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Establishing norms for echocardiographic measurements of cardiovascular structures and function in children

ECHOCARDIOGRAPHY IS A LEADING technology for evaluating cardiovascular structure and function in children. As a result, life-altering decisions are constantly made on the basis of quantitative echocardiographic measurements. For example, some clinical practice guidelines recommend withholding potentially lifesaving chemotherapy from children on the basis of echocardiographic measurements (11).

In the same manner, evidence-based and consensus guidelines have been issued by major cardiology organizations to guide the clinical application of echocardiography. These guidelines address many circumstances for which there is evidence or general agreement that quantitative echocardiography is useful and effective in children (1, 2). Examples include *1*) assessing the effects of medical therapy on the severity of valvular regurgitation and on ventricular compensation and function when it might change medical management; *2*) assessing patients with known cardiac defects to determine the timing of medical or surgical therapy; *3*) assessing suspected cardiomyopathy, heart failure, and changes in clinical status or to guide medical therapy; *4*) screening patients with genetically transmitted cardiovascular disease, such as cardiomyopathy, Marfan syndrome, or Ehlers-Danlos syndrome; *5*) conducting baseline evaluation and reevaluation of patients receiving cardiotoxic chemotherapy to determine the advisability of additional or increased dosages; 6) monitoring patients with suspected or documented Kawasaki disease, myopericarditis, human immunodeficiency virus (HIV), rheumatic fever, neuromuscular disorders with known myocardial involvement, postcardiac or cardiopulmonary transplant, thrombus and cardiac growth, pulmonary hypertension, thromboembolic events, donors undergoing evaluation for cardiac transplantation, atypical syncope or arrhythmia requiring treatment, exercise-induced chest pain, or severe renal disease with or without systemic hypertension; *7*) reevaluating after surgery or initiation of oral or parenteral vasodilator therapy for pulmonary artery hypertension; and *8*) reevaluating during withdrawal of extracorporeal cardiopulmonary support.

Therefore, the reliability and validity of these measurements are of great importance. Our laboratory addressed the reliability of selected echocardiography measurements in children (6) and found that the reliability of some of these measurements, such as left ventricular wall thickness and fractional shortening, were poor when different echocardiographers measured the same tracing. Substantial improvements were achieved by central and repetitive remeasurements.

The validity of these measurements remains problematic, however. Because decisions about the care of children depend on normed measurements, it becomes important to accurately define "normal" at different stages of childhood using indexes that remain valid across a broad range of children.

From a statistical point of view, an indexed echocardiographic measure needs to be independent of the anthropometric measure to which it was indexed (i.e., body surface area). Also, the indexed measure needs to have the same variability (i.e., be homoscedastic), regardless of whether it is calculated for children of small, medium, or large body surface area. From a practical point of view, this means that the indexed measure can be compared between individual children, or between cohorts of children, without being concerned about whether or not the children are of comparable body surface area.

As an example of poor standardization, we can look to Fig. 5*B* in the paper by Sluysmans and Colan (15). If the aortic valve annulus is simply indexed to body surface area and we are told that two children both have an indexed value of 1.5, we cannot be certain whether or not the annulus size is normal. If both children have the same body surface area of 1.3, then their annulus size is the same and normal. However, if both children have the same body surface area of 0.5, then the aortic valve annulus size would be the same for the two children but lower than normal for both. Alternatively, if the first child has a lower body surface area than the second, then that child has a reduced annulus size compared with the second child. The possibilities are clearly confusing.

For this reason, Sluysmans and Colan (15) have suggested indexing the aortic valve annulus by the square root of body surface area, as illustrated in their Fig. 5*D*. In this case, if two children both have an indexed value of 1.5, then both children have an identical normal annulus size. If two children both have an indexed value of 1.7, then both have an identical, elevated aortic valve annulus size. Clearly, interpretation and comparison is immensely easier if the cardiac measure is properly indexed.

As for homoscedasticity, let us consider another commonly misused counterexample: indexing left ventricular mass by height raised to the 2.7 power. Indexed in this way, the left ventricular mass measure will have greater variability for shorter children and less variability for taller children. Let us assume, for the sake of example, that the normal range for height-indexed left ventricular mass is 28 ± 8 for a child who is 180 cm tall and is 28 ± 16 g for a child who is 60 cm tall. Then a short child with an indexed left ventricular mass of 40 g is in the normal range of left ventricular mass, whereas a tall child with the identical indexed left ventricular mass will have significant hypertrophy. Had the variability been the same regardless of height, then we would not have encountered this contradiction. Simple indexing, as has been used by many authors, cannot overcome such limitations to clinical interpretation. If it is necessary to use height-appropriate normal ranges for an indexed variable, indexing has not really accomplished the goal of allowing comparison of populations of different heights or body surface area.

Conditions marked by extremes of weight, such as failure to thrive and obesity, may not be accurately captured by certain norms. Yet clinical decisions depend on the validity of such classifications. Conditions marked by extremes of heart rate, such as bradycardia in athletes and children with congenital complete heart block, may affect normed relationships that might be valid in settings where the heart rate is normal.

In this issue of the *Journal*, Sluysmans and Colan (15) used the theoretical construct of minimum energy loss that had been applied to coronary and other peripheral vessels to the central vasculature and heart to determine normative values for cardiac

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structures and functions in children. They also employ a subsequent systematic analytical approach to explore multiple alternative growth models in detail and select the simplest model that fits the data. The fact that the analytic model turns out to be the same model predicted by the theoretical analysis adds strength to the conclusions reached based on analyzing empiric data alone. Their conclusions have resulted in important advances in quantitative echocardiography.

IMPORTANCE OF ESTABLISHING NORMS

Pediatric echocardiographic measurements normed for age or size have permitted valid comparisons between children of differing sizes by rendering the indexed variable independent of body size and allowing measurements from children of different ages and sizes to be combined in analyses (5, 7, 10). Combining data in this way is not possible without norms because children of different ages have widely varying values for anthropometric and cardiovascular measurements.

IMPORTANCE OF VALIDATING NORMS

Some groups have been particularly vociferous in promoting the concept that left ventricular mass is related exclusively to height, a concept that may be fundamentally incorrect. The implications of the relationship between left ventricular mass or volume to body size should be explored further. The issue has been contentious ever since clinicians began to rely exclusively on an empirical approach to the problem and reached conclusions that are hard to justify on any but descriptive grounds.

The belief that height is the exclusive index of left ventricular mass leads to the conclusion that everyone who is overweight has left ventricular hypertrophy and everyone who is skinny has an atrophic heart. The effect of changes in weight on left ventricular mass is also independent of changes in blood pressure. It also ignores the observation that weight loss and weight gain increase cardiac output, left ventricular volume, and left ventricular mass (4). That is, a sustained change in cardiac output will change left ventricular volume, which in turn will change left ventricular mass because the mass-to-volume ratio is controlled within a narrow range by the wall-stress-controlled mechanical stimulus to hypertrophy (14). Ventricular volume is in turn primarily determined by cardiac output, and cardiac output is closely related to body surface area across species, including humans. Because cardiac output is independently related to both body mass and height in normal persons, ventricular mass and volume are also predicted to independently relate to both. The fact that the nonlinear relationship of heart rate to body surface area is the primary determinant of the complex relationship of left ventricular mass and volume to body surface area is also important (15).

In obese children, the best method of adjusting for left ventricular mass remains unclear. Fat has a lower metabolic rate than other body tissues, making the expected rise in cardiac output proportional to the rise in body surface area less than expected. This shortfall results in left ventricular hypertrophy being masked in obese children when left ventricular mass is adjusted for body surface area. Methods that adjust left ventricular mass for height, lean body mass, or ideal body surface area overdiagnose left ventricular hypertrophy because they do not account for obesity-related increases in lean body mass and cardiac output. The implications of obesity-related increases in left ventricular mass remain an area for study.

For young children, some left ventricular mass indexing methods are highly inconsistent, making them clinically useless and possibly dangerous.

Understanding the correct relationships between left ventricular mass, body surface area, height, weight, arm muscle circumference (as a marker of skeletal muscle wasting), and heart rate is helpful in following children with chronic illness and malnutrition. We found that HIV-infected children were significantly below age-adjusted standards for height, weight, triceps-skinfold thickness, and arm muscle circumference (12). Left ventricular mass normed to body surface area was below normal. Correlation analyses found significant inverse relations between left ventricular mass and weight z score, height z score, and arm muscle circumference percentile. Significant inverse relations were also found between heart rate and weight z score and arm muscle circumference percentile. In these malnourished children with HIV infection, the relationship between nutritional status and cardiac muscle mass is paradoxical. The inverse relation between heart rate and nutritional status suggested an altered metabolic rate with possible increased sympathetic tone. Norming left ventricular mass to body surface area allowed us to understand the relation between nutritional status and cardiac mass in ways that other methods could not.

NEED FOR VALIDATED BIOMARKERS IN PEDIATRIC CARDIOLOGY

The allometric relationship between somatic growth and cardiac growth is important. Measurements of cardiovascular structure and function are important predictors of outcome in children, although few populations of children have been prospectively followed to the point where enough vital status end points have been reached to reliably quantify the relationship. HIV-infected children are one such example where sufficient data do exist (8). In that population, left ventricular fractional shortening, contractility, posterior wall thickness, and body surface area-normed mass are some of the strongest independent predictors of all-cause mortality in multivariable modeling (8). In that study, we found that these noninvasive measurements were powerful enough to discriminate children with short-term survival from those with long-term survival, in some cases years before death. Validation of these echocardiographic measurements as surrogate markers for death now permits routine serial screening.

Another independent predictor of subsequent mortality in the same cohort was failure to thrive, which shows the importance of changes in somatic growth on outcome in HIV-infected children (3, 12). Thus the relationship of cardiovascular structure and function and anthropometry in children is clinically important in HIV-infected children and should be useful in other populations as well.

Validated biomarkers and surrogate end points for cardiac status are severely lacking for children (9). Such end points are essential for identifying high-risk populations and for testing the effectiveness of preventive and therapeutic strategies because many clinical end points, such as death, may take years to reach. We hope that the work of Sluysmans and Colan (15)

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will inspire others to test these normed echocardiographic measures as predictors of clinical end points in children.

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REFERENCES

1. **Cheitlin MD, Armstrong WF, Aurigemma GP, Beller GA, Bierman FZ, Davis JL, Douglas PS, Faxon DP, Gillam LD, Kimball TR, Kussmaul WG, Pearlman AS, Philbrick JT, Rakowski H, Thys DM, Antman EM, Smith SC Jr, Alpert JS, Gregoratos G, Anderson JL, Hiratzka LF, Hunt SA, Fuster V, Jacobs AK, Gibbons RJ, Russell RO; American College of Cardiology; American Heart Association; and American Society of Echocardiography.** ACC/AHA/ASE 2003 guideline update for the clinical application of echocardiography. *Circulation* 108: 1146–1162, 2003.
2. **Cheitlin MD, Alpert JS, Armstrong WF, Beller GA, Bierman FZ, Davidson TW, Davis JL, Douglas PS, and Gillam LD.** ACC/AHA guidelines for the clinical application of echocardiography. *Circulation* 95: 1686–1744, 1997.
3. **Hoffman M, Lipshultz SE, and Miller TL.** Malnutrition and cardiac abnormalities in the HIV-infected patient. In: *Nutritional Aspects of HIV Infection*, edited by Miller TL and Gorbach S. London: Arnold, 1999, p. 133–139.
4. **Karason K, Wallentin L, Larsson B, and Sjostrom L.** Effects of obesity and weight loss on left ventricular mass and relative wall thickness: survey and intervention study. *Br Med J* 315: 912–916, 1997.
5. **Lipshultz SE, Easley KA, Orav EJ, Kaplan S, Starc TJ, Bricker JT, Lai WW, Moodie DS, Sopko G, Schluchter MD, Colan SD; and Pediatric Pulmonary and Cardiovascular Complications of Vertically Transmitted HIV Infection (P^2C^2 HIV) Study Group.** Cardiovascular status of infants and children of women infected with HIV-1 (P^2C^2 HIV): a cohort study. *Lancet* 360: 368–373, 2002.
6. **Lipshultz SE, Easley K, Orav EJ, Kaplan S, Starc TJ, Bricker JT, Lai WW, Moodie DS, Sopko G, Schluchter MD, and Colan SD.** Reliability of multicenter pediatric echocardiographic measurements of left ventricular structure and function: the prospective P^2C^2 HIV study. *Circulation* 104: 310–316, 2001.
7. **Lipshultz SE, Easley KA, Orav EJ, Kaplan S, Starc TJ, Bricker JT, Lai WW, Moodie DS, Sopko G, McIntosh K, and Colan SD.** Absence of cardiac toxicity of zidovudine in infants. *N Engl J Med* 343: 759–766, 2000.
8. **Lipshultz SE, Easley KA, Orav EJ, Kaplan S, Starc TJ, Bricker JT, Lai WW, Moodie DS, Sopko G, and Colan SD.** Cardiac dysfunction and mortality in HIV-infected children. The prospective P^2C^2 HIV multicenter study. *Circulation* 102: 1542–1548, 2000.
9. **Lipshultz SE.** Ventricular dysfunction clinical research in infants, children and adolescents. *Prog Pediatr Cardiol* 12: 1–28, 2000.
10. **Lipshultz SE, Lipsitz S, Mone SM, Goorin AM, Sallan SE, Sanders SP, Orav EJ, Gelber RD, and Colan SD.** Female sex and higher drug dose as risk factors for late cardiotoxic effects of doxorubicin therapy for childhood cancer. *N Engl J Med* 332: 1738–1743, 1995.
11. **Lipshultz SE, Sanders SP, Goorin A, Krischer JP, Sallan SE, and Colan SD.** Monitoring for anthracycline cardiotoxicity. *Pediatrics* 93: 433–437, 1994.
12. **Miller TL, Easley KA, Zhang W, Orav EJ, Bier DM, Luder E, Ting A, Shearer WT, Vargas JH, Lipshultz SE; Pediatric Pulmonary and Cardiovascular Complications of Vertically Transmitted HIV Infection (P^2C^2 HIV) Study Group; and National Heart, Lung, and Blood Institute, Bethesda, MD.** Maternal and infant factors associated with failure to thrive in children with vertically infected HIV-1 infection: the prospective, P^2C^2 HIV multicenter study. *Pediatrics* 108: 1287–1296, 2001.
13. **Miller TL, Orav EJ, Colan SD, and Lipshultz SE.** Nutritional status and cardiac mass and function in children infected with the human immunodeficiency virus. *Am J Clin Nutr* 66: 660–664, 1997.
14. **Ruwhof C and Van der Laarse A.** Mechanical stress-induced cardiac hypertrophy: mechanisms and signal transduction pathways. *Cardiovasc Res* 47: 23–37, 2000.
15. **Sluysmans T and Colan SD.** Theoretical and empirical derivation of the cardiovascular allometric relationships in children. *J Appl Physiol* 99: 445–457, 2005.

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