Method Errors or Unexplained Biological Information?

To the Editor:

Left ventricular mass (LVM) is an indicator of cardiovascular status, integrating multiple adverse pathophysiological influences and a potent, independent predictor of prognosis, making definition of optimal methods to distinguish abnormal from normal LVM a matter of high clinical priority. Different methods have been used to account for body size in the definition of “normal” LVM, and there is agreement that the allometric approach is not sufficient to capture the extent of abnormalities, especially in obese populations. In the July issue of Hypertension, Chirinos et al1 studied apparently normal members of 2 adult populations aged 35 to 55 and 45 to 84 years old and proposed a new exponent of body height (height1.7) to normalize LVM. This exponent is substantially lower than the allometric signal (height2.7) that we initially proposed,3 from a normal-weight population including infants, children, adolescents, adults, and elderly. It is also lower than other allometric powers (2.5 to 3.0) identified in other young populations, as well as in children, adolescents, adults, and elderly. It is also lower than other allometric powers (2.5 to 3.0) identified in other young populations and even lower than the exponent of 2 proposed by the Framingham Heart Study in an adult population.

The allometric approach to identify left ventricular hypertrophy (LVH) increases the prevalence of LVH, without decreasing the LVH-associated relative risk,4,5 thus increasing the population risk attributable (PAR) to LVH.4,5 PAR is the proportion of the incident disease (cardiovascular event) in the (exposed and nonexposed) population that is attributed to the exposure to a risk factor (LVH). PAR, therefore, represents the potential number of events that could be avoided by removing the exposure, thereby identifying risk predictors most relevant for public health.

We measured PAR of different methods to define LVH in the cohort of the Strong Heart Study,4 using partition values for definition of LVH, obtained from a reference normal population of the same cohort (using mean+1.96 SD). We found that normalization for height2.7,5 maximized PAR for composite fatal and nonfatal cardiovascular events, compared with all other methods, both in the whole cohort (15.54%) and in the hypertensive subpopulation (16.58%), at similar (or slightly lower) age- and sex-adjusted hazard ratios (16.58%), at similar (or slightly lower) age- and sex-adjusted hazard ratios.

Because the prevalence of obesity is very high in the Strong Heart Study cohort, another population from Italy was also studied, the Massa Ventricolare Sinistra nell’Ipertensione population,3 with modest prevalence of obesity (<25%). In this population, we did not find any difference among the methods of normalization of LVM, with similar PAR, whatever approach was used.

After the report by Chirinos et al,2 we calculated the PAR using the new allometric signal (height1.7) in the same Strong Heart Study cohort used for our previous report.4 Characteristics of the 2400 participants and methods for calculation of PAR have been reported in detail.4 Briefly, we used a traditional formula merging age- and sex-adjusted hazard ratios for composite fatal and nonfatal cardiovascular events with a prevalence of LVH, based on LVM/height1.7. Thus, mean+1.96 SD of LVM/height1.7 in the same reference normal population of 251 Strong Heart Study subjects was used for the definition of LVH.4 The normal average value of LVM/height1.7 was 56.4±11.4 g/m-1.7 (ie, 59.2±2.6 g/m-1.7 in men and 54.3±9.9 g/m-1.7 in women).

When using the single partition value of 77.5 g/m-1.7, the sex-specific prevalence of LVH in the whole population was 17.5% in men and 18.4% in women (exact 2-tail P=0.614), whereas when using sex-specific partition value (83.2 and 73.6 g/m-1.7 in men and women, respectively), LVH was found in 10.1% of men and 25.6% of women (P<0.0001).

The age- and sex-adjusted hazard ratios in the whole Strong Heart Study population were 1.76 (1.21 to 2.55; P=0.003) for the single partition value and 1.53 (1.04 to 2.25; P=0.03) for the sex-specific partition value. Thus, the PAR was 12.03% (9.55 to 15.05) and 9.58% (6.98 to 12.18), respectively, both lower than the 15.54% found using LVM/height2.7 in our original report.4

In the hypertensive subpopulation (354 men and 672 women), prevalence of LVH based on LVM/height1.7, was 25.9% with a single partition value and 27.9% with a sex-specific cut point. The age- and sex-adjusted hazard ratios were 1.59 (1.01 to 2.47; P=0.04) with a single partition value and 1.47 (0.92 to 2.34; P=0.10) with a sex-specific partition value. Respective PAR percentages were 13.30% and 11.63%, both lower than the 16.58% found with LVM/height2.7.4

We also tested the new allometric signal (height1.7) in the Massa Ventricolare Sinistra nell’Ipertensione population,5 using the same criteria as in the original article.5 The mean normal value of LVM/height1.7 from our reference adult population (n=228) was 57.0±13.2 g/m-1.7, and the 95th percentile was 80.2 g/m-1.7. The sex-specific average values were 60.7±12.6 g/m-1.7 in adult men and 51.3±12.2 g/m-1.7 in adult women, and their 95th percentiles were respectively 81.5 and 74.6 g/m-1.7, respectively. The prevalence of height1.7-based LVH in the Massa Ventricolare Sinistra nell’Ipertensione population was 51.9% (57.4% in men and 48.5% in women; P=0.006), using the same partition value for men and women, and 58.3% (55.9% in men and 59.8% in women; P=0.024) with sex-specific partition values. The age- and sex-adjusted hazard ratio was 1.53 (0.87 to 2.68; P=0.141) with a single cut point and 1.05 (0.89 to 2.88; P=0.114) with sex-specific cut points. The PAR percentages were 21.6% and 26.1%, respectively, indistinguishable from the PARs obtained with the other indices.3 This finding confirms that, in the presence of a low prevalence of obesity, there is no appreciable prognostic difference among the different methods of normalization of LVM in the identification of LVH.

Thus, the new allometric signal proposed by Chirinos et al2 works but is less efficient than the allometric signal obtained using the entire life age span. In agreement with the findings of Chirinos et al,2 we find a significant negative relation between LVM/height2.7 and height (r=-0.30 in the Strong Heart Study; P<0.0001), but we do not have good reasons to affirm that this is attributed to error rather than to unexplained biological phenomena. The substantial method difference between our original reference populations3 and the populations studied by Chirinos et al2 is the age span, and we speculate that the allometric signal obtained from a wide range of age might include biological information that otherwise is lost with a more limited age span. This might well explain the discrepancy between mathematical evidence (residual relation) and prognostic relevance.
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