

Normal reference ranges for echocardiography: do we really need more?

Patrizio Lancellotti*

GIGA Cardiovascular Sciences, Department of Cardiology, University of Liege Hospital, Heart Valve Clinic, CHU Sart Tilman, Liege 4000, Belgium

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Echocardiography is the most widely used non-invasive cardiac imaging for assessing the cardiac structure and function. Echocardiography has the advantage of low cost, no radiation risk, and great availability. However, as for any diagnostic test, its interpretation depends on its ability to accurately detect abnormalities.¹ Actually, the definition of 'abnormal' relies on the definition of 'normal' and differs according to age, gender, body surface area, and ethnicity.^{2–4} Currently, available echocardiographic 'reference values' that define 'normality' are mostly based on cross-sectional observations and refer to earlier studies obtained in the 1970–80s from North American cohorts, which do not reflect the diversity of the world's population.⁵

Establishing 'normal' reference values for echocardiography represents a major need in the field of cardiology.⁶ Needless to say that the targeted population and the method used to collect the data are vital. Regarding the target population, if not otherwise specified, a standard 'reference' range generally denotes the one in 'healthy' individuals, or without any known condition that directly affects the ranges being established. Regarding the method used, prospective studies are very welcome but still scanty. Therefore, the compilation of large databases can be used to compare values between different ethnic groups, geographic regions, and countries.⁷

The present paper summarizes the process of creating the echocardiographic normal reference ranges of the left heart (EchoNoRMAL) collaboration, how the individual study datasets were combined, and how the reference ranges will be developed.⁸ This article follows the very successful call published in this journal a year ago.⁷ The EchoNoRMAL study is driven by a group of well-known experts in echocardiography. It represents an individual person data meta-analysis of standard echocardiographic measurements obtained from adult volunteers without clinical cardiovascular disease or significant cardiovascular risk factors resident in a wide range of countries. The EchoNoRMAL study aims to develop age-, sex-, and ethnic-appropriate normative reference ranges for common echocardiographic measurements of the left heart.

The population-based cohorts with echocardiographic measurements were identified through thorough literature searches and personal communication. All searches were limited to studies published between 1 January 1990 and 31 December 2011. Studies that recruited >50 volunteers aged ≥ 18 years were eligible for inclusion. Conversely,

studies that included patients referred for an echocardiographic examination, but who were later judged to have been free of disease, were not eligible for inclusion. Two types of echocardiographic studies were finally included. The first concerned published studies that used echocardiograms in acknowledged 'healthy' volunteers. The second derived from population studies in which echocardiograms were used to document the prevalence of a disease (not necessarily published). All these studies had echocardiographic measurements of at least one of left ventricular size or mass, left atrial size, mitral inflow or tissue Doppler, or pulmonary vein Doppler and used at least one measurement modality of M-mode, 2D, or 3D echocardiography.

A total of 43 studies were collected, representing 51 222 subjects, of whom 22 404 adults aged 18–80 years had no clinical cardiovascular or renal disease, hypertension, or diabetes. Wide ranges of ethnic groups were included (African, American black, Asian, Australian Aboriginal, European, Middle Eastern, Pacific, and South Asian). Reference values will be derived using quantile regression or an appropriate parametric regression method to model the relationship between age and pre-defined centiles of each echocardiographic measurement (5th and 95th centiles).

Although this initiative is timely, represents a unique dataset of several multi-ethnic echocardiographic measurements, limitations and sources of variability of the EchoNoRMAL study are inherent to the study design. Several levels of random variation may contribute to the echo measurements, i.e. the quality of the echo exams, images, and measurements cannot be guaranteed, which may impair the quality and strength of the data provided. Other factors may also limit the interpretation of the data such as the definition of 'normal' subjects, the protocol of echocardiographic measurements, and the types of machine and settings (harmonic vs. fundamental mode) utilized. However, despite all these limitations and owing to the lack of consistency in current echocardiographic reference values, the EchoNoRMAL study is a fair representation of 'real-world' echocardiographic measurements. It will provide unique and applicable reference ranges in different ethnic groups for use in echocardiography laboratories worldwide. The EchoNoRMAL study will certainly enhance the value of echocardiography in both clinical and research cardiology.

All these considerations underline the urgent need for large prospective studies involving well-defined 'normal' subjects, carried

* Corresponding author. Tel: +32 4 3667504; Fax: +32 4 3667195. Email: plancellotti@chu.ulg.ac.be

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out in expert centres with standardized protocols for images acquisition, using modern echocardiographic machines and settings, and with centralized readings to ensure homogenous interpretation and high quality data measurements. To date, very few studies have been conducted using these features in the world.⁹ The Normal Reference Ranges for Echocardiography study (NORRE study) is the first European large multi-centre study involving accredited echocardiographic laboratories of the European Association of Cardiovascular Imaging (EACVI).¹⁰ The NORRE study aims to prospectively provide a set of 'normal' values in a large cohort of healthy adults over a wide range of ages (25–75 years old) using both conventional and advanced echocardiographic techniques. Inclusion of the patients has been recently completed, and data interpretation and analysis are underway in the central EACVI laboratory. The first results should be available in early January 2014. One limitation of the NORRE study is that the results will mainly pertain to white individuals. Thus, conclusions concerning other ethnic populations will be limited. Furthermore, a call for comparison with studies conducted with the same high quality standard for images acquisition and analysis will also help to prospectively define sex and ethnic specific reference values for echocardiography.

Meanwhile, the echocardiographic community should continue to use existing echocardiographic reference values and to monitor the emergence of new data defining normality. Among those, the results of the EchoNoRMAL study and the NORRE study will be swiftly implemented in our echocardiographic laboratories.

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