Title
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Journal
Medicine and science in sports and exercise, 54(5)

ISSN
0195-9131

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Publication Date
2022-05-01

DOI
10.1249/mss.0000000000002894

Peer reviewed

Pediatric Cardiopulmonary Exercise Testing: Interoperability Through Domain Analysis Modeling and a National Survey

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ABSTRACT

COOPER, D. M., R. BAR-YOSEPH, R. I. LIEM, T. G. KEENS, S. A. MCCOLLEY, and S. RADOM-AIZIK. Pediatric Cardiopulmonary Exercise Testing: Interoperability Through Domain Analysis Modeling and a National Survey. Med. Sci. Sports Exerc.,Vol. 54, No. 5, pp. 741-750, 2022.

Purpose: The electronic health record, data science advances, and dynamic environmental and infectious threats to child health highlight the need for harmonized and interoperable approaches to pediatric cardiopulmonary exercise testing (CPET). Accordingly, we developed a terminology harmonization in exercise medicine and exercise science domain analysis model (THEMES DAM) to structure CPET data elements.

Methods: THEMES DAM identified 114 data elements, including participant information, calibration, equipment, protocols, laboratory personnel, encouragement strategies, and analysis procedures. We used the THEMES DAM, vetted by the international data standards organization HL7, to construct a current-state survey of pediatric CPET centers in the United States. Forty-eight of 101 centers responded to a questionnaire covering seven major topic areas (38 items).

Results: Centers predominantly performed between 100 and 500 tests annually. Cardiac disease represented 55%of referrals. Almost all centers calibrated gas concentrations and flow daily, but 42% never calibrated their treadmill or cycle ergometers. All centers measured VO_2peak but calculated differently. Centers used a variety of protocols (e.g., for treadmill: 61%, Bruce; 43%, modified Bruce; 59%, other); 44% calculated CPET slopes from submaximal portions of CPET (e.g., VO_2-HR). All centers verbally encouraged participants, but only 40% used a standardized approach. The interpretation of CPET was done by physicians (60%), exercise physiologists (25%), exercise technicians (10%), nurses (1%), or others (4%). Ninety-one percent would agree to collaborate in multicenter research, 89% to establish dynamic reference values, and 83% to better interpret CPET.

Conclusions: The survey data and the implementation of THEMES DAM could accelerate interoperability across multiple centers. This would facilitate a nimble approach to create

pediatric reference values responsive to the constantly changing health environment and stimulate novel approaches to CPET research and clinical application.
Key Words: GAS EXCHANGE, DATA SCIENCE, REFERENCE VALUES, TREADMILL, ERGOMETER

The nearly universal implementation of the electronic health record (EHR) in the United States has revolutionized the scope of clinical research and practice (1). Rather than rely solely on prospective, highly structured, and often expensive randomized clinical trials, mining the HER is increasingly seen as a valid means to improve diagnosis and therapy over a wide range of health conditions and disease. Recognizing this, in 2015, an international group of clinicians and researchers in exercise medicine and science convened to enhance the use of cardiopulmonary exercise testing (CPET) in pediatric research and clinical application (2). We identified key challenges to expanding the use of CPET in these activities, including the lack of formal approaches to data interoperability, terminology and protocol armonization, and training and qualifications of CPET laboratory faculty and staff. We outlined the steps necessary to ensure that tests performed at different laboratories could produce reproducible and comparable physiological results and would not be confounded by variability in laboratory calibration, exercise equipment, or in the implementation of the CPET protocols themselves. We also suggested mechanisms to ensure that clinical CPET data could be rapidly incorporated in the EHR.

In this study, we report the results of a survey of procedures and terminologies used in major pediatric CPET centers in the United States. Our goal was to identify specific CPET data and laboratory components that might interfere with optimal sharing of data in pediatric exercise research and clinical care due to lack of standardization or harmonization. The survey was designed for all CPET centers and not solely for pediatrics. The lack of terminology harmonization and data interoperability is, in general throughout clinical research and application, a major cause for clinical study failure, ineffective collaborations, or inability to translate research discovery into clinical applications in many areas of health and medical research (3). Research in children and adolescents often requires multicenter collaboration to achieve sample sizes of sufficient power that allow investigation of conditions and diseases associated with a smaller incidence in pediatric populations.

Our survey was the direct result of our group's completion of a formal process known as a domain analysis model (DAM) developed to facilitate interoperability in health care and research. HL7 is a not-for-profit, ANSI-accredited standards-developing organization that provided us with a structured approach to creating a DAM, an approach increasingly used to improve the quality of clinical processes and enhance interoperability across distinct health care providers and systems (4). The formal concept of the DAM originated from collaborations between health care providers and information scientists working to improve the efficiency and harmonization of complex health care activities (personal communication, W. Ed Hammond, PhD, Duke University).

The flow of data in virtually every clinical interaction involves a heterogeneous and intertwined array of participants and patients (screening, diagnosis), concepts and terminologies (disease, health condition), personnel (physicians, nurses, technicians), laboratory procedures (blood tests, physical measurements), devices (testing equipment), and reporting metrics and outreach. Over the past 30 yr, formal software development tools were introduced (such as the

Unified Modeling Language [UML] [5]), which were used in the development of our terminology harmonization in exercise medicine and exercise science (THEMES) DAM. The technical definition of a DAM is available through HL7, and we present a visualization of the THEMES DAM in Figure 1. The complete vetted THEMES DAM can be found on the HL7 Web site (6). Once completed, we used the specific CPET and terminologies identified in THEMES DAM to build a survey to identify challenges to data sharing and interoperability in pediatric CPET centers.

METHODS

Identifying survey elements from the THEMES DAM.

The foundation for the THEMES DAM was a set of data element definitions prepared by a panel of experts in CPET. The data elements included in the THEMES DAM were identified from several sources, including the following:

- Current terminologies used in clinical CPET derived from major texts and published national and international guidelines
- Exercise and physical activity terms used by national societies such as the American Thoracic Society, the American College of Sports Medicine, and the American Heart Association
- Exercise and physical activity variables used in large data sets associated with clinical trials (e.g., NHANES [7], CARDIA [8], and Project Healthy [9]).

The review process was managed by the HL7 Clinical Interoperability Council (CIC). The Council provides a mechanism for clinical domains to develop common approaches to standards-related activities and to form consensus on issues of interest among multiple groups. CIC supports a process whereby a master set of data elements with their attributes are defined and harmonized using a common process and a common set of attributes. The CIC, together with clinicians and the rest of the HL7 community, helps define clinical domain requirements.

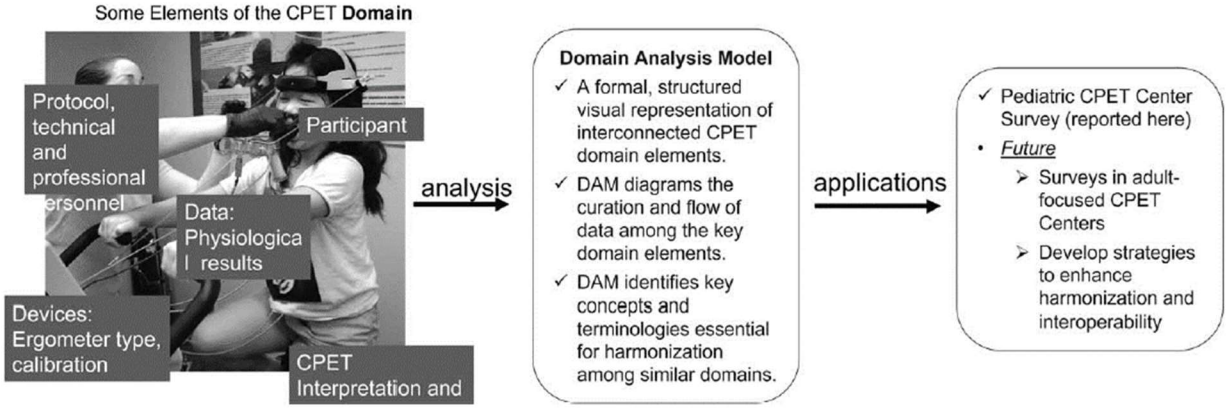


FIGURE 1—The THEMES DAM. The DAM was developed for both pediatric and adult CPET centers. The DAM identifies the essential elements of CPET and provides a structured graphical presentation and set of algorithms using UML. Building on the THEMES DAM, we developed a survey for pediatric CPET centers to gather data about concepts, terminologies, participants,

devices, and analyses that can be used in the future to improve CPET quality and accelerate data sharing among different centers. The DAM was formally reviewed, critiqued, and vetted by the Clinical Interoperability Council of HL7 internationally.

TABLE 1. Organization of pediatric CPET laboratory survey.

Survey Category and Corresponding (THEMES DAM Subject Area)	Key Survey Topics	Survey Item No.
CPET laboratory setting (1,4)	Participant and disease categories; number of tests performed annually; business model	1–6
Device (2)	Type of metabolic cart; ergometer type	7–12
Calibration protocols (2)	Ergometer; metabolic cart	13–17
Personnel (5)	Type of personnel; credentialing and training of personnel; participant monitoring considerations for disease type/risk	18–23
CPET protocols (1,3)	Progressive tests; constant work rate; recovery; maximal or peak; submaximal	24–27
CPET results: physiologic landmarks (3,5)	Criteria for exercise cessation; motivation strategies; CPET interpretation format; $\dot{V}O_{2peak}$ criteria; ventilatory threshold interpretation; submaximal CPET data elements	28–35
Next steps	Pediatric CPET data exchange mechanism	38

Survey construction and recruitment. The THEMES DAM outlined five major subject classes. There was a total of 114 data elements in the DAM data collection form. Using standard approaches for online surveys, we adapted the key features of THEMES into a questionnaire consisting of seven major topic areas with 38 items (Table 1; see Document, Supplemental Digital Content, THEMES Pediatric Exercise Survey, for the complete survey, http://links.lww.com/MSS/C523). The questionnaire was designed to take approximately 40 min to complete. In constructing the survey, we used the principles outlined by Regmi et al. (10) and piloted the online questionnaire with directors and technicians of several regional CPET laboratories.

The survey was sent online to 101 pediatric CPET laboratories. We identified potential qualifying laboratories (those that tested a majority of pediatric clients) by our own experience and contacts, and by membership in organizations such as the North American Society of Pediatric Exercise Medicine (11). Each recipient was offered a $50 gift card upon completion of the survey. A total of 48 pediatric CPET laboratories completed the survey over a period of 8 months (9/2019 to 5/2020) for a survey response rate of 48%. The survey responders were well distributed across the United States with no difference geographically between responding and nonresponding laboratories. The centers identified themselves as follows: hospital-based, 57%; outpatient facility, 29%; research center, 6%; and other, 8%. The project was certified as nonhuman subject research by the UCI Institutional Review Board, and no consenting process was required.

RESULTS

Pediatric CPET survey. A total of 111 CPET terms were identified and defined from the THEMES DAM. In Table 2, we show representative examples of the data definitions vetted by the HL7 CIC and relevant to the survey. In addition, a data entry form was developed for future use by individual laboratories to facilitate the collection of key data from different centers and to begin to harmonize CPET data.

CPET laboratory–annual testing and disease distribution. The CPET laboratory respondents predominantly performed between 100 and 500 tests in pediatric clients annually (Fig. 2). Possible cardiac disease represented the largest single category of referral (55%). A large percentage of pediatric clients were classified as healthy, probably because CPET laboratories represented in the survey are often involved in research studies.

TABLE 2. Selected elements from the THEMES DAM data dictionary vetted by HL7.

Cardiopulmonary exercise test	CPET Provides a Global Assessment of the Integrative Exercise Responses Involving the Pulmonary, Cardiovascular, Hematopoietic, Neuropsychological, and Skeletal Muscle Systems.
Device calibration	The determination of the accuracy of an instrument, usually by measurement of its variation from a standard, to ascertain necessary correction factors.
Cycle ergometer	A fixed cycling machine that allows a precise estimation of the work rate from the rpm and the resistance to pedaling. Leg cycling may be performed sitting or supine.
Carbon dioxide output ($\dot{V}CO_2$)	The amount of carbon dioxide (CO_2) exhaled from the body into the atmosphere per unit time, expressed in milliliters or liters per minute ($mL \cdot min^{-1}$ or $L \cdot min^{-1}$), standard temperature and pressure dry (STPD).
Oxygen uptake ($\dot{V}O_2$)	The amount of oxygen (O_2) extracted from the inspired gas in each period, expressed in milliliters or liters per minute ($mL \cdot min^{-1}$ or $L \cdot min^{-1}$), standard temperature and pressure dry (STPD).
$\dot{V}O_{2peak}$	The highest modality-specific oxygen uptake ($\dot{V}O_2$) attained by an individual encouraged to perform physical exercise with maximal effort and ability, and limited by attainment of a physiologic limit to oxygen transport or utilization, intolerable symptoms, or medically indicated constraint.
$\dot{V}O_{2max}$	The highest oxygen uptake ($\dot{V}O_2$) attainable by an individual. It is the $\dot{V}O_2$ attained during aerobic physical exercise of sufficient metabolic demand by a sufficient mass of skeletal muscle to require or exceed the integrated capacity of the whole body for oxygen transport and utilization. Maximum $\dot{V}O_2$ is demonstrated by failure to further increase $\dot{V}O_2$ despite further increment in metabolic requirement. $\dot{V}O_{2peak}$ is frequently used as a functional approximation of maximum $\dot{V}O_2$ when demonstration that a measured value is maximal is not practical or expected.
$\Delta\dot{V}_E/\Delta\dot{V}CO_2$	The increase in minute ventilation ($\dot{V}_E$) in response to a simultaneous increase in carbon dioxide output ($\dot{V}CO_2$). This may be used to estimate the effect of ventilatory dead space, ventilation-to-perfusion ($\dot{V}/\dot{Q}$) mismatch, and/or changes in the CO_2 set point during exercise.
$\Delta\dot{V}O_2/\Delta WR$	The increase in oxygen uptake ($\dot{V}O_2$) in response to a simultaneous increase in work rate (WR). Under appropriate conditions (e.g., steady-state aerobic work), this may be used to estimate the efficiency of muscular work. In patients with impaired oxygen delivery to the working muscle, alterations in the slope may be observed not indicating cellular changes in the efficiency of muscular work.
Physiologic validation	A procedure to check the CPET system (including the gas exchange measuring system and the ergometer) for accuracy at any given time point and the precision over time in terms of metabolic rate. Without accurate measurement of the metabolic response, further subject testing on the given system is not recommended. Physiologic validation is suggested to be done quarterly, estimated duration of the process is 30 min, and it requires a second person to perform the exercise while the operator is conducting the test.

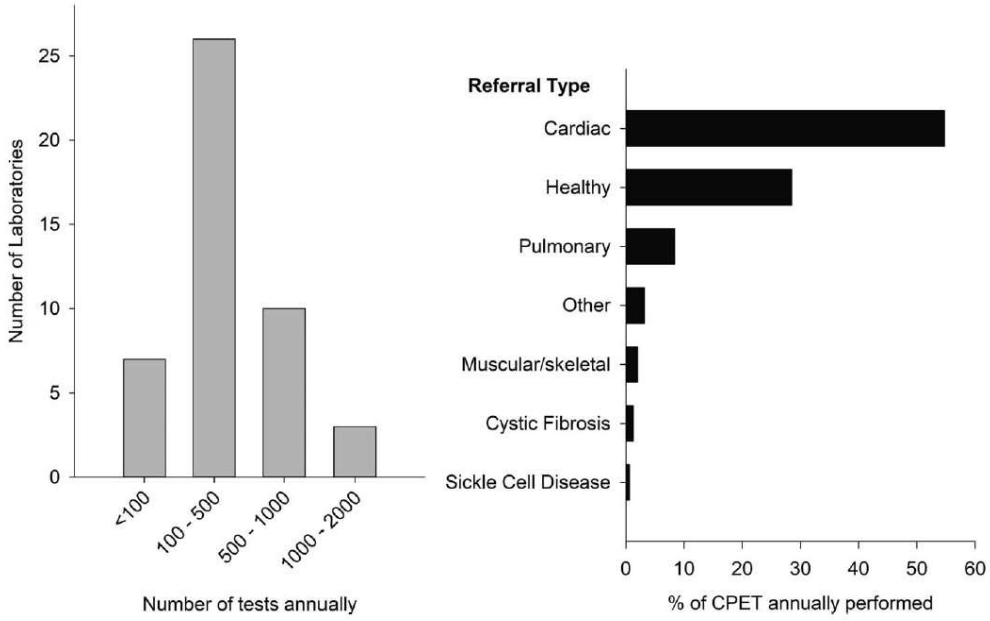


FIGURE 2—Annual volume of pediatric CPET (*left panel*). Distribution of diseases and conditions studied (*right panel*).

Device. All responding centers used metabolic carts and collected breath-by-breath gas exchange data. The two leading manufacturers of metabolic carts used in surveyed laboratories were Sensormedics (more recently known as CareFusion and currently, Vyaire) (n = 22) and MedGraphics (n = 20), with the remaining laboratories using carts made by Parvo system (n = 8) or Cosmed (n = 2), or carts that were assembled with various components by local technologists (n = 5). Most centers conducted CPET using either a cycle ergometer or a treadmill, and 78% of laboratories had both cycle ergometers and treadmills. Seven centers did not use cycle ergometers, and only three did not use treadmills.

Calibration protocols. No uniform or validated approach to the timing and procedure of calibrating CPET devices was identified by the survey (Fig. 3). Temperature and pressure recording is essential for CPET accuracy. Thirty-five percent of the centers measured temperature and barometric pressure before each test, 35% daily, 4% weekly, and 4% monthly, and 21% did not routinely record these measurements. The metabolic carts have their own calibration procedures, which tend to be automated, fairly simple, and rapid. There is even less uniformity regarding the calibration of the ergometers. As shown in Figure 4, laboratories reported variability in calibration procedures for the ergometers that differed substantially from the metabolic cart automated calibration of flow, volume, and gas concentration. Forty-two percent of laboratories never calibrated their ergometers.

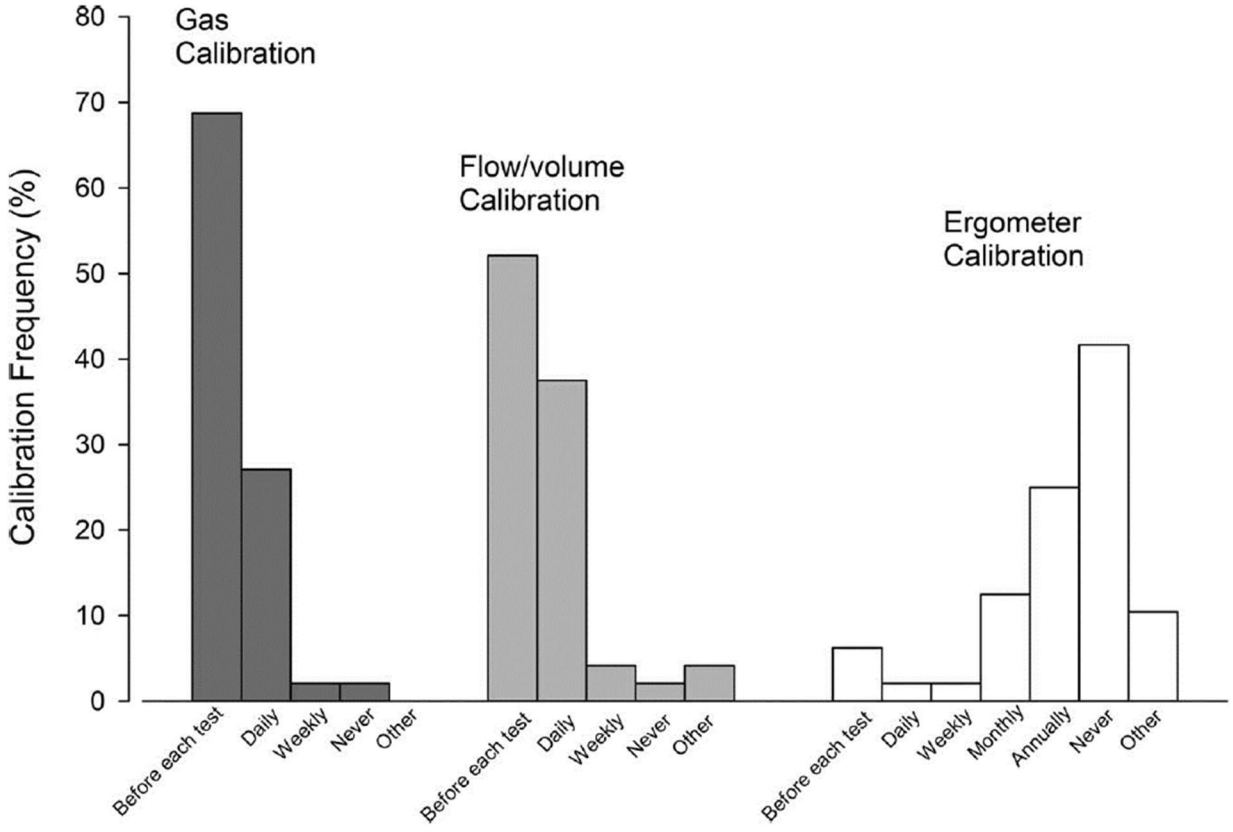


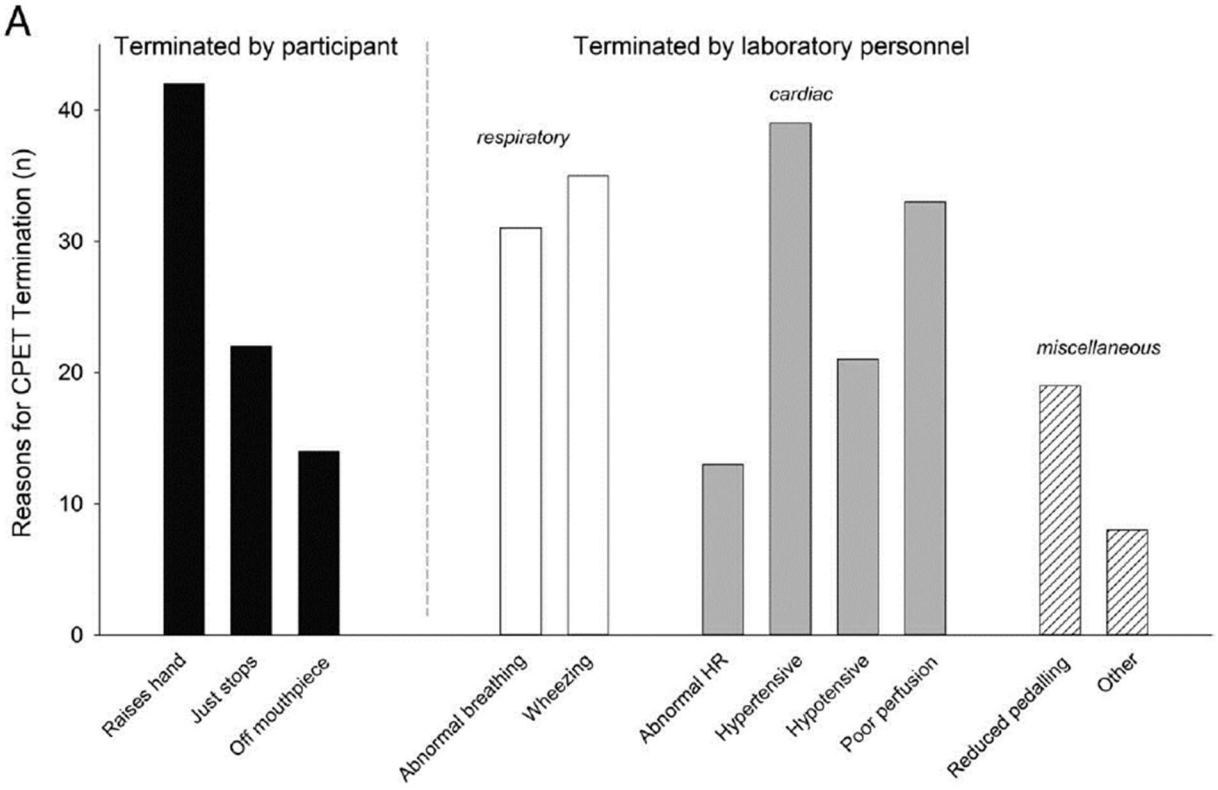
FIGURE 3—Pattern of calibrations (percentage of laboratories responding).Gas and flow calibrations were performed far more frequently than ergometer calibration. Forty-two percent of laboratories never calibrated their ergometers.

CPET laboratory directors, training, and supervision during testing. The directors of pediatric CPET laboratories varied across the surveyed centers. Physicians led in 63% of the centers, followed by exercise physiologists (PhD) at 19%, nurses and respiratory therapists at 2%, and other healthcare professionals in 14%. Among the physician directors, 77% were board

certified in pediatric cardiology, 20% were in pediatric pulmonology, and 3% were general pediatricians. Training of laboratory technicians was varied. Forty percent received formal training by the equipment manufacturers, whereas 60% learned through on-the-job training or informally from other technicians. Onsite supervision during testing varied across the sites, but there was little difference in supervision between more routine and complex cases.

CPET protocols. Pediatric CPET laboratories use both treadmills and cycle ergometers, and there are currently no standardized guidelines for equipment selection. The majority of CPET protocols involve progressive exercise tests, in which the work performed increases steadily to determine the peak or maximal oxygen consumption (VO_2). There is substantial variability in the pattern and degree of exercise-intensity progression. For treadmill exercise, work performed is increased by altering the speed and incline of the treadmill. Twenty-eight centers used the Bruce protocol (12), 20 used the modified Bruce protocol (13), and 27 used a variety of different treadmill-intensity protocols. For cycle ergometer exercise, work is increased by adding resistance to an electronically braked flywheel and attempting to ensure a relatively constant pedaling rate throughout CPET. Thirty-eight centers used a ramp protocol (14), 10 used stepwise increments in work rate, and 6 used a variety of different treadmill-intensity protocols.

The determination of a peak or maximal CPET variable is critically dependent on when exercise is terminated. As shown in Figure 4A, the termination of exercise can occur when the participant decides to stop exercising or when CPET personnel determine that exercise should cease because of, primarily, safety factors. As CPET work increases, every pediatric laboratory surveyed uses some sort of motivational strategy to encourage participants to continue to exercise, but only 40% use a standardized motivational protocol. As shown in Figure 4B, there is great variability in when and for how long such motivation (typically, on the part of the laboratory technical personnel) is implemented.



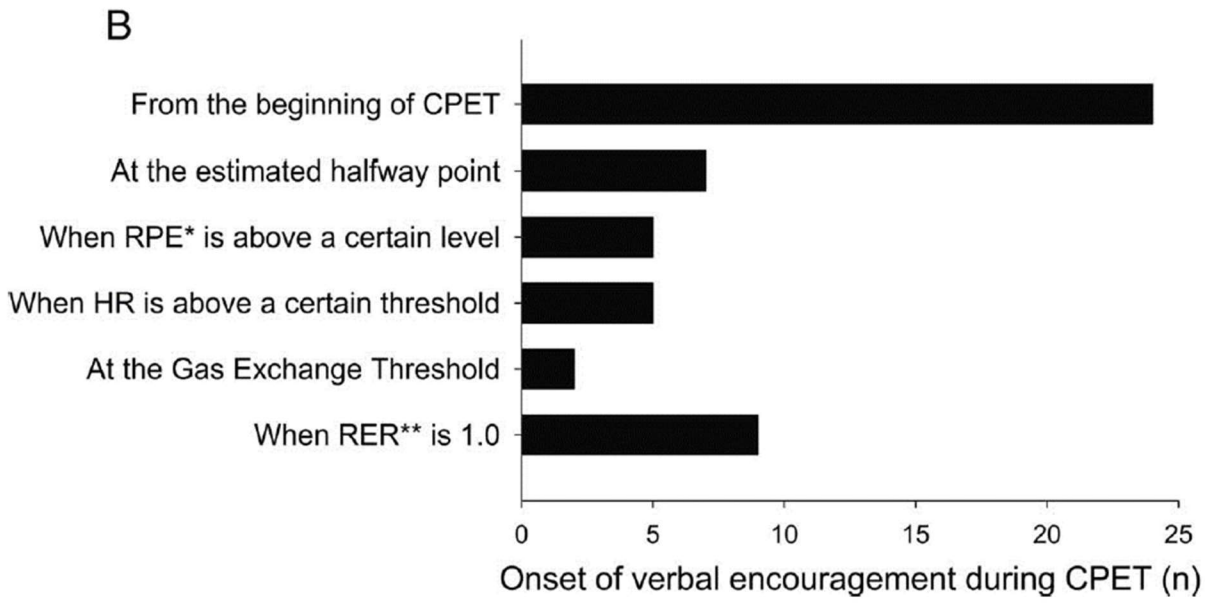


FIGURE 4—A, Reasons for terminating CPET (progressive work rate tests). B, Verbal motivation procedures (by laboratory personnel) of participants during progressive CPET.

CPET results–physiological landmarks. All laboratories surveyed calculated peak or maximal VO_2, and 8% also used supramaximal testing to validate the peak or maximal values. As shown in Figure 5, the centers used a variety of techniques to determine peak values. All laboratories calculated the gas exchange threshold (anaerobic threshold, lactate threshold, etc.), again using a variety of strategies. Forty-four percent of the centers calculated CPET slopes (e.g., $\Delta VE/\Delta VCO_2$) from submaximal portions of CPET. The majority of centers relied on physicians for the formal interpretation of CPET (60%). In addition, exercise physiologists (25%), exercise technicians (10%), and nurses (1%) played a role in CPET interpretation.

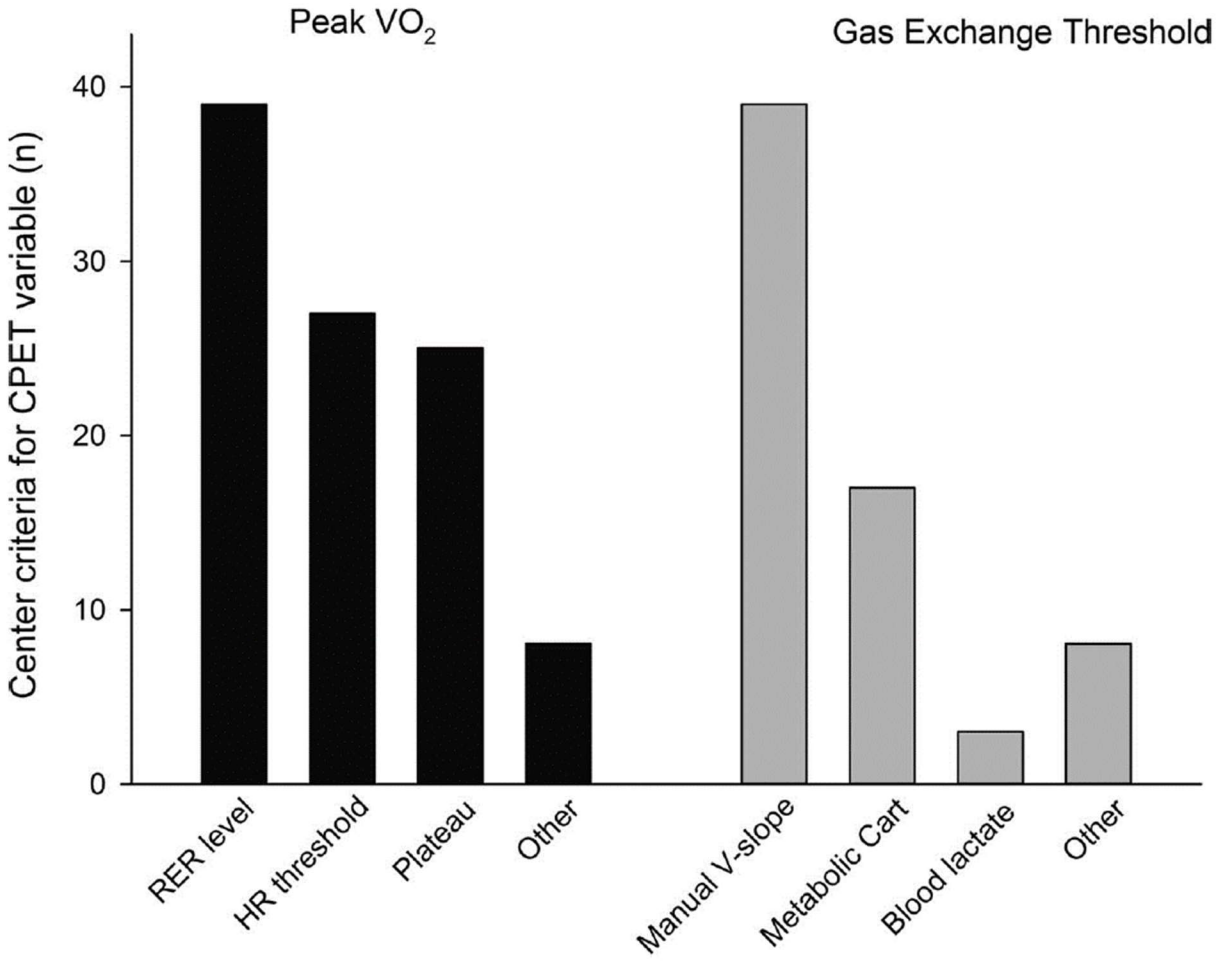


FIGURE 5—Methods used to calculate CPET variables.

Next steps. All 48 centers expressed willingness to participate in a national collaborative of pediatric CPET centers. There was substantial enthusiasm for a variety of objectives of such collaboration with 91%of the centers willing to collaborate in multicenter research, 89% developing reference values, and 82%d developing standardization in interpreting pediatric CPET data.

DISCUSSION

The THEMES DAM and the results of the pediatric CPET survey reported here are essential steps in accelerating multicenter clinical and research applications of cardiopulmonary fitness testing in the pediatric population (Table 3). Widespread implementation will accelerate incorporation of CPET data into the EHR and enhance both traditional prospective multicenter trials and innovative mining of stored CPET data. Future THEMES-informed surveys targeting adult CPET centers will prove useful particularly considering the need to address fundamental issues of exercise responses across the life span and the need to improve data curation and interoperability in the transition of many chronically ill patients from pediatric to adult care (15).

To date, a major deficiency in pediatric exercise science and medicine has been the absence of acceptable reference values, an essential component of CPET analysis. For example, in 2015, Blais et al. (16) noted that "contemporary pediatric reference values for CPET are scarce and are based on heterogeneous exercise protocols and normalization modalities." The authors also highlighted the need in pediatric CPET to normalize data to body size and composition changes that occur with growth and development and advocated for a systematic and robust approach to normalization, which they applied to a prospectively recruited sample undergoing standardized exercise

TABLE 3. Some proposed action items to improve pediatric CPET interoperability based on the survey.

Survey Item	Proposed Action
Variability among CPET ergometers and metabolic carts.	Test individual pediatric participants at different laboratories and compare results. This was an approach used by FBIRN for fMRI comparability.
Calibration	• Identify the optimal timing of calibration and promote standardized calibration reporting across different centers. • Include testing of healthy participants as part of overall calibration procedures. • Calibrating of ergometer (treadmill or cycle) should be performed routinely.
Laboratory personnel	Develop standardized training and certification of pediatric CPET laboratory technicians and directors.
Protocols	Support research that better matches the type of protocol with the specific research or clinical question addressed. For example, submaximal protocols may be more acceptable for pediatric participants with known physiological constraints (sickle cell disease, certain congenital heart disease, etc.)
Analysis of CPET results	Achieve consensus on best approaches to calculate $\dot{V}O_{2peak}$ or gas exchange threshold.
Encouragement	Support research that leads to common approaches and procedures for the verbal encouragement and coaching that inevitably accompanies progressive exercise testing in children.
Networks	• Create a national collaboratory of pediatric CPET centers that share reference values, terminologies, procedures, and protocol. • Encourage mechanisms to share clinical trial opportunities and create a compendium of CPET findings across a wide range of pediatric diseases and conditions. • Build links with adult CPET laboratories to facilitate transition of care in children and adolescents with chronic diseases as they enter adulthood.

protocol. Finding the most useful approach to scale pediatric CPET reference values to body size remains a major challenge because gas exchange variables (e.g., VO_2peak) are highly body mass dependent whereas frequencies (e.g., HR) are less so (17). Different approaches to scaling pediatric CPET variables have been proposed, such as simple ratios using body weight or lean body mass, allometric scaling, or statistical adjustments (18,19). Lively debate and discussion continue to surround each of these approaches. Despite this, whatever scaling or normalization approach is used, the ultimate value of the normalized data depends on the accuracy with which the primary CPET data were collected. The present survey was designed to improve that accuracy.

Blanchard et al. (20) published a carefully conducted reference value study for pediatric CPET in 2018. Their team recruited 228 healthy 12- to 17-yr-old children and performed CPET at two laboratories with different metabolic carts. To ensure standardization, these workers provided common protocols, training of laboratory personnel, and even had study personnel compare their own CPET results at the two laboratories. The investigators did not provide these data or calibration results but did note that there were no significant differences in CPET results in the participants between the two laboratories. Multicenter studies will be needed to ensure truly representative pediatric CPET studies and to develop reference values that can account for regional, racial, and environmental factors as well as the effect of social determinants of health, which are increasingly seen as a modulator of anatomic and physiologic function (21,22).

Procedures for cross-calibration and CPET validation in multicenter research studies have been developed predominantly for studies in adults (23). Among the current studies enrolling both adults and children is the NIH-funded Molecular Transducers of Physical Activity Consortium, which is in the process of enrolling approximately 2700 participants as young as 10

yr old and extending into adulthood with no upper age limit (24). Pediatric participants will be studied at a single center, whereas the adults will be tested at 11 different sites. The molecular pathways linking physical fitness to key biomarkers of health will be scaled to extensive CPET data, which will be collected at several time points in each individual. Common data dictionaries, calibration procedures, and device validation are essential if the results of this large study are to contribute to a life span view of physical fitness and health.

For pediatric CPET, there are limited examples of multicenter clinical research studies. A PubMED search of clinical trials using CPET from 1990 to the present revealed 10 publications in children and adolescents compared with 97 in adults. No consistent standards for harmonization and interoperability exist for pediatric multicenter CPET studies. For example, Amedro et al. (25) conducted CPET in 798 children with a history of congenital heart disease using two centers, which was one of the few pediatric studies that have reported standardization procedures. The strategy used by the investigators for CPET harmonization was to use identical equipment at each of the centers, although no calibration or human-based interoperability data were presented. Implementing a standardization plan requiring clinical CPET laboratories to purchase only one brand of devices and equipment is clearly unfeasible. Moreover, even if multiple laboratories use identical equipment, discrepancies in calibration and technical support can cause discrepancies in data collection.

The CPET survey highlighted the need for data interoperability between major pediatric CPET laboratories in the United States and revealed gaps in implementation of CPET as a diagnostic modality in pediatric conditions. In the context of generalizability theory, the response rate of 48% is considered robust, and research suggests that attempts to increase the response rate would not have improved survey accuracy (26,27). Moreover, the survey responders were well distributed across the U.S. population with no difference between responding and nonresponding centers. Fifty-seven percent of the laboratories performed between 100 and 500 tests per year and 28% more than 500; 56% of referrals were for cardiac/congenital heart disease patients, and only about 9% for pulmonary diseases (like asthma or cystic fibrosis).

These data might represent a true underutilization of pediatric CPET. In 2010, Gilboa et al. (28) estimated the number of children in the United States with congenital heart defects at about one million, whereas there are an estimated 3.5 million children under the age of 18 who suffer from asthma (29). There is an increasing recognition of the value and safety of CPET in chronic, often debilitating conditions like sickle cell disease (30) and cystic fibrosis (31). We found that the percentage of CPET performed for cystic fibrosis was more than twice as large as for sickle cell disease, although there are an estimated 30,000 people in the United States with cystic fibrosis (32) and 100,000 with sickle cell disease (33). The data that could emanate from creating larger coalitions and consortia among pediatric CPET laboratories could also benefit ongoing national efforts to deal with pervasive disparities that continue to negatively affect healthcare across the country (34).

With few exceptions, our survey revealed substantial variability in each of the thematic areas. In the United States, two companies dominate the metabolic carts, the suite of devices that measure flow, gas concentration, and volumes with 48% using Vyaire and 43%MedGraphics. There are, in addition, locally built systems in which engineers at each center assembled separately acquired flow and gas analyzers and developed individualized computer algorithms for key CPET variables. To our knowledge, there have been no published studies examining pediatric CPET reproducibility across the different systems in which, for example, a group of

volunteers were tested at multiple clinical laboratories, nor is there currently any requirement among commercial vendors to conduct such comparisons.

Potential variability in CPET data is not limited to the metabolic cart. We found that most pediatric CPET laboratories conducted studies using either treadmills or cycle ergometers, but we did not ascertain the distribution of protocol type or reasons for which a particular ergometer was chosen among the surveyed centers. In a previous study published in 2019 (35), we noted that in clinical trials involving CPET in children over the past 5 yr, a PubMed search revealed 40 published studies that used cycle ergometers and 113 that used treadmills. The study also found that although data from treadmill and cycle ergometer CPET similarly reflect maturation during critical periods of growth in children and adolescents, neither peak nor submaximal biomarkers are interchangeable. Peak oxygen uptake, for example, was about 6% higher with treadmill exercise testing.

With commercially available metabolic carts, calibration is automated. This has eased the time required to calibrate each component of CPET gas concentration and flow devices. In the early days of breath-by-breath system in the 1980s, before the advent of commercially available metabolic carts, one of this article's authors (D.M.C.) estimated that daily calibration took about an hour. Although automated calibration is convenient and quick, it can inadvertently hide serious system inaccuracies. For example, if a particular laboratory decides to use a different precision grade of test gases (often in an effort to reduce costs) than the one recommended by the manufacturer, measurements of key variables like oxygen uptake could be distorted. This is because the automated calibration paradigms modulate the gas-sensor output to fit the assumed, not measured, concentrations. The majority of pediatric CPET centers calibrated flow and gas concentration daily. Far less consistency was found for an equally critical component of CPET, the treadmill or ergometer, for which 43% of the laboratories never performed calibration. Treadmill and ergometer calibration is less routine and automatic and more time consuming than metabolic cart calibration, but its importance in ensuring the accuracy of CPET data has long been recognized (36).

Pediatric and adult CPET centers perform many tests in people with underlying disease and health conditions, and, fortunately, CPET has proven to be remarkably safe in children and adolescents across a wide range of pediatric diseases and conditions. The issue of onsite and/or available, appropriately trained health care providers is paramount in clinical CPET aimed at children with disease or chronic conditions. There was marked variability in the types of personnel present during testing. In most cases, there was little difference when testing children or adolescents with a known condition, although for such cases a physician was present in 46% of centers compared with 38% with more routine referrals. In 2014, Myers et al. (37) published a comprehensive review of supervision standards for CPET and made several recommendations regarding the training and qualifications of physicians and nonphysicians involved in clinical CPET. Their review, however, focused on adult CPET with an emphasis on safety issues related to atherosclerotic coronary artery disease and other conditions rarely encountered in pediatric CPET.

Beyond the variability in CPET related to the type of ergometer (treadmill or cycle ergometer), the pattern of progressive exercise, the specific protocol, can also affect CPET results in adults (38,39). Few, if any, similar large sample studies exist in the pediatric CPET literature, and there was substantial variability in protocols used in the CPET centers. VO_2peak, still regarded for pediatric centers as the critical CPET variable, is highly effort dependent, and its determination rests on when the participant stops exercise. The pediatric CPET laboratories

differed considerably in the criterion used to determine the end of exercise. Only 2 of the 46 centers used so-called "supramaximal" testing procedures to aid in the determination of VO_2max (40). Moreover, the type and extent of encouragement applied by staff during CPET can also influence test results (41). All of the pediatric centers used verbal encouragement, but without any clear uniformity or standardization. Similarly, the methods used to determine either VO_2peak or the anaerobic/lactate/gas exchange threshold were quite variable.

An encouraging result was the near unanimous willingness of the surveyed centers to become involved in activities that would promote data sharing and communication. Participating in multicenter research, building reference values, and advancing clinical use of CPET and disease pathology in children and adolescents are all critical components of true harmonization. The goal of such efforts is to identify and account for center-specific differences in protocols, devices, calibration, and analytics. Collaborative activities to find best practices for pediatric CPET will accelerate clinical and research applications. Such harmonization need not impose rigid procedures that would constrain centers from tailoring their clinical testing and outreach strategies to meet the needs of their particular environment and population or to inhibit clinical research creativity.

A model to consider in moving toward pediatric CPET interoperability is the Functional Biomedical Informatics Research Network (FBIRN). FBIRN was an NIH-funded program designed to develop methods and tools to enable multicenter functional brain MRI (fMRI) studies (42,43). The challenges identified here for pediatric CPET are surprisingly similar to the challenges limiting multicenter brain MRI studies recognized in the early 2000s that led to the FBIRN initiative. Obstacles to successful collaboration included scanner (device) proprietary and nontransparent data processing and variability, lack of normative data, non-standardized data acquisition protocols, and insufficient reference values from healthy volunteers. The FBIRN project led to the creation of an open-access data repository (44), which is designed to advance both clinical and research applications of MRI to neuroanatomy. The FBIRN model is still used to guide clinical fMRI studies (45). Similarly, the THEMES DAM could become the basis for efforts to harmonize multicenter studies that use pediatric CPET.

The global healthcare environment is constantly changing because of the often unpredictable environmental, economic, and infectious factors. The ability of a child or adolescent to exercise is a bellwether for health and disease and a useful predictor of health across the life span (46). In the past 18 months alone, the COVID-19 pandemic has affected millions of children, and emerging data suggest a profound effect of the disease, or the shutdowns, on patterns of physical activity in children and adults with potential lifelong consequences (47–49). The need for harmonization and interoperability in pediatric CPET has never been greater. Implementing THEMES DAM across multiple centers would create a nimble and responsive mechanism to collect large and robust pediatric CPET data from a variety of laboratories and accelerate the development of reliable reference values, clinical applications, and innovative translational research.

This study was supported by National Institutes of Health Grants: 1) Project REACH (Revamping Exercise Assessments in Child Health) National Center for Advancing Translational Science (NCATS) U01 TR002004, and 2) the UCI Clinical Translational Science Award (CTSA) NCATS UCI TR0001416. None of the authors have conflicts of interest. The authors thank Abdul Malik Shakir and Anita Walden for their contribution to the THEMES DAM.

The results of this study have been presented clearly, honestly, and without fabrication, falsification, or inappropriate data manipulation. The results of the present study do not constitute endorsement by the American College of Sports Medicine.

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