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EDITORIAL COMMENT

One Size Does Not Fit All

A Cliché or a Hard Fact in Cardiac Chamber Quantification?*

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Despite the pivotal role that echocardiography plays in the evaluation of cardiac size and function, visual assessment, which has long been the standard in clinical practice, is known to be fraught by considerable variability due to its subjective nature and experience dependency. This limitation gradually led to the wide recognition that quantitative measurements are needed to avoid subjective interpretation and reduce inter-reader variability. However, quantitative measurements of chamber size and function cannot be clinically meaningful in the absence of normal values. Accordingly, multiple studies aimed at establishing normal values for a variety of parameters of chamber size and function have been performed, ranging from linear dimensions and shortening fraction by M-mode to volumes and ejection fractions by 2-dimensional (2D) imaging, and, more recently, by 3-dimensional (3D) echocardiography.

However, establishing normal values, by definition, relies on studying large numbers of normal subjects. Obviously, this requires a significant commitment of time, effort, and resources. As a compromise, investigators have often settled on reporting data obtained in smaller than optimal samples of a normal population, which have been published to satisfy the need for normal values. As another cost-saving alternative, normal values have been derived from existing databases of images and/or measurements or via meta-analyses of previously published data. For example, the recently published chamber quantification guidelines of the American Society of Echocardiography created normal values from 6 databases (1). In contrast, the study by the EchoNoRMAL Collaboration (2) in this issue of *iJACC* used meta-analysis from >40 studies (2).

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Both approaches have well-known limitations that potentially include the use of nonstandardized methodology, in terms of imaging equipment, as well as acquisition and measurement techniques. For example, combining studies published over long periods of time may be risky, because imaging technology has evolved considerably and has affected image quality and endocardial border definition. Similarly, standards and guidelines for specific measurements change over time, resulting in methodological inconsistencies among studies.

The by-product of the small samples and the nonuniform methodology is variability in normal values among studies, which makes it difficult to detect the potentially important differences between subpopulations with statistical confidence. Nevertheless, multiple studies have reported data that suggest that such differences among sexes, age groups, and ethnicities do exist (1,3). These observations may be important, because clinical decisions are frequently made on the basis of these measurements. Lack of knowledge of intergender or inter-racial differences in normal reference values may lead to suboptimal treatment, and thus, contribute to undesirable outcomes.

The paper by the EchoNoRMAL Collaboration (2) is the largest meta-analysis study to date aimed specifically at addressing the issue of age-, sex-, and ethnicity-specific normal values for the left heart as assessed by M-mode and 2D echocardiography. The investigators should be commended for the amount of work invested to complete this task, which resulted in an extremely useful set of values that summarized the existing knowledge in several tables and diagrams. These data were derived from >22,000 normal subjects, including 5 different ethnic groups. This meta-analysis allowed the investigators to demonstrate the ethnic differences in normal values with statistical confidence, which were previously

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described as "likely," rather than "proven." From this perspective, the study by the EchoNoRMAL Collaboration (2) is a milestone study that fills an important knowledge gap and will likely affect clinical echocardiography practice around the world.

This said, it is important to remember that this was a meta-analysis study, and that the aforementioned limitations inherent to all such studies (4,5) could not be avoided. Therefore, despite the invaluable information we gained, caution still needs to be made when interpreting the findings in view of the nonstandardized methodology used by the studies included. Although the obvious way to avoid these limitations is a prospective study design, it cannot be realistically expected that any investigators would undertake a prospective study with >20,000 normal subjects. Nevertheless, large-scale prospective studies with fully standardized equipment and methodology can be organized (6) and should be on the basis of multicenter collaborations of geographically diverse groups of investigators who serve different ethnic populations, who could be jointly trained to acquire and measure images.

Such future studies should also include newer techniques for the assessment of cardiac chambers that are quickly transitioning from the research arena into clinical practice, such as myocardial deformation by speckle-tracking techniques (7) and volumes by 3D echocardiography (8). Understandably, normal values for these parameters were not included in the meta-analysis by the EchoNoRMAL Collaboration (2), because there were not enough sufficient data to establish them with confidence (8). However, the need for such normal values becomes more obvious as these techniques gain widespread clinical acceptance.

Although this study established the existence of ethnic differences in geographically diverse populations, the influence of changing environments and socioeconomic status remains unknown. In other words, would normal values be the same for a certain ethnic group residing in their home country compared with their counterparts living in a culturally and economically different environment? It is well known that changes in habitat often entail different nutrition, life style, and as result, body habitus, which require indexing to neutralize these confounding factors, which are usually on the basis of body surface area (9,10). However, it remains unclear whether indexing by other allometric measures would provide better-defined normal values in different subpopulations.

Furthermore, because multiple studies have reported consistent differences in values of cardiac chamber size and function indexes measured by different imaging modalities (e.g., 2D or 3D echocardiography, cardiac magnetic resonance, and computed tomography) (11), it is conceivable that multiethnic-, sex-, and age-specific normal values also need to be established for each of these modalities. Thus, multimodality studies, designed to perform measurements in the same subjects would allow intermodality comparisons. Clearly, such a study design would be overly ambitious and costly. As a result, it is likely that we will have to rely on meta-analysis techniques to obtain this valuable information.

One other important issue the EchoNoRMAL Collaboration (2) alluded to in their paper is the cutoff values for different degrees of abnormalities. Although from the clinical point of view, such cutoff values are as important as normality thresholds, there is neither a simple solution nor consensus on the best way to derive such "partition" values. As the investigators correctly pointed out, pursuing this goal would require studying patients with disease, because different grades of abnormalities cannot be obtained from a purely normal population (1). This is because most parameters are not normally distributed. In addition, partition values of abnormalities for the same parameter may vary among disease states. Ideally, partition values of different parameters for different disease states should be established on the basis of outcomes, which is a lofty goal by itself.

From the study by the EchoNoRMAL Collaboration (2) we learned again, and this time with statistical confidence, that one size does not fit all when it comes to quantifying cardiac chamber size and function in different age, sex, and ethnicity groups. Although this study sheds light on this topic, additional studies are needed to fully understand the ethnic differences in the human heart.

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