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EDITORIAL

Normal reference values for echocardiography: a call for comparison between ethnicities

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Doppler echocardiography has become the standard imaging modality for the assessment of heart valve disease severity and ventricular diastolic function.[1] However, due to the variability in Doppler parameters according to age, it is mandatory to establish reference limits that define normality.[2] Furthermore, differentiation between normal and abnormal diastolic function depends on the targeted population, the method used to collect the data, and the potential overlap between Doppler indices values in healthy individuals and those with diastolic dysfunction.

Currently available Doppler echocardiographic reference values are derived mainly from North American and European population studies with wide heterogeneity of inclusion and exclusion criteria, which may not applicable to other populations. Although several recent studies have attempted to overcome these limitations [i.e. the echocardiographic normal reference ranges of the left heart (EchoNoRMAL) collaboration], particularly for the estimation of cardiac chamber size, very few have focused on Doppler data.[3,4] The Normal Reference Ranges for Echocardiography Study (NORRE Study) is the first European large multi-centre study involving accredited echocardiography laboratories of the European Association of Cardiovascular Imaging, which first provided reference values for the most useful Doppler parameters according to age and gender using conventional recommended echocardiographic approaches and contemporary echocardiographic machines.[5–7]

The NORRE Doppler study confirmed that normal ageing is associated with a number of changes in the heart and vascular system, especially slowing of LV relaxation, which can account for a decrease in mitral *E*/*A* ratio and in e′ velocity. Therefore, age reference values should be taken into account when analysing diastolic function. The e′ velocity recorded from the mitral annulus is a reliable index of myocardial relaxation due to its relative independency on cardiac preload. Some authors preferred to measure e′ at the septal mitral annulus, while others were in favour of measuring e′ at the lateral mitral annulus. In the NORRE study, although only a small proportion of patients with 20–40 years had a septal or lateral e′ <8 cm/s, there was nearly 20% of patients in the 40–60 years group with a septal e′ <8 cm/s, and in the ≥ 60 years group, more than half of these healthy volunteers had a reduced septal e′ <8 cm/s. In contrast, lateral e′ remained >8 in all age categories in most patients. Some indices were however less age dependent. Although there was a progressive increase in *E*/e′ ratio with age, the cut-off value of average *E*/e′ or lateral *E*/e′ remained <15 or 13, respectively, in the majority of patients. None of the patients in the ≥ 60-year group had an elevated *E*/e′ ratio and only a small proportion ($<1\%$) in the 40–60 years group presented with an increased *E*/e′ ratio. Interestingly, there were no significance differences in most of these parameters between men and women. The left atrial volume index, another parameter frequently used in the algorithm for the diagnosis of diastolic function, was increased in 12–18% of the subjects, without significant differences according to age categories. Of note, mitral s′ wave velocities were higher in men than in women with lower values in the elderly. Intriguingly, the tricuspid s′ wave was not affected by age and gender.

Whether the NORRE study results can be extrapolated to non-Caucasian European individuals is still unknown. Ethnicity has been shown to be an important determinant of cardiovascular adaptation of systolic and diastolic function in athletes. Racial and gender differences in large-artery structure and function,[8] endothelial function,[9] the renin-angiotensin system,[10] and levels of vasoactive cytokines[11] are recognized and may partially explain the differences. In the Japanese Normal Values for Echocardiographic Measurements Project (JAMP) study, Doppler data also showed significant differences according to age and gender.[12] Indeed, diastolic parameters assessed by mitral inflow and mitral annular velocities declined with age. As in the NORRE study, the left atrial volume index did not differ in the different age categories. These data are of paramount. Indeed, there has for many years been a discussion in the literature about whether or not left atrial size increases with advancing age in healthy subjects. In the NORRE and JAMP studies, the absence of linear correlations between age and indexed left atrial size strengthens the general hypothesis that ethnicity might not affect some chamber dimensions values when reported to body surface area.

In the Echocardiographic Measurements in Normal Chinese Adults (EMINCA) study, the authors aimed to establish normal reference values of Doppler echocardiographic parameters in a nationwide, population-based cohort of healthy Han Chinese adults.[13] In this study, 40–80% of the conventional Doppler parameters differed with gender and age groups. In accordance with the NORRE

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and JAMP studies, mitral inflow *E* velocity and *E/A* ratio decreased, while *A* and DT increased gradually with ageing in both men and women (with lower values in this latter group). So, an inversion of *E/A* ratio with age should thus likely be considered as a physiologic pattern in elderly subjects in the absence of other abnormal findings. However, the age-related changes in these diastolic function parameters, somehow reflecting a prolonged LV myocardial relaxation, may partially explain why older individuals maybe more prone to develop heart failure with preserved ejection fraction.[14] The authors also found a negative correlation between s′ and e′ waves and age, with values being higher in younger. Conversely, e′ measurements did not differ between men and women in the whole population but declining more rapidly with advanced age in women. These data suggest that LV diastolic relaxation is related to other factors than age and gender. The post-menopausal hormonal status in women might play a role, though this was not tested in the study. As in the NORRE study, *E*/e′ ratio was correlated with age and remained <13 or <15 in all patients. For average *E*/e′ values between 9 and 13 in subjects aged >60, changes in mitral inflow velocities with Valsalva manoeuvre, the difference in duration between pulmonary vein Ar velocity and mitral A velocity (<0 ms), and left atrial volume index (<34 mL/m^2) were in the normal ranges, indicating that the LV filling pressures were normal in these subjects. As in previous studies, septal (<8 cm/s) and lateral e′ (<10 cm/s) velocities were reduced in some patients >60 years, though the exact percentage per category was not reported. As in the NORRE study, the tricuspid s′ wave was not affected by age and gender.

As with the JAMP study, direct comparisons between the NORRE Doppler and the EMINCA studies have not been performed. However, all these studies concerning healthy populations have highlighted the need for age- and gender-specific reference values especially for the diagnosis of ventricular systolic and diastolic dysfunction and for the estimation of left ventricular filling pressures. Though the effect of ageing on function parameters is understandable, the reasons for the differences between genders are not completely understood.

Finally, the NORRE, the JAMP, and the EMINCA studies clearly demonstrated that we are moving into the right direction. They call for comparison with other studies conducted with the same high-quality standard for images acquisition and analysis to prospectively define sex- and ethnic-specific reference values for echocardiography.[15]

Conflict of interest: None declared.

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