



## Editorial

## Normal reference range values in adult echocardiography: Further evidence that race matters



### Keywords:

Echocardiography  
Ethnicity  
Left ventricle

Transthoracic echocardiography (TTE) remains, by far, the most widely used technique across the globe for assessment of cardiac chamber dimensions and volumes. TTE is safe, low cost, free from ionizing radiation, portable, and quick to perform. Accurate quantification of chamber dimensions and volumes is a fundamental aspect of any TTE study. Although these measurements are performed almost as a reflex by an experienced sonographer or physician, the confirmation of a structurally normal heart is frequently of great help to the clinician managing a symptomatic patient.

The presence of normal left ventricular (LV) wall thickness, chamber dimensions, and cardiac volumes helps to rule out a myriad of pathologies; but in case pathology is detected, we tend to quantify these abnormalities as mild, moderate, or severe, often based upon the degree to which the obtained values differ from our assumption of 'normal' – that is, *how* abnormal are the values. Therefore, we must have a clear idea of what is 'normal' before we can define what is 'abnormal'.

Accordingly, international societies provide guidance on 'normal ranges' for use when making measurements of cardiac structures, for example LV chamber dimensions and volumes. These 'reference ranges' have usually been derived from population or community studies, but it is precisely for that reason that difficulties in extrapolation of such data arise. The previous ASE chamber quantification guidance, dating back to 2005,<sup>1</sup> was dependent upon unpublished data derived predominantly from North American populations between the 1970s and 1980s. More recently, updated combined European/American guidance acknowledges these limitations and suggests need for further study in this area.<sup>2</sup>

A recent, large international collaborative meta-analysis – the Echocardiographic Normal Ranges Meta-Analysis of the Left Heart (EchoNoRMAL) study – confirmed that, amongst over 22,000 adults, upper reference values for LV and left atrial chamber dimensions and volumes were highest amongst (white) Europeans and lowest amongst south Asians.<sup>3</sup> The London Life Sciences Population (LOLIPOP) atherosclerosis substudy compared echocardiographic parameters between healthy individuals – free from

known cardiovascular or cerebrovascular disease – of south Asian and European white ethnic background. In this study, individuals were defined as being of Asian ethnicity if all four grandparents were born in the Indian subcontinent. Asians were found to have significantly smaller LV chamber dimensions and cardiac volumes than western individuals.<sup>4</sup> There is also evidence that these differences are not restricted to Asian populations – the Echocardiography Study of Latinos (ECHO-SOL study)<sup>5</sup> demonstrated variability between the Hispanic population studied and the ASE reference range values, and in addition, complicating matters even further, revealed differences between different Hispanic populations themselves (e.g. Mexicans vs. Cubans). As awareness of the importance of accounting for ethnicity when categorizing echocardiographic measurements increases, a number of studies have emerged proposing normal reference ranges for specific populations,<sup>5–12</sup> as listed in Table 1.

Consistent with this prevailing wind, in this issue of the *Journal*, Bansal and colleagues throw further light on the potential pitfalls in application of western-world normal range values to non-western populations.<sup>13</sup> In a pilot study of 100 healthy Indian volunteers (mean age 34 years), they demonstrate that Indian subjects have smaller cardiac dimensions than the ASE reference ranges. These data from native Indian subjects are consistent with the findings of Chahal et al.<sup>4</sup> who studied migrant Indians in the LOLIPOP study. Furthermore, Bansal and colleagues found that only 58–61% individuals had values that would be classed as 'normal' by currently available reference ranges and also showed that indexing values to correct for body surface area (BSA) reduced – but did not resolve – these discrepancies completely.<sup>13</sup> Interestingly, unlike chamber dimensions, all individuals had an ejection fraction within the normal range – thus implying a similar degree of variation between end-diastolic and end-systolic volumes, such that the EF (dependent on both values) is unaffected.

These preliminary data are limited by the sample size and the relatively young age of the studied subjects; however, it is the first such data in native Indian subjects and highlights the urgent need for appropriate reference ranges for use in India. As this study was conducted in north India, the reader must assume the subjects studied are of north Indian origin and, bearing in mind the variation noted between different Hispanic communities in the Echo-SOL study, it would be important to clarify – in future studies on this subject – if there are significant differences between north and south Indian populations or whether one reference range is applicable cross the entire subcontinent.

**Table 1**

Published studies that produced echocardiographic normal reference range values for male and female subjects from healthy individuals in well-defined ethnic populations. Many parameters were assessed, but as an example, left ventricular diastolic dimensions are listed for men and women in each study.

Study	Population studied	n	Mean age (years)	% male	Mean LVEDD (mm) – men	Mean LVEDD (mm) – women	Important findings/possible limitations
NORRE <sup>5</sup>	European White	734	45.8 ± 13.3	44	46.2 ± 4.8	43.0 ± 4.1	Upper and lower reference limits were higher in men than in women.
EMINCA <sup>6</sup>	Han Chinese	1394	47.3 ± 16.0	49	46.2 ± 4.0	43.2 ± 3.3	Upper and lower reference limits were higher in men than in women. Only Han Chinese race was studied.
ECHO-SOL <sup>7</sup>	US Hispanics	525	53.0 ± 0.5	34	48.0	43.0	Significant differences between different Hispanic races (e.g. Mexican vs. Cuban vs. Central American vs. South American).
JAMP <sup>8</sup>	Japanese	700	47.3 ± 16.0	55	48.0 ± 4.0	44.0 ± 3.0	Most chamber dimensions were smaller than ASE reference range values, but indexing to BSA corrected discrepancies.
Saghedpour et al. <sup>9</sup>	Persian Iranian	368	47.6 ± 9.7	46	47.0 ± 4.2	44.0 ± 4.2	Most chamber dimensions were smaller than ASE reference range values, even after indexing to BSA.
Angelo et al. <sup>10</sup>	Brazilian	295	47.1 ± 9.8	38	49.9 ± 3.8	45.5 ± 3.9	All measurements made using M-mode echocardiography only.
Schwartzman et al. <sup>11</sup>	Brazilian	100	44.2 ± 14.2	48	50.0 ± 4.0	47.0 ± 4.0	Urban population of Porto Alegre studied.
Prajapati et al. <sup>12</sup>	Nepalese	97	27.9 ± 6.6	52	47.5 ± 4.3	43.4 ± 4.1	Studied healthy hospital employees only.

NORRE, Normal REference Ranges for Echocardiography; EMINCA, Echocardiographic Measurements In Normal Chinese Adults; ECHO-SOL, ECHOcardiographic Study Of Latinos; JAMP, JAPANESE Normal Values for Echocardiographic Measurements Project; US, United States; LVEDD, Left Ventricular End-Diastolic Diameter; ASE, American Society of Echocardiography; BSA, Body Surface Area.

Why should any of this matter? Is it clinically relevant if Indians have smaller cardiac dimensions than white populations? It matters clinically for a number of reasons. One obvious example is in relation to valvular heart disease, in particular aortic and mitral regurgitation. Clinical guidelines quote threshold values for LV cavity dimensions above which patients should be referred for surgery. Clearly, this premise relies upon absolute confidence in the normal range values and the growing body of evidence alluded to above strongly suggests that these values should be corrected not just for age, gender, and body size but also ethnicity. Diagnosis of cardiomyopathy is another area of concern – for example, Indian subjects with a mild dilated cardiomyopathy may be falsely reassured if western reference range values are utilized.

A number of other questions remain unanswered in this field. Should we measure end-diastolic and end-systolic dimensions by one-dimensional (M-mode) or 2D echocardiographic techniques? Are the values interchangeable? Do we need to abandon existing reference ranges, derived from old studies with nonstandardized methodologies and performed using considerably older machines with inferior ultrasound technologies? Should we index values for BSA for all ages and all races or only some? Finally, are race and ethnicity interchangeable terms for the purposes of normal range studies?

The existing data suggest that we require age, gender, and ethnicity-specific normal ranges for racially distinct populations for use in daily clinical practice. Reference ranges for dimensions and volumes of all four cardiac chambers are required, as well as normal ranges for spectral and tissue Doppler velocities. Existing studies suggest that, for a country with a population exceeding one billion, a meaningful study in India is likely to require thousands rather than hundreds of subjects – a nationally, coordinated, multicenter study could achieve this lofty goal. The pilot study by Bansal et al. demonstrates that such a study is warranted in the world's most populous democracy for use in India's clinical practice.

### Conflicts of interest

The author has none to declare.

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