Editorial Comment

Need for a Global Definition of Normative Echo Values—Rationale and Design of the World Alliance of Societies of Echocardiography Normal Values Study (WASE)

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DEFINING NORMAL IN ECHOCARDIOGRAPHY: CURRENT APPROACHES AND LIMITATIONS

In cardiac imaging, as in any other medical discipline, understanding what is "normal" within a population is fundamental to define the concept of abnormal. While this is straightforward in the presence of a tumor (a yes/no assessment) or an abnormal blood count, defining normal dimensions of cardiac chambers or the normal values of cardiac function poses a significant challenge. Echocardiography is the most widely used imaging modality to assess cardiac size and function, but despite the importance of having "reference limits" to define normal cardiac structure and function in echocardiography, the currently available studies fail to reflect the diversity of populations from around the world.

The American Society of Echocardiography (ASE) and the European Association of Cardiovascular Imaging (EACVI) have recently taken a significant step into defining "normality" in echocardiography. The ASE/EACVI chamber quantification recommendations update published in 2015 made significant progress relative to its previous 2005 version by including normal values and ranges for a variety of left ventricular (LV), right ventricular (RV), right atrial (RA), and left atrial (LA) measurements frequently reported in standard echocardiographic reports.[1,2] These reference values have been derived by accessing the data from a variety of well-designed population-based studies.[3-5] However, the meta-analysis performed to obtain the normal values in the ASE/EACVI document has several limitations, mostly related to the lack of representation of the wider global international community. First, as seen in Table 1, the vast majority of subjects were Caucasian. Few subjects of black race were enrolled, and no Latinos, Asians, or Africans were included in these studies. Second, all studies were conducted in the United States or Europe, further limiting the diversity of the populations assessed. These limitations are particularly important in view of recent publications from different regions around the world suggesting disparities among individuals from different geographies. For example, normative data from China,[6] Japan,[7] and Iran[8] appear to indicate that their "normal" heart dimensions and volumes are smaller compared with those reported in U.S. or European studies. Moreover, the Multi-Ethnic Study of Atherosclerosis (MESA) study has shown differences in heart dimensions between different ethnic groups within the United States.[9] Third, while all studies enrolled adult individuals, the overall population predominantly reflects middle-age adults, with limited representation of young adults or elderly populations. Fourth, each study followed its unique acquisition and analysis protocol, resulting in a heterogeneity of reported measurements. For example, data from only two studies were used to obtain the normative values of the linear measurements reported from the parasternal long-axis view (such as LV wall or internal diameters). Consequently, the normative values reported were each derived from a different number of individuals obtained from different studies. This latter concept is well demonstrated when considering that the normative data reported for biplane LV ejection fraction (LVEF) were derived from only 520 mostly Caucasian adult subjects.

Therefore, while useful for restricted populations in the United States and Europe, the ASE/EACVI recommendations for normative values may not be applicable to individuals of black race or individuals from Asia, Africa, Australia, or Latin America.

The hypothesis that people from certain regions in the world may have cardiac chambers that have different structure and function values compared with European or American Caucasian individuals has been proposed by Lancellotti and others who suggest that direct comparison of cardiac size and function from multiple geographic regions should be performed using standardized protocols that follow strict guideline recommendations and core laboratories to obtain high-quality, reproducible measurements.[10,11] To date, few studies have been conducted following these principles. The recently published Normal Reference Ranges for Echocardiography (NORRE) study is the first large multicenter European study involving accredited echocardiographic laboratories of the EACVI, where image interpretation was performed in a centralized core lab.[12] The main limitation of this study, however, is that the results are mostly representative of a white European population. Studies from countries such as Brazil, Iran, Japan, China, Nepal, or individual European countries have been elegantly conducted and reported.[3-8,13,14] Each of them, however, used different protocols reporting on

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Table 1 Basic demographic characteristics of studies supporting ASE/EACVI chamber quantification recommendations for normal reference values[2]

	Parasternal long-axis view	Apical four-chamber view	Apical two-chamber view	Biplane view
Total number	1,271	2,278	993	520
Data sources	Asklepios (1,019) Flemengho (252)	Cardia5 (1,027) Asklepios (1,006) Flemengho (245)	Cardia25 (588) Asklepios10 (161) Flemengho (244)	Padua (111) Asklepios10 (161) Flemengho (248)
Male, %	39	42	41	40
Race, %				
Male	100 white	80 white	84 white	100 white
Female	100 white	81 black	87 white	100 white
Age				
Male	45 ± 8	37 ± 10	50 ± 8	45 ± 8
Female	45 ± 7	37 ± 10	50 ± 7	

a variety of parameters (Table 2). For example, some studies reported on M-mode measurements, while others published two-dimensional (2D) normal values using a variety of formulas to calculate LVEF or LA volumes. No studies have used a centralized, independent core laboratory for image analysis. Moreover, images were frequently acquired with older, noncontemporary ultrasound machines using a variety of different settings (harmonic vs fundamental imaging). A large meta-analysis has been recently published to provide global normal reference values.[19,20] This meta-analysis of echocardiographic measurements reports on data acquired in 43 studies representing 22,404 subjects. Unfortunately, this study has the same limitations as the other meta-analysis mentioned above. The random variability of the quality and measurements of the different studies used for the meta-analysis confounds the validity of the reported findings. Interestingly, despite these limitations, the meta-analysis study suggests differences in diameters of the LV and LA among different ethnic groups with larger chambers seen in Europeans compared with Asians.

Given the heterogeneity of the methodologies used in single-country studies or the design of the above-mentioned meta-analysis, it is impossible to date to determine with certainty whether the differences in normal values reported in different populations are due to technical reasons or if they indeed indicate real physiological differences in cardiac size and function. Nevertheless, a large subgroup of the LOLIPOP study enrolled 978 healthy individuals of Indian Asian or white European ethnicity living in London.[21,22] Following a standardized acquisition and analysis protocol for LV 2D and three-dimensional (3D) images, this study reported ethnic differences in LV volumes (but not in LVEF), thereby suggesting that the hearts of Asian Indian individuals are smaller than those of white Europeans even after adjusting for age and body size.

The normal reference values for 3D LV and RV volumes reported in the recent chamber quantification guideline document were predominantly derived from the Padua and NORRE studies that reported on medium sized exclusively white populations.[23-25]

ADDRESSING THE LIMITATIONS OF CURRENT STUDIES: RATIONALE FOR THE WORLD ALLIANCE OF SOCIETIES OF ECHOCARDIOGRAPHY (WASE) NORMAL VALUES STUDY

As proposed in the WASE Normal Values Study, many of these limitations will be addressed by performing a head-to-head comparison in which all technical differences in data acquisition between regions will be minimized and standardized by following strict ASE/EACVI recommendations and data analysis interpretation conducted by central and independent core laboratories. The discrepancies in age and gender distribution from many previous studies will be addressed by enrolling individuals from multiple countries, races, and ethnicities equally distributed among gender and adult age groups.

Accordingly, the aims of the WASE Normal Values Study are to (1) prospectively establish normal echocardiographic values for chamber size and function across different nationalities, races, and ethnicities worldwide in a multinational study and to (2) describe and characterize similarities and differences between these groups using standardized protocols for image acquisition, modern echocardiographic machines, and centralized readings to ensure uniform high-quality measurements.

WASE NORMAL VALUES STUDY—METHODS

WASE is an observational, prospective, cross-sectional study of healthy adult individuals. A single encounter with each individual is required for basic collection of demographic information and acquisition of a comprehensive transthoracic echocardiogram (TTE).

Study Organization and Population

The WASE Study is sponsored by the American Society of Echocardiography Foundation in collaboration with MedStar Health (Washington, DC) and the University of Chicago (Chicago, IL) with in-kind donations from TOMTEC (Munich, Germany) and Intelemage/Medidata (Cincinnati, OH). The American Society of Echocardiography Foundation provides funding and strategic support with a staff liaison (Ms. Rhonda Price). The study is coordinated by two principal investigators, Federico M. Asch, MD, FASE, and Roberto M. Lang, MD, FASE. ASE invited all international societies who were members of the ASE International Alliance Partners (as of March 2016) to participate in this study and named a WASE Steering Committee to oversee study operations.

Each participant International Society named a local principal investigator (PI) to lead the efforts in their respective countries and be part of the Scientific Committee. Each PI is tasked with enrolling 100 "normal" healthy adult volunteers not including more than two

Table 2 Characteristics of the main studies reporting normal values to date

	Population	n	2D/3D/Strain/Doppler	Chambers	Standard acquisition	Standard analysis by core lab	Multiethnic	Study design
NORRE[15]	European multicenter study	734	Y, all parameters	2D/3D LV RV LA RA	Guideline recommended echocardiographic approach	Y	N, mostly white European	Prosp
IRAN[8]	Iran, single center	368	2D Simpsons, M-mode diam, tissue Doppler imaging e'	LV RV LA diam	Y	N	N	Prosp, poor image excluded
India[16]	Indian residents, single center	100	2D, Doppler, diastolic function	LV diam and volumes, LA vol, diastolic function with tissue Doppler imaging	Y	N	N	Prosp
JAMP[7]	Japanese	700	LV linear dimension, LV volumes, LVEF, maximum LA volume, LV mass, aorta root diameters and mitral inflow and mitral annular velocities	LV, LA, and aorta	Y	Y	N	Prosp
EMINCA[6]	Han Chinese, multicenter	1,394	2D and M-mode	LV, LA, RV, RA, and Doppler	Y	Y	N	Prosp
South Korea[17,18]	South Korea	1,003	2D and Doppler	LV, LA, RV, RA, and Doppler	Y	Y	N	Prosp
Brazil[13]	One city	295, ages 25–64	M-mode	LV, RV, LA, aorta diam, LV mass	Y	N	N	Prosp
Nepal[14]	One city	126	2D and M-Mode	LV, RV, LA, aortic diam, LV mass	Y	N	N	Prosp

Diam, Diameter; *N*, no; *Prosp*, prospective; *Y*, yes.

centers per country. A "normal" subject is defined as one without history or clinical evidence of heart, lung, or kidney disease. Detailed inclusion and exclusion criteria are listed in Table 3.

Individuals recruited in each country are evenly distributed among six predetermined subgroups according to age and gender (Supplemental Table 1, available at www.onlinejase.com), to allow for adequate intercountry comparisons. Accordingly, only countries enrolling a minimum of 100 individuals with the suggested age and gender distribution will be included in the final analysis. The sample size was arbitrarily determined by the Steering Committee considering previous individual regional reports, perceived scientific needs, and feasibility of study completion (ability of centers to recruit, study costs, logistics at enrolling centers and core laboratories, etc.).

At the time of enrollment, each study subject is informed of the study rationale and methods and provides consent as mandated by each of the enrolling center's institutional review boards or ethics committees.

At the time of echocardiographic acquisition, basic demographic information is collected, including age, gender, race, ethnicity, nationality, height, weight, and blood pressure. For the purpose of the WASE study, the definition of race and ethnicity is adapted from the proposed definitions for the U.S. 2020 census, U.S. Food and Drug Administration, and the United Kingdom 2011 census.[26-28]

ECHOCARDIOGRAPHIC IMAGE ACQUISITION AND ANALYSIS PROTOCOL

A comprehensive TTE is acquired by a physician or sonographer following a study-specific standardized acquisition protocol based on recent ASE guidelines, including 2D and 3D imaging.[2] The protocol was created by the WASE Core laboratories following ASE/EACVI guideline recommendations for cardiac chamber quantification and evaluation of LV diastolic function.[2,29] The use of ultrasound enhancing agents is not allowed in this study to maximize uniformity of data collection, as use of these agents is variable around the world. Moreover, the cost of these agents would be prohibitive in many regions and several measurements planned for this study would be confounded by the use of these agents (3D and strain analysis, several 2D standard measurements). Ultrasound machines used for data acquisition are contemporary (purchased or updated within the last 5 years), with no specific requirement of machine manufacturer, but must be able to acquire 2D, Doppler, and 3D images using uniform settings. Compatibility of acquired images with the workstations used in the core laboratories and compliance with study-specific acquisition protocols is also required and tested for approval for each enrolling center prior to the initiation of subject enrollment.

Demographic information and echocardiographic images (DICOM format) are digitally recorded and transferred to the echocardiographic core laboratories in the United States at the original acquisition frame rate through a web-based, secured transmission platform (Intelemage/Medidata, Cincinnati, OH).

One of the core laboratories is responsible for the 2D, Doppler, and strain data analysis (MedStar Health Research Institute, Washington, DC), while the second is responsible for 3D analysis (University of Chicago, Chicago IL). All image analysis is being performed using a vendor-neutral workstation (Image Arena, TOMTEC, Munich, Germany) following standard protocols. The extensive list of measurements being performed is adapted from the ASE/EACVI chamber quantification and diastolic function guidelines and includes 2D, 3D, Doppler, and longitudinal strain parameters (dimensions and function) for the four cardiac chambers and aorta. Indexing measurements by body surface area will be performed as recommended by the guidelines. Normal values will be reported as a range (upper and lower limits based on mean and standard deviations). Normal values will be presented for the entire population and for subgroups for comparisons (by nationality, race, ethnicity, age groups, and gender). Inter- and intraobserver variability will be tested by recirculating a subset of deidentified cases for a blinded second read by the same operator and by a second operator from the other core lab. This variability analysis will include 2D, Doppler, 3D, and strain measurements.

Table 3 WASE inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
≥18 years old	Pregnant women
No previous cardiac disease	Competitive athletes
No previous lung disease	History of alcoholism
No previous kidney disease	Significant renal insufficiency (blood Cr > 2 mg/dL/ 177 μmol/L)
No history of (or receiving drugs for)	
Hypertension*	
Dyslipidemia*	
Diabetes	
Blood pressure < 140/90 mm Hg	
Body mass index 20–30 kg/m^2†	
≤Mild valvular disease	

*In June 2017, a protocol amendment was approved for allowing, only in the groups age > 65 years, a history of hypertension or hyperlipidemia as long as the blood pressure and hyperlipidemia were well controlled with not more than two medications and there was no evidence of LV hypertrophy in the echocardiogram. This was decided on the basis of the difficulty identifying elderly subjects with no history of hypertension and hyperlipidemia.

†A body mass index of 18–30 was allowed in countries with a smaller body habitus, as perceived to be normal by their regional PI (Japan).

WASE—CURRENT STATUS

After completion of the agreement to participate in the WASE study by the ASE International Alliance Partners, additional centers were invited to enroll subjects to guarantee adequate global representation from all continents. In the United States one center was tasked with enrolling African American subjects, whereas a second one exclusively enrolled Caucasians; in India two centers were included to represent ethnic groups from the southern and northern regions of this country; due to slow enrollment in some of the centers, additional European centers were also invited to participate.

Enrollment started in the fourth quarter of 2016. By June 2018, 22 centers from 18 countries have been recruiting individuals for the WASE study. Latin America is represented by Argentina, Brazil, and Mexico; North America by Canada and two centers in the

United States; Europe by the United Kingdom, France, Belgium, and two centers in Italy; the Middle East by Iran; Africa by Nigeria; Asia by China, South Korea, and two centers each from Japan and India; and the Pacific islands by Australia, Philippines, and Indonesia. The entire list of enrolling centers and their respective PIs is depicted in Supplemental Table 2 (available at www.onlinejase.com). Enrollment is expected to be completed during the fourth quarter of 2018 and will include over 2,000 subjects. Only countries that have completed enrollment of the assigned 100 individuals will be included in the final analysis.

WASE STUDY LIMITATIONS

Some limitations of the WASE study must be acknowledged in advance. While an attempt has been made to be inclusive and represent multiple regions around the world, there will be areas that will be underrepresented such as Africa and the Middle East. Additionally, the diversity of ethnic groups within each country could not be fully represented. We acknowledge that, for example, not all populations within China or Africa may be equally represented as inclusion of all ethnic groups was not feasible. We hope that in the future, the model and study design of WASE can be replicated so that additional countries can be studied. Arguably, the number of individuals enrolled in each country could be larger, an issue particularly relevant to address ethnic diversity within a country. However, we had to find a proper balance between inclusivity of the global international echocardiographic community and feasibility with the available budget and resources. Depending on the results of WASE, countries could consider starting regional projects to address ethnic differences within a country in a more comprehensive manner.

SUMMARY

The current ASE and EACVI recommended echocardiographic normal chamber quantitation values are used worldwide, but, unfortunately, most were derived from Caucasian subjects from the United States and Europe. In addition, methods used for image collection and analysis have not been uniform in studies from individual countries. Therefore, the use of the published normative "reference limits" remains limited. The WASE Normal Values Study provides a unique opportunity to define normal values for cardiac chamber dimensions, morphology, function, and hemodynamics across a widely diverse population of individuals from different races, ethnicities, and nationalities. Furthermore, with the use of strictly standardized image acquisition and analysis protocols, meaningful comparison of groups will be possible to understand similarities and differences among populations worldwide.

SUPPLEMENTARY DATA

Supplementary data related to this article can be found online at https://doi.org/10.1016/j.echo.2018.10.006.

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APPENDIX

Supplemental Table 1 Required distribution of subjects per enrolling center according to age group and gender

Age	Male, n	Female, n
18–40	20	20
41–65	15	15
>65	15	15

The same distribution is enforced in the United States, India, Italy, and Japan for each of their two centers.

Supplemental Table 2 Regional PIs and their respective enrolling institutions (as of June 2018)

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Greg Scalia, MD, FASE	The Prince Charles Hospital, Brisbane, Australia
Patrizio Lancellotti, MD	University of Liege, Belgium
Ana Clara Tude Rodrigues, MD	Albert Einstein Hospital, Sao Paulo, Brazil
Wendy Tsang, MD	University of Toronto, Toronto, Canada
Mei Zhang, PhD	University of Shandong, China
Gilbert Habib, MD	Hôpital La Timone, Marseille, France
V. Amuthan, MD, DM	Jeyalakshmi Heart Center, Madurai, India
Ravi Kasliwal, MD, FASE	Medanta Heart Institute, Medanta, India
Ario Soeryo Kuncoro, MD	National Heart Centre, Harapan Kita, Jakarta, Indonesia
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Kofo Ogunyankin, MD, FASE	Lagos, Nigeria
Edwin S. Tucay, MD	Philippine Heart Center, Quezon City, Philippines
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