Pediatric Cardiology

Isovolumic Acceleration at Rest and During Exercise in Children

Normal Values for the Left Ventricle and First Noninvasive Demonstration of Exercise-Induced Force-Frequency Relationships

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Objectives	This study aimed to determine the normal variation of left ventricular (LV) isovolumic acceleration (IVA) in healthy children and to assess the feasibility of an entirely noninvasive method for demonstration of the LV force-frequency relationship (FFR).
Background	Pediatric cardiologists continue to seek noninvasive, load-independent indexes for the assessment of LV contractility and myocardial reserve.
Methods	Resting LV IVA was measured by echocardiogram in 236 healthy children and compared with their clinical characteristics. Further measurements were made in 51 children at incremental heart rates during semi-recumbent exercise. For these, FFRs were constructed by plotting LV IVA against heart rate. To assess potential clinical applications, pilot FFR data were collected from 16 children previously treated with anthracyclines.
Results	In healthy children, median resting LV IVA was 1.2 m/s^2, interquartile range 0.9 to 1.6 m/s^2. Resting LV IVA was unaffected by age, sex, weight, height, and body surface area but associated with baseline heart rate ($r = 0.18$, $p = 0.0006$). Noninvasive evaluation of the LV FFR was possible in 98% of subjects. Positive FFRs were confirmed in all the healthy children. By comparison, several of the children with anthracycline exposure demonstrated flattened force-frequency curves that were largely independent of resting LV ejection fraction and suggest reduced contractile reserve.
Conclusions	In children over 7 years, it is possible to demonstrate the LV FFR by interval measurement of IVA during exercise. The availability of pediatric normal values for both this relation and resting LV IVA might facilitate future investigation of LV contractility and myocardial contractile reserve during childhood. (J Am Coll Cardiol 2011; 57:1100–7) © 2011 by the American College of Cardiology Foundation

Management of children with congenital or acquired heart disease often requires evaluation of left ventricular (LV) systolic function. Although the gold standard measure of ventricular contractility (end-systolic elastance) requires invasive quantification (1), most noninvasive contractile in-

dexes (e.g., ejection fraction [EF], myocardial performance index, and tissue Doppler imaging-derived velocities or strain) are highly sensitive to loading conditions and therefore might not reflect intrinsic myocardial performance (2–4). Measurement of LV myocardial acceleration during isovolumic contraction (IVA) affords a potential solution.

This index, derived from tissue Doppler imaging, closely correlates with invasive measures of contractility (5,6), is relatively insensitive to loading conditions, and has good reproducibility (5–8). In addition, if IVA is measured in the same subject at a variety of heart rates, it can be used to construct a curve that demonstrates an important ancillary

aspect of the nature of myocardial contraction: the force-frequency relationship (FFR) (5,6,9).

Despite increasing use of IVA as an index of contractility (10–14), as yet there are no studies specifically addressing normal values in childhood, and it remains unknown whether IVA varies with age or is affected by height and weight. Furthermore, previous studies using IVA to investigate the FFR have increased heart rate either with cardiac pacing (5,6,9) or with intravenous inotropes (12)—methods not suitable for routine clinical use and that limit research applications. Therefore, the aims of the present study were 2-fold: first, to define the normal variability of LV IVA at rest in healthy children and its relationship to clinical characteristics; and second, to investigate the potential for noninvasive characterization of the LV FFR in children by incremental measurement of LV IVA during exercise.

Methods

The main study cohort consisted of healthy children ages 0 to 18 years with echocardiographically proven normal cardiac anatomy and function. Children were excluded if they had known significant disease or if abnormalities were revealed during baseline echocardiography. For technical considerations, only children ≥7 years of age and able to pedal a bicycle were invited to take part in the exercise portion of the study. A smaller, second group of clinically well children with previous exposure to anthracycline therapy were recruited from the oncology clinic and studied at rest and exercise. The purpose was to gather preliminary feasibility data regarding potential clinical applications of noninvasively derived force-frequency curves. The majority of the echocardiograms to assess age-related normal values at rest were performed at Great Ormond Street Hospital, London, whereas all of the exercise studies were performed at The Hospital for Sick Children, Toronto. The institutional research ethics board of each hospital approved this study, and written consent was obtained from the participants or their guardians.

Clinical data. At the time of study the age, sex, height, weight, and resting heart rate of all participants were recorded. From this data, body surface area was calculated with the Mosteller formula (15,16). In addition, the medical notes of children with previous anthracycline exposure were obtained and examined.

Echocardiography. Echocardiography was performed by experienced investigators, with a Vivid 7 echocardiographic system (GE Corp., Wauwatosa, Wisconsin), with probe frequencies selected as appropriate for patient size and simultaneous electrocardiograph recording. The heart was imaged in a transthoracic apical 4-chamber view. Parameters were optimized to yield the highest possible frame rate (always >120 frames/s). Pulse repetition frequency was set at between 0.24 and 0.4 to provide images without aliasing. Recorded images contained color-coded myocardial velocities for the LV free wall with baseline recordings made after

the child had rested for at least 2 min. For children who also participated in the exercise part of the study (see the following text), further images were recorded at every 10- to 15-beat/min increase in heart rate while pedaling. At each heart rate, image loops of at least 10 beats were captured to ensure sufficient images for offline analysis without respiratory or movement artifact.

Bicycle ergometry. Children were asked to lie on the bed of a bicycle ergometer, which was adjusted to a semi-recumbent, left lateral decubitus position. Bicycle pedals were adjusted according to the height of the subject. The first 25 children were studied while pedaling a Collins Pedalmate (Warren E. Collins, Inc., Braintree, Massachusetts), and the second 25 were studied while pedaling a Lode Angio Echocardiac Stress Table (Lode B.V., Groningen, the Netherlands). The reason for the change was a departmental equipment upgrade. Children exercised in a similar physical position, following identical protocols, whichever bicycle was used. Baseline heart rate was recorded by electrocardiogram after resting comfortably for 5 min. Children were asked to pedal the bike, initially without added resistance, at 50 revolutions/min. Subsequently, an investigator encouraged the children to pedal at rates that caused a slow steady increase of heart rate but avoided excessive chest movement or fatigue. Resistance was then gradually added to further increase heart rate until the child showed signs of exhaustion or requested to stop cycling.

Echocardiographic analysis. Resting and exercise data were analyzed offline with Echopac software (GE Vingmed, Horten, Norway). The sample volume was set at 5 mm × 5 mm and placed in the middle of the myocardium at the basal third of the LV free-wall. Manual tissue tracking was performed to ensure the sample volume remained within myocardium throughout the cardiac cycle. The resulting Doppler spectral trace was displayed, and data points were smoothed with a 3-sample average. The IVA was measured, as described previously (5,6), with electronic calipers as the slope of a straight line intersecting the onset of the signal and its peak. For each beat the baseline was maximally expanded to minimize measurement error. At each heart rate 5 measurements of IVA were made and an average was recorded.

Reproducibility. To assess interobserver variability 2 observers measured IVA independently at each heart rate in 15 of the exercise studies. To assess intraobserver variability the primary observer performed repeated measures of IVA at each heart rate in these 15 studies. In total, each variability test compared 80 observations.

Statistical analysis. Statistical analysis was performed with a commercially available package, SAS (version 9.1, SAS

Institute, Cary, North Carolina). Descriptive statistics of skewed continuous data are presented as the median (interquartile range). Linear regression was employed to assess associations between resting IVA and continuous variables such as age and body surface area. Mean IVA was compared between male and female subjects with a 2-tailed unpaired Student t test and between subjects at rest and peak exercise with a 2-tailed paired Student t test. Intra-class correlation coefficients were calculated for inter- and intra-observer variability. For exercising children, IVA was plotted against heart rate to plot force-frequency curves for each individual. The data from healthy subjects were combined to draw a locally weighted scatterplot smoothing, moving average curve.

To permit subjective assessment of the FFRs from children with previous exposure to anthracyclines, an independent quadratic regression was run to assess the relationship between IVA and heart rate in healthy children and to estimate 95% confidence intervals (CIs) for the data. This was roughly equivalent to taking each heart rate and calculating the mean and SD of IVA associated with that specific heart rate and plotting that mean and its associated 95% CI and running a smoother through these estimates. These 95% CIs for the data were then superimposed on the pilot data from children with anthracycline exposure to give a boundary expected to enclose 95% of the data in a normal population.

Results

A total of 236 healthy children (132 male) were included in the study; all were studied at rest, and 51 also were studied during bicycle ergometry. The age and sex distributions of

the children studied, together with median resting IVA for each yearly age group, are given in Table 1. An additional 16 children who had previously been treated for malignancy with therapeutic regimens that included anthracyclines were studied at rest and during exertion.

Normal values for resting LV IVA. In the healthy children, LV IVA followed a negatively skewed normal distribution (Fig. 1) with a median value of 1.2 m/s² (interquartile range: 0.9 to 1.6 m/s²) and mean of 1.3 ± 0.6 m/s². Mean resting LV IVA did not differ between boys and girls (1.26 m/s² vs. 1.36 m/s², p = 0.16), and there was no relation to age (r = −0.05, p = 0.46), weight (r = −0.01, p = 0.93), height (r = −0.07, p = 0.39), or body surface area (r = −0.03, p = 0.69) (Fig. 2). As expected, resting LV IVA was affected by the subject heart rate (r = 0.18, p = 0.006) and RR interval (r = −0.28, p = 0.002) at the time of measurement (Fig. 2).

LV FFR in healthy school children. All children studied at exercise were able to pedal the cycle ergometer and effectively increased their heart rate (mean heart rate at rest vs. mean heart rate at peak exercise = 67 beats/min vs. 164 beats/min, p < 0.0001). The median percentage increase in heart rate between rest and peak exercise was 151% (interquartile range: 132% to 167%). In 1 child, movement artifact from increased respiration during exercise made the images impossible to analyze. Therefore FFR curves are reported for 50 children (Fig. 3).

Interobserver and intraobserver reliability. We found an intraclass correlation coefficient of 0.94 (95% CI: 0.91 to 0.96) for intraobserver measurements of IVA throughout the range of heart rates studied and of 0.92 (95% CI: 0.87 to 0.95) for interobserver measurements. Anecdotally, both observers noted that it was sometimes necessary to move the region of interest down 0.5 to 1.0 cm on the lateral wall of the LV to obtain satisfactory velocity curves for IVA measurement during exercise, presumably reflecting dynamic changes in heart size and position and that measurable IVA spikes were most often seen with good angle alignment

Children with exposure to anthracycline. Clinical characteristics of the children previously exposed to anthracycline, together with conventional echocardiographic indexes of ventricular function and their measurements for IVA at rest and peak exercise, are reported in Table 2. The FFR curves for these children are depicted in Figure 4. The corresponding EF is given for each curve, and the 95% CIs for normal children are superimposed for comparison (Fig. 4). At rest, there was no significant difference between IVA in the healthy children and those exposed to anthracycline (1.3 m/s² vs. 1.1 m/s², p = 0.13). However, although the majority of children with previous exposure to anthracycline demonstrate FFRs that fall within the 95% CIs for the data in control subjects, several patients' curves are flattened to an extent where they fall below the lower confidence limit, suggesting reduced contractile reserve. There was no relationship between the peak LV IVA

Table 1	Subject Demographic Data and LV IVA in Healthy Children Grouped by Age				
Age (yrs)	Total Subjects, n	Boys, n	Girls, n	Median LV IVA (m/s²)	IQR
<1	18	10	8	1.45	1.23–1.68
≥1–<2	1	0	1	1.00	N/A
≥2–<3	3	3	0	1.50	N/A
≥3–<4	10	4	6	1.25	1.00–1.38
≥4–<5	10	6	4	1.00	0.83–1.58
≥5–<6	11	8	3	1.10	0.85–1.90
≥6–<7	8	5	3	1.55	1.33–1.67
≥7–<8	11	8	3	1.20	1.05–1.44
≥8–<9	16	8	8	0.86	0.78–1.24
≥9–<10	18	7	11	1.20	1.02–1.67
≥10–<11	14	7	7	1.33	0.93–1.48
≥11–<12	13	10	3	1.14	1.10–1.44
≥12–<13	17	9	8	1.00	0.80–1.34
≥13–<14	13	10	3	1.20	0.80–1.42
≥14–<15	25	16	9	1.02	0.81–1.69
≥15–<16	25	10	15	1.17	0.98–1.70
≥16–<17	13	7	6	1.20	0.73–2.08
≥17–<18	10	4	6	1.39	1.04–1.68

IQR = interquartile range; IVA isovolumic acceleration; LV = left ventricular.
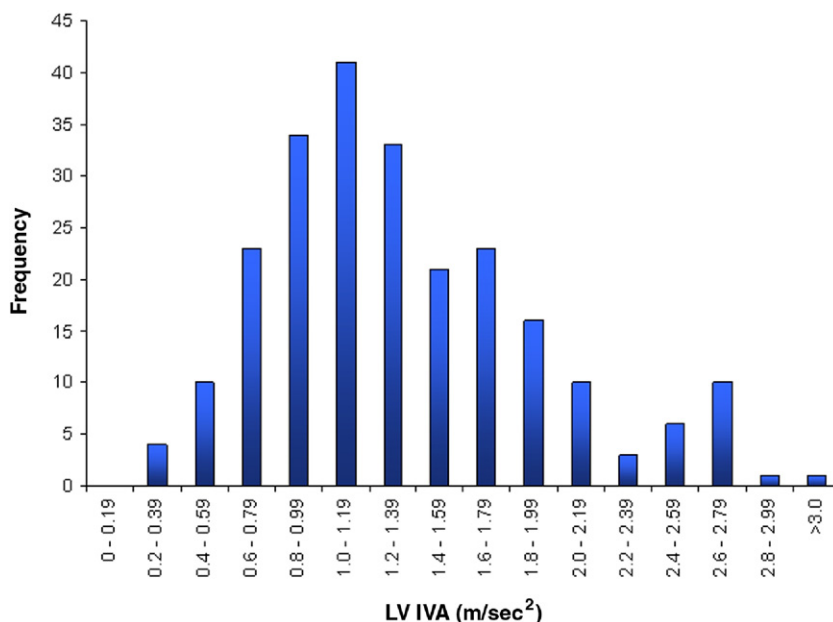
Figure 1   Distribution of Resting Values of LV IVA in Children 0 to 18 Years of Age

This figure shows graphically that resting left ventricular (LV) isovolumic acceleration (IVA) follows a negatively skewed normal distribution in children.

achieved by children previously exposed to anthracycline and their resting LVEF (r = 0.33, p = 0.22).

Discussion

To our knowledge this is the first study to describe normal values of resting LV IVA during childhood and the first demonstration of IVA measurement during exercise as a feasible, entirely noninvasive method for the assessment of the LV FFR. We found resting LV IVA fell within a fairly narrow spectrum (mean LV IVA ± 2 SD was 0.69 to 2.40 m/s^2) in healthy children and that, during childhood, LV IVA is unrelated to age, sex, weight, height, or body surface area.

Relationship of resting IVA to resting heart rate. The positive correlation between resting heart rate and LV IVA was not unexpected, given our previous data with regard to pacing-induced FFRs in children (9), because—as we will discuss in the following text—contractility is intrinsically related to heart rate. Although this relation is largely not measurable or ignored by "traditional" invasive (1,2,17) and noninvasive indexes (18), the heart-rate dependency of IVA should not be seen as a flaw. Rather, it reflects the instantaneous and sensitive nature of IVA and its ability to assess contractile function. Although the correlation with heart rate was highly statistically significant (p = 0.006), the between-individual variability was wide, a finding that has significant implications. For example, although it would be attractive to "normalize" IVA for RR interval, the relationship between heart rate and IVA is neither linear nor consistent between individuals or in the ascending and descending limbs of the FFR, reflecting individual variability in excitation–contractile coupling. Therefore, it is inappropriate to apply a single generic heart rate adjustment to the measurement of IVA. Nonetheless, the potential change in IVA with heart rate should be taken into account when assessing the effects of drug therapy or other interventions on any individual patient. This further underscores the potential value of recording the FFR across a range of heart rates, particularly when assessing response to treatments that might also modify resting or peak heart rates.

The FFR. In most mammals and humans an increase in heart rate results in an increase in cardiac contractile force (19–22). This fundamental characteristic of healthy myocardium is known as a positive FFR and reflects increased and more efficient calcium cycling at higher heart rates (20,23,24). It is a key mechanism by which the heart is able to respond to changes in physiological demand. Analysis of ventricular FFRs provides insight into cardiac physiology, electro-excitation coupling, and the limits of contractile reserve (20,23–26) but to date has been limited by the requirement for invasive techniques, both to assess force (typically measurement of the rate of the rise of LV pressure in the catheter laboratory) and to increase heart rate. In animal and human studies, IVA compares favorably with conductance catheter data as a surrogate for contractility (5,6,14) and thus presents an opportunity to simplify FFR investigation. Several groups have already explored FFRs in humans with IVA as a noninvasive index of ventricular force (5,6,9,12). However, thus far, their methods required the use of either pacing or inotropes to increase heart rate and so confined application
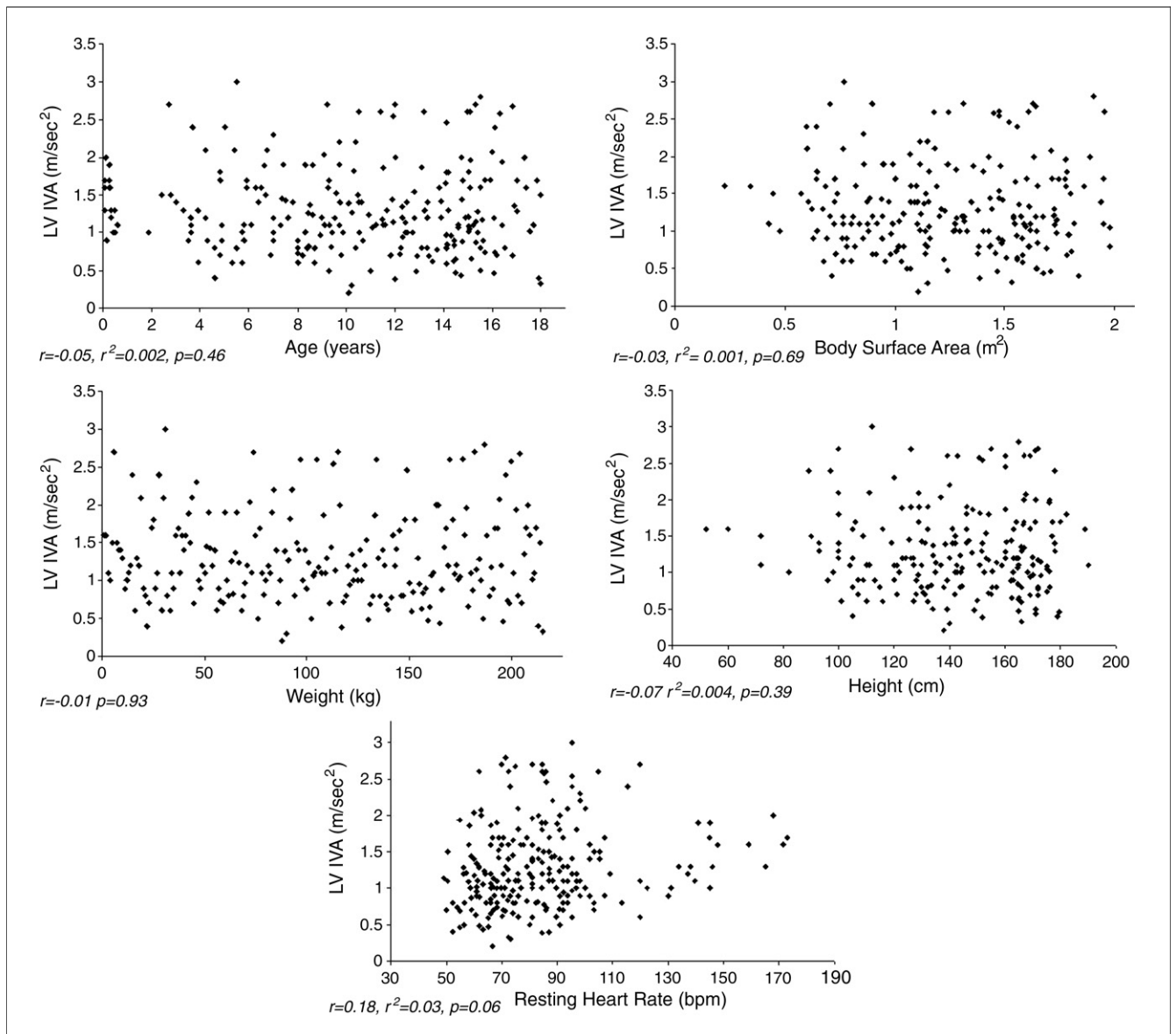
Figure 2   **Relationship of Resting LV IVA to Subject Characteristics**

These graphs illustrate the lack of association between resting LV IVA and most subject characteristics. There is a statistically significant but individually variable relationship between resting IVA and resting heart rate. Abbreviations as in Figure 1.

to limited patient groups. In the present study, exercise was used to increase rather, and IVA was used as an index of force. The success of this method widens the potential for force-frequency assessment.

The dynamic appraisal of cardiovascular parameters can make an important contribution to patient assessment, and growing attention has been given to the use of exercise echocardiography as a means of testing cardiac reserve (27). Although the present study used exercise primarily to increase heart rate, the effects of exercise on the myocardium are also important. Exercise causes a marked increase in adrenergic stimulation and has been shown to augment the FFR (28,29). Therefore, one would expect FFRs developed with exercise to afford increased sensitivity for detection of

contractile impairment. Two previous studies have reported IVA at peak exercise; each showed a significant increase from baseline, but neither presented force-frequency curves (13,30). One other group has used exercise echocardiography to demonstrate FFRs but, in contrast to the present study, chose a rarely used and unvalidated ejection phase measurement (systolic blood pressure/end systolic volume) as their index of contractility (31).

Some authors have argued that IVA is less load-independent than initially suggested (32,33). However, one of the studies on which this conclusion is based altered pre-load in a manner likely also to trigger significant hemodynamic compensatory mechanisms (including an increase in heart rate), which would clearly confound the effects of load on IVA
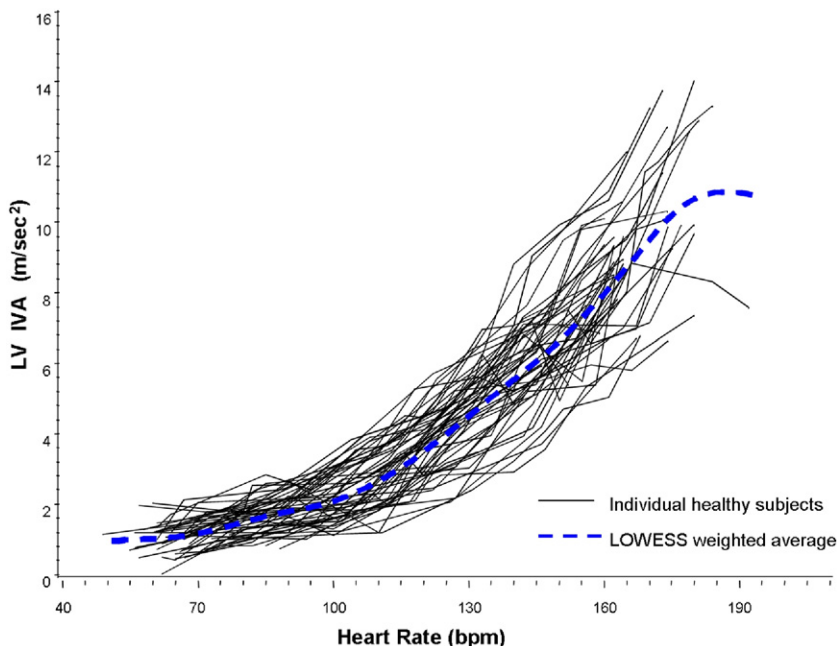
Figure 3 **Variability of LV IVA With Heart Rate During Exercise in 50 Healthy School Children**

It is possible to demonstrate a positive force-frequency relationship in healthy school children, with exercise to increase heart rate and left ventricular isovolumic acceler-ation as a measurement of contractile force. The individual curves for each study participant are shown together with a locally weighted scatterplot smoothing (LOWESS) weighted average. Abbreviations as in Figure 1.

(32,34). The other study induced alterations in pre-load that far exceeded those expected in health or disease, although during more physiological changes, IVA remained relatively stable (33,35). Indeed, the evidence from carefully controlled experimental and clinical studies shows that IVA correlates well with the maximal rate of the rise of LV pressure and is minimally affected by pre-load and afterload changes within a

physiological range (5,6,8). Furthermore, we have demon-strated that it is possible to plot FFRs with a curve typical of that seen with invasive studies, resulting from exercise-induced increases in heart rate, with an acceptable interobserver and intraobserver reliability.

Several of the children previously exposed to anthracy-clines demonstrate a highly abnormal FFR, with a flattened

Table 2 **Clinical and Echocardiographic Data for Children With Prior Anthracycline Exposure**

Patient #	Age (yrs)	Diagnosis	Anthracycline Dose (mg/m^2)	Time Since Treatment End (yrs)	LVIDd Z-score	EF (%)	Resting LV IVA (m/s^2)	Peak Exercise LV IVA (m/s^2)
1	10.7	Promelocytic leukemia	400	<1	−0.1	57	0.7	5.3
2	11.7	Ewing sarcoma	356	8	2.1	53	0.4	1.8
3	17.8	AML	250	8	0.7	44	0.9	1.2
4	14.4	Wilm's tumor	360	11	0.8	42	0.7	1.0
5	15.5	Wilm's tumor	468	11	1.3	63	0.5	5.3
6	10.1	Mediastinal sarcoma	300	8	0.2	60	1.3	4.1
7	8.9	Rhabdomyosarcoma	240	5	0.5	54	0.9	8.9
8	8.0	Ewing sarcoma	375	4	2.0	62	1.4	7.6
9	18.0	Neonatal ALL	185	18	−0.7	70	2.2	6.1
10	17.3	ALL	200	13	1.8	67	1.2	6.1
11	17.9	ALL	200	10	1.0	63	1.1	10.4
12	10.4	ALL	200	8	−0.3	67	1.4	5.8
13	11.2	ALL	200	8	−1.8	64	1.5	9.8
14	13.7	ALL	200	5	0.3	70	0.8	2.8
15	14.9	ALL	200	5	0.4	61	1.5	6.8
16	16.9	Ewing sarcoma	375	4	0.1	61	0.7	10.4

ALL = acute lymphocytic leukemia; AML = acute myeloid leukemia; EF = ejection fraction; LVIDd = left ventricular internal diameter at end diastole; other abbreviations as in Table 1.
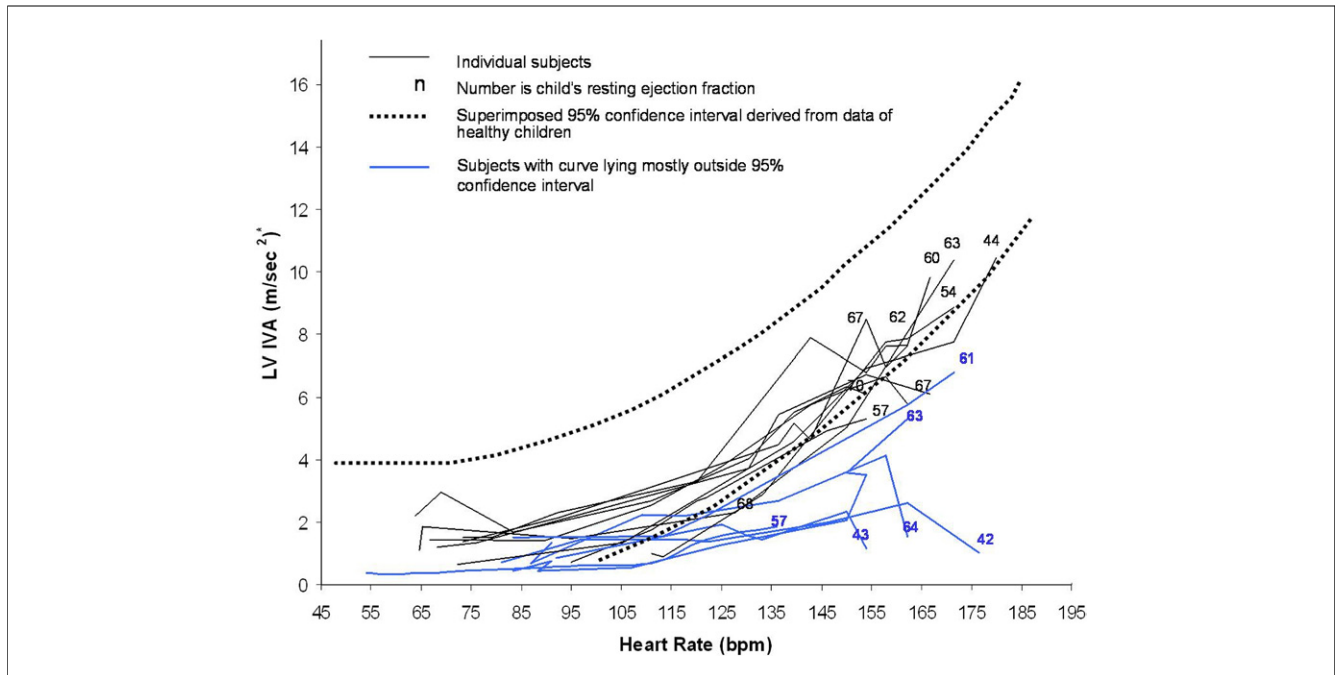
Figure 4   Force-Frequency Curves of Children Previously Exposed to Anthracycline

There was wide variability in the force-frequency curves of children previously exposed to anthracyclines. The shape of the curves seems to bear little relationship to resting ejection fraction. Compared with the 95% confidence interval for IVA curves in control subjects, the curves of children exposed to anthracycline were flattened, suggesting an impairment of contractile reserve. Abbreviations as in Figure 1.

response to exercise. In these patients, as heart rate increased, the corresponding development of LV force seemed suboptimal, suggesting less efficient cycling of calcium. This is particularly interesting, given current understanding of the mechanisms of anthracycline cardiotoxicity. While the precise pathophysiology remains unclear, a favored suggestion is that anthracyclines cause oxidative stress as a result of free radical generation, and this alters mitochondrial calcium transport (36)—a theory that certainly fits well with our findings. It is important to note that, although subjectively the FFR seemed most abnormal in those with decreased resting EF, this was not a consistent finding. Indeed the resting LV EF was >60% in 3 of 6 patients whose curves lay almost entirely outside the 95% confidence limits. Although obviously preliminary and limited by small sample size, our data allude to the potential clinical applications of this noninvasive technique for assessment of LV contractility and myocardial reserve. It seems likely that noninvasive assessment of the FFR could find a role in children with known or even potential cardiac disease, perhaps alerting investigators to myocardial impairment at an early stage, before ventricular remodeling impacts conventional indexes such as EF. Furthermore, it might provide a technique for assessing sub-clinical response to treatment in those with essentially normal resting function but an adverse long-term prognosis.

Study limitations. In any attempt to define normal values, the primary limitation is sample size. Although we studied more than 200 children, when divided into age groups, the numbers in each group are limited. In particular, there were relatively few children between the ages of 1 and 3 years. This age group was challenging because we required children to be resting calmly but without sedation for our data to be valid. Children of this age would equally be difficult to include in research studies; so in some ways this potential deficiency is less relevant than it might otherwise be. However, our sample size should be taken into account in future studies. A second limitation of our study was the technical necessity of using 2 different cycle ergometers for the exercise part of the study. Although identical exercise protocols were used, we cannot exclude the possibility of bias introduced by this upgrade of equipment, however unlikely.

Conclusions

LV IVA is largely unaffected by age, sex, and body habitus over a wide range in childhood. Baseline values do vary with resting heart rate, and this should be taken into account when assessing potential changes in individuals undergoing therapeutic interventions that might influence RR interval. However, the very nature of this heart rate dependency forms the basis of the FFR, which hitherto has required invasive techniques for its measurement. We show, for the first time, that a typical LV FFR curve can be generated in healthy children with an entirely noninvasive combination of exercise and IVA. These data should provide the substrate for further studies of FFR in health and disease.

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