Age-Specific Reference Intervals for Indexed Left Ventricular Mass in Children

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Background: In older children, one of the standards for indexing left ventricular mass (LVM) is height raised to an exponential power of 2.7. The purpose of this study was to establish a normal value for the pediatric age group and to determine how, if at all, LVM/height$^{2.7}$ varies in children.

Methods: M-mode echocardiography was performed in 2,273 nonobese, healthy children (1,267 boys, 1,006 girls; age range 0-18 years). Curves were constructed for the 5th, 10th, 25th, 50th, 75th, 90th, and 95th quantiles of LVM/height$^{2.7}$.

Results: In children aged > 9 years, median LVM/height$^{2.7}$ ranged from 27 to 32 g/m$^{2.7}$ and had little variation with age. However, in those aged < 9 years, LVM/height$^{2.7}$ varied significantly, and percentiles for newborns and infants were approximately double the levels for older children and adolescents: the 95th percentile ranged from 80 g/m$^{2.7}$ for newborns to 40 g/m$^{2.7}$ for 11-year-olds.

Conclusion: For patients aged > 9 years, quantiles of LVM/height$^{2.7}$ vary little, and values > 40 g/m$^{2.7}$ in girls and > 45 g/m$^{2.7}$ in boys can be considered abnormal (ie, > 95th percentile). However, for patients aged < 9 years, the index varies with age, and therefore, measured LVM/height$^{2.7}$ must be compared with percentile curves, which are provided. This variation in LVM/height$^{2.7}$ in younger children indicates that a better indexing method is needed for this age group. Nevertheless, these data are valuable in that they provide normal values with which patient data can be compared. (J Am Soc Echocardiogr 2009;■:■-■.)

Keywords: Left ventricular mass, Children, Normative values, Left ventricular hypertrophy

The echocardiographic measurement of left ventricular mass (LVM) and defining left ventricular hypertrophy (LVH) is important in the stratification of cardiovascular risk, is predictive of outcomes, and may affect treatment decisions in conditions such as extreme overweight, systemic hypertension, dilated cardiomyopathy, and kidney failure in children. Indexing LVM measurement by height or height raised to specific exponential powers or by body surface area allows comparisons across individuals of varying body sizes. However, the complex relationship between heart growth and body growth in children has made indexing difficult for younger ages. Different LVM indexing methods have been proposed in pediatric patients.[1-7] The goal of indexing methods is to account for differing body sizes without discounting the effects of overweight and obesity. In this regard, indexing by lean body mass makes the goal possible. However, lean body mass can be cumbersome to measure, because it requires either bioelectrical impedance or dual-energy x-ray absorptiometry techniques. In adults, studies have shown that height exponentiated to the power of 2.7 may be the best indexing method because it most closely approximates lean body mass.[8,9] Indeed, this indexing method has become a standard for indexing LVM to height for children and is currently recommended in the fourth report on high blood pressure in children as the method of choice in LVM evaluation.[10] The fourth report recommends using a single LVM/height$^{2.7}$ cut point to define LVH. However, the utility of LVM/height$^{2.7}$ in children was recently questioned by Foster et al[7] because of variation in the index in younger age groups. Those investigators demonstrated the failure of a single LVM/height$^{2.7}$ to define LVH across the pediatric age range. On a practical level, this might lead to inaccurate diagnosis of LVH, especially in younger children.

Recently developed statistical methodology is now available to allow the development of quantile curves for indexed LVM in children. Therefore, our purpose was to use echocardiographic data from the Cincinnati Children's Hospital Medical Center Echocardiography Laboratory to generate a normal value and quantile (centile) curves for LVM/height$^{2.7}$ in children aged 0 to 18 years for clinicians to determine if their patients' LVM results are age and height appropriate.

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Presented in part at the 15th Annual Scientific Sessions of the American Society of Echocardiography, June 26 to 30, 2004, San Diego, CA.

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0894-7317/$36.00

doi:10.1016/j.echo.2009.03.003

METHODS

Patients

The data base of the Echocardiography Laboratory at Cincinnati Children's Hospital was queried for all patients with structurally normal hearts and no systemic disease. These patients were children referred

to the laboratory for the evaluation of innocent murmurs or noncardiac chest pain who were then determined by echocardiography to have normal cardiac anatomy and physiology. Patient date of birth, height (or length), weight, and gender were obtained. Height was measured by a wall-mounted stadiometer; length was measured by a length board. Body mass index (BMI) was calculated.

Specific exclusion criteria included (1) any systemic disease, including systemic or pulmonary hypertension; (2) dysrhythmia; (3) any structural heart disease; (4) myocardial dysfunction; (5) valve regurgitation of more than trivial severity; (6) BMI > 85th percentile (to remove the likelihood that data from overweight and obese subjects would contribute to elevation of the "normal" centiles); (7) hematologic or oncologic disease; (8) Kawasaki disease; (9) Marfan syndrome; (10) renal problems; (11) sleep apnea; and (12) genetic syndromes.

Echocardiography

Patients were in the left lateral decubitus position, resting comfortably. Sedation was administered (5 mg/kg pentobarbital orally) as necessary. All echocardiographic studies were performed with the patients in a quiet, resting state. Two-dimensionally guided M-mode echocardiography was performed from a parasternal long-axis view. Using the leading edge–to–leading edge technique, the left ventricular end-diastolic dimension (LVED), posterior wall thickness, and interventricular septal thickness were measured at end-diastole at the level just below the mitral valve leaflets. LVM was calculated using the following equation[11]: $0.8\{1.04[(\text{LVED} + \text{left ventricular posterior wall thickness} + \text{interventricular septal thickness})^3 - \text{LVED}^3]\} + 0.6$.

Statistical Analysis

All variables involved in the analyses were examined for plausibility. Any subject's data that had a value outside the range of plausibility (ie, clearly inappropriate compared with the subject's other data) were removed from the database. Children were excluded if their body size was inappropriate for their age. For children aged > 2 years, this was based on BMI *z* score. For children aged < 2 years, there are no BMI *z* scores, so they were excluded if their length, weight, and/or weight-to-length ratio was not age appropriate.

The average of 3 readings was used for LVED, left ventricular posterior wall thickness, and interventricular septal thickness. Curves were constructed for the 5th, 10th, 25th, 50th, 75th, 90th, and 95th quantiles of indexed LVM for ages 0 through 18 years using the quantile regression methods of Koenker and Bassett[12] in SAS PROC QUANTREG (SAS Institute Inc, Cary, NC). Briefly, quantile regression involves global, as opposed to local, smoothing for creating centile curves. There are no a priori assumptions on the distribution of the data, and all data are used simultaneously to calculate the level each of quantile. Quantile regression is robust to extremes of the response variable. Polynomial modeling was incorporated, using powers of age, specifically age, $\text{age}^{1.5}$, age^2, age^3, 1/age, and √(age) as possible predictors in the quantile regressions, as suggested by Chen.[13] Selection of the powers of age was done by adding the most common ones sequentially until nonsignificance, according to the *P* values. Separate intercepts and interaction terms for gender were also included in the models. A separate regression was run for each quantile of interest. All models were examined for the significance of each of the effects in the models. Only effects that were significant ($P < .05$) were kept in the models. A smooth curve for each quantile of indexed LVM was generated from the results of each regression, and these curves were plotted against age for boys and girls separately.

Table 1 Demographic and clinical characteristics

	Boys (n = 1,267)		Girls (n = 1,006)	
Variable	Mean	SD	Mean	SD
Age (y)	9.547	5.378	9.675	5.221
Height (cm)	134.6	36.33	132.2	31.94
Height *z* score	0.16	1.158	0.06	1.139
Weight (kg)	35.87	20.96	34.18	18.25
BMI (kg/m^2)	17.51	2.712	17.58	2.919
BMI *z* score	−0.15	0.86	−0.09	0.821
IVS (cm)	0.642	0.169	0.615	0.151
LVPW (cm)	0.606	0.171	0.575	0.148
LVED (cm)	4.046	0.889	3.912	0.775
LVM (g)	78.33	45.7	67.73	34.95
LVM index (g/m$^{2.7}$)	33.64	10.45	31.19	10.14

IVS, Interventricular septal thickness; *LVED*, left ventricular end-diastolic dimension; *LVPW*, left ventricular posterior wall thickness.

RESULTS

Table 1 shows summary statistics for our data. There were 2,273 children (1,267 boys, 1,006 girls) in the analyses after exclusions. Average BMI and height *z* scores were close to zero. LVM ranged from < 6 to > 250 g for the entire population.

Table 2 shows the 10th, 25th, 50th, 75th, 90th, and 95th percentiles and ranges for LVM and LVM indexed to height$^{2.7}$ for the subjects by 2-year age groupings. The only powers of age needed to create smooth (ie, fitting the calculated percentiles closely without crossing of each) quantile curves were age, $\text{age}^{1.5}$, and age^2. Gender was included in the models, boys having slightly higher LVM for a given height than girls. Interaction terms between gender and the powers of age were not significant and therefore not included in the prediction equations.

The prediction curves for LVM index (g/m$^{2.7}$) resulting from the 7 quantile regressions are presented in Figure 1A for girls and Figure 1B for boys. The equation for the 95th quantile curve for boys is predicted $\text{lvmi95} = 77.5265 - \text{age} \times 15.8939 + \text{age}^{1.5} \times 5.2322 - \text{age}^2 \times 0.4671 + 2.7380$ and for girls is predicted $\text{lvmi95} = 77.5265 - \text{age} \times 15.8939 + \text{age}^{1.5} \times 5.2322 - \text{age}^2 \times 0.4671$. Percentiles for newborns and infants were about double the levels for older children and adolescents. The 50th and 95th percentile values for subjects aged > 9 years were approximately 27 g/m$^{2.7}$ and approximately 40 g/m$^{2.7}$, respectively, for girls and approximately 32 and 45 g/m$^{2.7}$, respectively, for boys. There was a slight upward trend in the upper quantiles (ie, > 75th percentile) for the older children and adolescents. However, in children aged < 9, years there was considerable variation in the measure and a single, constant 50th or 95th percentile value could not be obtained.

DISCUSSION

This study was performed specifically to address the need for a reference value for one of the most commonly used LVM indices in the pediatric population. The significant findings of this study are that indexing LVM to height$^{2.7}$ must be age specific. In children aged > 9 years, values of 40 g/m$^{2.7}$ in girls and 45 g/m$^{2.7}$ in boys can be considered abnormal. However, in those aged < 9 years of age, a single value cannot be used, and instead, an alternative indexing method

Table 2 LVM (g) and LVMI ($g/m^{2.7}$) percentile values

Age	Gender	n	Variable	Percentile						Minimum	Maximum
				10th	25th	50th	75th	90th	95th		
< 6 mo	Boys	62	LVM	7.22	9.04	10.94	14.16	16.28	16.5	6.27	21.18
			LVMI	40.19	46.92	56.44	66.41	75.72	85.6	32.41	83
	Girls	43	LVM	7.59	9.27	11.15	13.76	16.05	17.6	5.49	28.74
			LVMI	39.05	48.62	55.38	65.98	73.47	80.1	21.22	109.2
6 mo ≤ 2 y	Boys	73	LVM	16.95	20.25	23.88	27.84	32.47	34.6	9.43	36.32
			LVMI	36.17	40.66	44.95	53.29	61.27	57.1	26.71	74.75
	Girls	53	LVM	15.39	17.45	22.25	26.46	31.98	33.7	12.22	35.98
			LVMI	32.91	38.67	42.04	49.85	52.86	68.6	24.18	61.06
2 ≤ 4 y	Boys	124	LVM	24.37	28.52	33.31	38.79	45.48	46.1	13.27	58.13
			LVMI	28.44	33.88	39.5	45.19	48.74	55.3	21.25	77.07
	Girls	84	LVM	24.7	28.4	33.34	38.15	43.88	48.4	17.9	50.98
			LVMI	28.87	31.85	37.88	43.11	47.65	52.4	20.63	66.58
4 ≤ 6 y	Boys	133	LVM	34.36	39.13	45.49	52.62	59.26	57.3	22.92	83.51
			LVMI	27.68	30.68	36.96	40.2	45.12	44.3	18.76	57.25
	Girls	111	LVM	29.24	34.57	39.67	46.59	50.38	63.2	17.68	76.64
			LVMI	25.85	28.06	32.29	36.43	43.47	48.1	18.17	59.25
6 ≤ 8 y	Boys	117	LVM	40.23	45.14	51.73	62.06	70.48	72.1	25.95	97.29
			LVMI	24.47	28.56	31.79	36.28	40.18	43.5	20.27	59.47
	Girls	110	LVM	36.88	40.6	48.38	55.84	65.54	77.4	25.29	89.3
			LVMI	23.15	25.77	29.71	33.15	37.73	44.6	20.11	54.76
8 ≤ 10 y	Boys	111	LVM	45.32	51.49	62.09	73.42	84.61	83.6	32.35	122
			LVMI	22.45	24.85	29.11	34.57	38.25	36	15.24	53.19
	Girls	99	LVM	39.22	48.08	54.76	70.87	75.49	91.1	31.6	91.82
			LVMI	19.07	22.12	26.63	30.37	34.3	41	13.46	44.35
10 ≤ 12 y	Boys	122	LVM	57.76	66.28	74.1	89.43	105.3	102	37.94	124.7
			LVMI	21.88	24.71	28.18	31.87	36.42	35.7	14.72	43.05
	Girls	92	LVM	57.12	62.94	71.66	85.44	98	111	26.53	149.1
			LVMI	20.22	23.25	26.11	29.63	33.05	38.2	13.06	44.88
12 ≤ 14 y	Boys	180	LVM	66.88	82.5	97.76	117.8	138.1	128	51.18	202.3
			LVMI	21.02	24.38	28.8	32.84	39.08	38.2	12.61	47.75
	Girls	144	LVM	60.79	78.37	92.36	108.8	119.8	150	37.56	165.9
			LVMI	20.47	23.63	26.68	29.86	34.65	41.4	10.21	43.59
14 ≤ 16 y	Boys	194	LVM	90.53	106.9	125.7	145.3	167.2	143	38.51	212
			LVMI	22.22	25.11	28.77	33.49	38.47	36.9	8.905	46.01
	Girls	167	LVM	72.67	84.97	98.73	114.7	130	181	39.53	235
			LVMI	20.69	23.55	26.51	29.97	34.89	40.5	12.31	54.33
≥16 y	Boys	151	LVM	93.1	111.3	131.5	154	183.1	154	64.74	256.7
			LVMI	20.72	24.62	29	32.81	37.73	40	13.86	46.33
	Girls	103	LVM	73.9	85.06	101.6	118.8	139.5	204	45.48	201.4
			LVMI	20.06	22.94	26.35	31.4	37.93	39.4	11.21	50.74

LVMI, LVM index.

must be used. Percentile curves as provided in this study provide a facile alternative. Boys have slightly larger LVM for a given height, but this difference appears to be consistent throughout childhood and adolescence. The results of this study will aid in the diagnosis of inappropriate LVM for height and allow the tracking of LVM into adulthood for children with chronic diseases that affect heart structure and function. The results also indicate that an alternative indexing method may be more appropriate in children aged < 9 years.

LVH and LVM as Cardiovascular Risk Factors

LVH is well established as an independent risk factor for cardiovascular morbidity and mortality in adults.[14] In children, LVH may result from cardiac congenital malformations, such as valvular aortic stenosis or familial hypertrophic cardiomyopathy. It is also associated with arterial hypertension,[15-17] obesity,[18-20] and chronic kidney disease[21-23] in pediatric patients. Although the majority of physicians are concerned with LVH and its consequences relative to coronary artery disease risk, the assessment of LVM is equally and critically important for patients with small and, specifically, borderline left ventricles caused by aortic valve stenosis, aortic coarctation, or hypoplastic left-heart syndrome, relative to suitability of a univentricular or biventricular surgical approach.[24] In these latter situations, LVM is one of the most important echocardiographic indices used to determine surgical approach.

Challenges in Indexing LVM in Children

Efforts to define a healthy or normal left ventricular size relative to body proportions (left ventricular allometry) began well before echocardiography became a standard diagnostic tool.[25] Early efforts focused on weight and body surface area.[26] Ideally, an indexing method should correct for differences in lean body mass. Some investigators have successfully indexed several cardiac structures (other

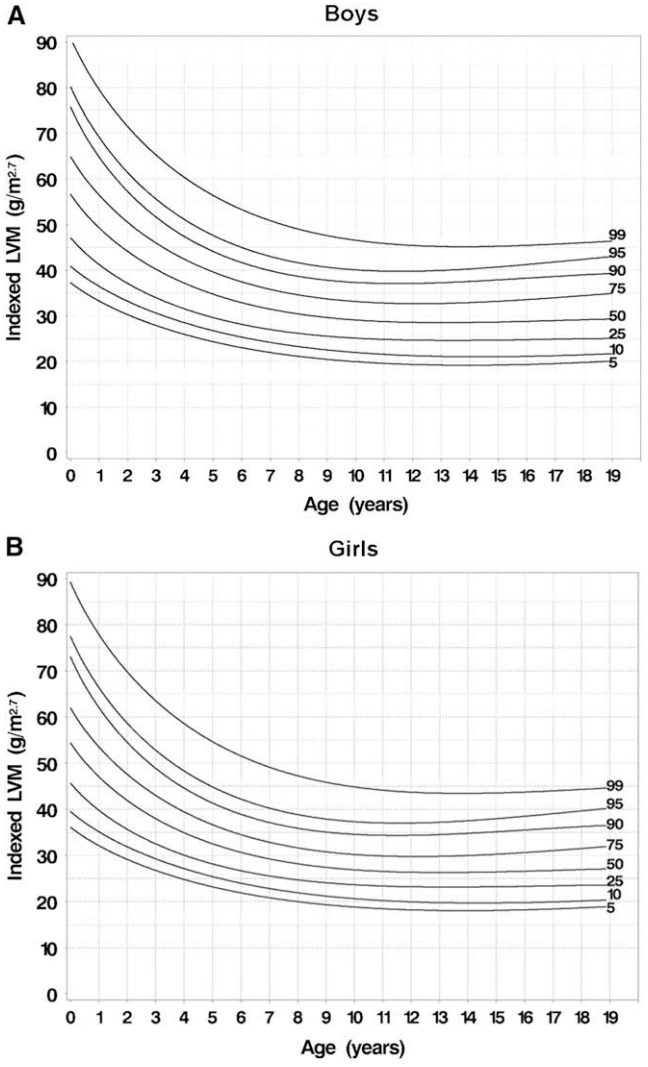

Figure 1 Estimates of the 5th, 10th, 25th, 50th, 75th, 90th, and 95th quantiles of LVM indexed to height$^{2.7}$ for ages 0 through 18 years using the quantile regression methods of Koenker and Bassett.[12] Values are displayed separately for boys (**A**) and girls (**B**).

than LVM) against body surface area.[27] However, indexing LVM by body surface area may inappropriately normalize LVM in obese patients. Indexing to height is an alternative to body surface area because height is not influenced by body weight, as is body surface area. However, we and other investigators have shown that LVM continues to show variation when indexed by height.[7]

Measuring fat-free mass is an even better indexing method, because it is not disproportionately affected by fat mass. Indeed, in adults, cardiac output, stroke volume, and LVM are most strongly predicted by fat-free mass, more so than by other body size indices.[28-31] Using dual-energy x-ray absorptiometry, we have shown that fat-free mass is even more strongly predictive of LVM in children.[3] Other investigators have not only shown the same in adults but have also shown that LVM is dependent on no other measures of body size or composition.[32] In an elegant longitudinal study in children, fat-free mass was found to be most predictive of change in LVM from baseline to 5 years later.[33] Because obtaining fat-free mass can be onerous, recent studies have used an allometric power of height as a surrogate for lean body mass. This method of indexing better describes the relationship between heart and body size without obscuring the adverse efforts of obesity in cardiac geometry.[10,34,35] Applying similar techniques to the evaluation of LVM in children is essential, because the increasing prevalence of obesity is leading to a greater recognition of the metabolic syndrome and its cardiovascular complications in youth.[36]

The allometric relationship of height to left ventricular size changes during childhood. Although standardization of echocardiographic measurements has been a long-term goal for adults,[37] there is a noticeable lack of pediatric reference values. The ideal would be to have a single LVM index cut point to define LVH in children. Daniels et al[3,38] suggested the use of height^3 or height$^{2.7}$ for indexing LVM on the basis of studies relating LVM to lean body mass in older children. But this method is not applicable to younger children, especially newborns and infants, because the allometric relationship of height to body size and left ventricular size changes drastically during childhood and into adulthood. Body proportions change during childhood, and the relationship between LVM and height changes at different developmental stages. Therefore, a single indexing value may not be sufficient to cover all situations. Significant left ventricular size changes, especially during early childhood, also create problems with the tracking of LVM. Even though information on tracking LVM in children[5,39] has been collected, these data do not address the central issue of appropriateness of heart size in relation to body size.

Recently, investigators studying adult patients found that when LVM was indexed by fat-free mass, significantly fewer patients were classified as having LVH than when their LVM values were indexed by height$^{2.7}$, suggesting that the latter technique may not be a completely accurate surrogate for fat-free mass.[40] In addition, Foster et al[7] recently questioned the utility of LVM/height$^{2.7}$ in children because of the variation in the index in the younger age groups, a finding also demonstrated in our study. Their study, like ours, demonstrates the failure of a single LVM/height$^{2.7}$ to define LVH across the pediatric age range. Their suggestion is not dissimilar to the one we advocate. Whereas we propose comparing a patient's given LVM/height$^{2.7}$ value with LVM/height$^{2.7}$-for-age centile curves, these investigators suggested comparing a patient's absolute LVM value with LVM-for-height centile curves.

Until a better indexing method is found, our results emphasize the need for age-appropriate LVM index cut points. These results suggest that it might be preferable in some cases to use multiple indexing powers of height that would change by age and that would produce reference curves that are flat for all ages. Some may argue that this approach would be confusing and would introduce unnecessary uncertainty. Therefore, in lieu of multiple referencing curves, the approach illustrated here is a reasonable, simple compromise that conforms to the most widely recognized standard.

Limitations

The method for determining LVM in this study was M-mode echocardiography. Two-dimensional echocardiographic determination of LVM is another equally valuable means of determining LVM. It was not the intent of this study to determine which method may or may not be more advantageous. Each clearly has its benefits and drawbacks. The Echocardiography Laboratory of Cincinnati Children's Hospital has had a long and successful use of M-mode determination of LVM, so this was the method used in this study. As mentioned earlier, other investigators have chosen to generate centile curves using height, rather than age (as we chose for this study), as the

independent variable. Using age centile curves is not without precedent. For example because of its widespread use in adults, BMI-for-age centile curves were developed in children, even though some have argued that weight-for-height curves might be preferable. It is recognized that although age and height correlate closely, the correlation is imperfect. Both age and height have advantages and limitations when used in this manner. For example, an older child who has growth failure may be more appropriately compared with centile curves of younger patients. Clinicians need to be aware of these caveats when using quantile curves based on age (such as in this study) when evaluating abnormally tall or short children. In these instances, a misclassification of LVH could result. Because the allometric relationship between heart size and body size changes not only with body size but also with age, given normal growth patterns, we felt that it was crucial to include age in our centile charts. Because the data are from subjects from a single metropolitan area, this may limit the generalizability of our results to sites with differences in patient demographics. In addition, many of the data were obtained before the Echocardiography Laboratory had a means to track patient race. Therefore, analyses of LVM on the basis of race, which would be both extremely interesting and obviously valuable, were not possible but are a subject of future studies. Nevertheless, the data can be expected to nearly or reasonably reflect the general population of Cincinnati, which is racially diverse.

The goal of indexing LVM is to account for the natural differences in body size without discounting the pathologic effects of obesity. Lean body mass would, therefore, seem to be the most ideal indexing method. Because lean body mass is difficult to measure, allometric powers of height have traditionally been the most useful surrogates. However, others have pointed out that using a power of height to index LVM in children will not necessarily yield a better index than using a power of body surface area.[41] Ideally, what is ultimately needed is a large-scale study that evaluates the relationship of LVM with a variety of anthropometric measures, including lean body mass, in younger children. Still, with such an approach, it might be difficult, if not impossible, to find a single indexing method that would work for all ages and/or heights.

Despite limitations, LVM/height$^{2.7}$ is the most commonly used method for determining the appropriateness of LVM for pediatric patients as well as for adults, and our data provide updated results on a larger sample and include for the first time normative values for young children. It is critically important for cardiologists, as well as other clinical specialists, to have an accurate assessment of their patients' LVM status to help them to make informed decisions. The proposed age-based quantile curves should help clinicians better attain this goal.

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