass [21], the precise mechanism of high *E*/*e′* in infants has not been clear and there has been no evidence for the correlation between LA pressure and *E*/*e′* in infants. Therefore, although there is the possibility that basal IVPD/IVPG reflects LA pressure, it is not clear at this stage.

### The timing of events

The absolute time between cardiac events increased with older age groups as heart rate decreased. However, when adjusted for systolic duration, the timing of mitral valve opening, peak total, and mid–apical IVPD occurring around 120% of systole duration, peak *e′*, and peak *E* did not change among the age groups, despite the differences in heart rate. Total and mid–apical IVPDs always preceded the peak *E*, which is understandable because rapid filling during diastole is mainly caused by IVPD, which sucks the blood from the LA into the LV in normal hearts. These results corresponded to the results of a previous study by Notomi et al. [20], which showed that peak total IVPD preceded both peak longitudinal lengthening velocity and peak *E*. Yotti et al. [9] reported that the timing of peak IVPD occurred later in patients with dilated cardiomyopathy compared to normal controls. Furthermore, peak IVPD at a fixed apical position (3.7 cm apart) showed a more obvious delay. Therefore, timing of peak mid–apical IVPD will be useful for evaluating the properties of diastolic function in heart disease.

### Clinical implications

The clinical implication for measuring IVPD and IVPG is to accurately estimate active suction using a non-invasive method, which is the fundamental factor of active diastolic function. Furthermore, IVPD and IVPG can be early markers of cardiac dysfunction, as diastolic dysfunction is thought to predate LV systolic dysfunction or clinical symptoms in various diseases [1–4]. Conventional measurements that are derived from PWD of mitral inflow are not useful for this purpose, because they have shown a very poor correlation with invasive parameters of LV diastolic function [24]. As an alternative, routine usage of *e′* rather than *E* is recommended in the current practice guidelines [5], and *e′* shows a moderate correlation with IVPD in normal subjects in this study. However, *e′* still lacks the ability to estimate the diastolic function in clinical settings.

Recently, we demonstrated that mid–apical IVPG significantly decreased in older patients with tetralogy of Fallot, despite no decrease of *e′* compared to age-matched healthy controls [6]. This result was not surprising as IVPG correlated not only with *e′*, but also with torsion, untwisting rate, and circumferential and longitudinal strain. Furthermore, IVPG also correlated with QRS duration, which indicated a dyssynchronous motion of the LV wall [6].

In patients with various congenital heart diseases, the morphological LV functions as the systemic chamber, even when abnormal muscular structure in LV remains after the surgery [28, 29]. Furthermore, an abnormal right ventricle with an abnormal volume and pressure overload also affect the motion of the LV. Therefore, as *e′* can only capture a maximum velocity of 1-dimensional annular motion, it is impossible to estimate suction force using only *e′* in various congenital heart diseases. In this article, we showed the normal value of IVPDs and IVPGs in each age group for the first time. To evaluate active diastolic function accurately even in patients with complex heart disease, our data will be useful as the normal value to be compared with IVPDs and IVPGs in these patients.

## Limitations

Although the accuracy of IVPD measurements using echocardiography has been validated through comparison to direct measurements using micromanometers [9, 15], no validation study has been done in human children, as validation of IVPD using invasive hemodynamics in healthy children is unethical.

Although we separated the LV into two segments (i.e., one-third of the total LV length from the mitral valve and the remaining two-thirds from the mid–apical segment), it is unclear whether this was the best position to separate LV to capture LV active suction. It may not be possible to separate LV into segments that clearly delineate where active suction of the blood during diastole occurs, including a segment that is mainly affected by LA pressure. Nevertheless, we chose to separate the heart into one-third and two-thirds in an effort to maintain consistency with previous publications [8, 14] and allow a meaningful discussion.

In conclusion, in normal infants, children, and adolescents, the suction force during early diastole primarily increased at the mid–apical segment, which correlated with growth of the heart and development of LV relaxation, even after adjusting for LV length. These are new insights into the development of diastolic function in infants, children, and adolescents.

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## Compliance with ethical standards

**Conflict of interest** The authors declare that they have no conflict of interest.

**Ethical approval** All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

**Informed consent** Informed consent was obtained from the parents or legal guardians of all individual participants included in the study.

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