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Ratios and regressions in body size and function: a commentary

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RECENTLY, Toth et al. (4) found that the ratio of peak oxygen consumption ($\dot{V}O_2$) to fat-free mass (FFM) was greater in a group of men than in a group of women. They suggested that the ratio approach was inherently misleading in assessing cardiorespiratory fitness and recommended that regression-based approaches [e.g., analysis of covariance (ANCOVA)] should be used to compare any and all size-related variables in different groups of subjects. We believe that the spurious results suggested by Toth et al. have little to do with ratios per se; rather, problems may result from the inappropriate use of ratios, or any other analytic tool, used to compare physiological values in populations that differ in size or gender. Ratios of physiological function to body size have proven to be a convenient, often revealing, and useful first step in analyzing the underlying biology of size and function. An overzealous interpretation of Toth et al. could inhibit investigators from using these approaches that are effectively and widely used in physiology and clinical medicine.

Toth et al. studied the relationship between peak $\dot{V}O_2$ and FFM in groups of men and of women. They calculated the linear regression of peak $\dot{V}O_2$ vs. FFM in both groups and found that the regression slopes were positive, significantly greater than 0, and not different between the men and the women. In addition, the y-intercepts of the regression equation were negative and differed significantly from 0. They found, as expected, that men had greater values of FFM and absolute peak $\dot{V}O_2$. Finally, when the peak $\dot{V}O_2$ was normalized to FFM, the values of this ratio were greater in men than in women.

In Fig. 3 of the article by Toth et al., the peak $\dot{V}O_2$ and the peak $\dot{V}O_2/\text{kg}$ are presented and, as noted, were greater in men than in women. However, in Fig. 3 (middle), the authors presented the covariance data showing that the ANCOVA "adjusted" mean peak $\dot{V}O_2$ was the same in men and women. They concluded that by using the regression method, "no difference [in peak $\dot{V}O_2$] between males and females was noted." The authors suggested that the contradictory results of the ratio analysis and the regression (ANCOVA) analysis resulted from inherent inaccuracies of ratios. We believe there is no contradiction in these results; rather, both ratios and regression methods are valid but designed to answer different questions. Ratios are helpful in providing information about size-function relationships in a given individual, whereas the regression analysis can help one to understand the mechanisms responsible for different mean ratios that occur between specific study samples or population groups.

It is first useful to examine the mathematical relationship between the ratio of two variables (peak $\dot{V}O_2$ and FFM) for a given subject and the regression between peak $\dot{V}O_2$ and FFM in a group of subjects (Fig. 1). Linear regression analysis of peak $\dot{V}O_2$ as a function of FFM leads to

$$\text{peak } \dot{V}O_2 = a \cdot \text{FFM} + b$$

where a is the regression slope and b is the y-intercept. Thus

$$\text{peak } \dot{V}O_2/\text{FFM} = a + b/\text{FFM}$$

The relationship between the ratio of peak $\dot{V}O_2/\text{FFM}$ and FFM in this case is an hyperbola. As FFM increases, peak $\dot{V}O_2/\text{FFM}$ reaches an asymptote that is equal to a . If b is positive, then peak $\dot{V}O_2/\text{FFM}$ will tend to decrease with increasing FFM; if b is negative, then peak $\dot{V}O_2/\text{FFM}$ will increase with FFM. If b is zero, then the ratio peak $\dot{V}O_2/\text{FFM}$ is a constant a and is independent of the FFM.

It can be seen from this analysis that the observations of Toth et al. are internally quite consistent. As shown above, the positive regression slopes and negative y-intercepts from their regression analysis of the male and female groups would predict that the ratio of peak $\dot{V}O_2/\text{FFM}$ would be greater in men (whose mean FFM was larger than in women). This observation from the ratio analysis is no more artifactual than are observations derived from linear regression analysis. Using ratios is another way to express the naturally occurring relationship between peak $\dot{V}O_2$ and FFM in the sample population of men and women studied by Toth et al.

At the core of the criticism of ratios by Toth and other investigators (2, 3) is a repeated argument concerning underlying assumptions. Toth et al. write, "Mathematically . . . the expression of peak $\dot{V}O_2$ as a ratio assumes a linear relationship between peak $\dot{V}O_2$ and fat-free mass . . . with a y-intercept equal to zero." This statement is only true in a very narrow sense (i.e., for an individual), and it inadvertently tends to confuse the difference between ratios of x, y variables of individual subjects and the statistically derived slope of the regression of x and y variables in a sample population (Fig. 1). When the linear regression slope is calculated in a population of x, y pairs, the y-intercept is not assumed to be 0; the method determines the single straight line that best fits the data in a given population. Neither "slope" is inherently fallacious, just different.

However, the recommendation of Toth et al. that "a

FIG. 1. Linear regression slope, ratio slope, and the relationship between ratios and fat free mass (FFM) in data set generated by Toth et al. (4). Solid circles are arbitrary data points. *Top:* ratio of single x , y pair can be described as a slope with a 0 y -intercept, but this is not the same as linear regression slope of best-fit line through a population of points. *Bottom:* in case of data set of Toth et al., ratio of peak $\dot{V}O_2$ to FFM increases with increasing FFM. This reflects negative y -intercept and positive slope that was observed in sample population studied by Toth et al. Women (whose FFM is generally lower than men) do have lower ratios of peak $\dot{V}O_2$ to FFM. This is not an artifact but reflects real differences in population studied. Ratio and regression slope yield different but equally valid insights into particular biology of size and function in this sample of men and women.

regression-based approach should be used to normalize peak $\dot{V}O_2$ " (seemingly, under all circumstances) may lead to substantial misinterpretations. As noted, Toth et al. contrasted the male-female difference in the ratios of peak $\dot{V}O_2/\text{FFM}$ with their finding that the ANCOVA-adjusted means were the same in men and women. The apparent discrepancy between the "ratio method" and the regression approach (of which ANCOVA is a special case) results from the nature of the statistical "adjustment" used in ANCOVA. ANCOVA defines an "expected" value of peak $\dot{V}O_2$ as a linear function of FFM and then computes the "residual" or difference between the observed and expected values. The "adjusted value" for a subject is the expected mean peak $\dot{V}O_2$ (derived from combined data of both groups) plus the residual for that subject (see their Eq. 7). The "adjusted mean" (see their Eq. 11) is the average of the adjusted individual values. The adjusted means in the data of Toth et al. are equal

because both the men and women were equally well fit by the regression model.

The fact that the adjusted mean peak $\dot{V}O_2$ is the same in men and women cannot be construed to indicate that there was no real difference between the mean peak $\dot{V}O_2$ or the ratio of peak $\dot{V}O_2/\text{FFM}$. Rather, the ANCOVA finding suggests the possibility that the observed differences might be accounted for by the covariate, that is, by the fact that FFM was different in the men and women. The ratio method and ANCOVA are not inherently contradictory; rather, they are analytic tools used to gain different kinds of information about the relationship among variables in a given data set.

Toth et al. found that the peak $\dot{V}O_2/\text{FFM}$ is greater in men than in women. Per unit FFM, men generally achieved larger peak $\dot{V}O_2$ than did women, and this a convenient and illustrative first step in attempting to determine how body size may influence cardiorespiratory function. The finding of different ratios in men and women should not be construed to mean that men are "fitter" than women. Body size and perhaps gender are determinants of peak $\dot{V}O_2/\text{FFM}$; thus, these factors need to be considered when establishing normal standards for as controversial a concept as fitness. However, the observation should stimulate investigation into the underlying mechanisms. Is the difference in peak $\dot{V}O_2/\text{FFM}$ purely size related; i.e., do smaller humans in this age group, regardless of gender, have a smaller proportion of FFM as muscle? Is muscle mitochondrial density the same in men as in women?

The labeling by Toth et al. as inaccurate "the ratio method as an approach to compare biological data that are body size dependent" is overstated. In fact, many size-dependent ratios are used effectively in physiology and clinical medicine, even though it is not recognized that the values are normalized to some aspect of body size. For example, even though one cannot measure whole body hemoglobin in a living organism, the amount of hemoglobin in an aliquot of blood is easily determined. The normalized value (g/dl) is, in effect, the total circulating hemoglobin normalized to plasma volume, a variable that is clearly dependent on body size. Real differences in this ratio, the hemoglobin concentration, exist between adults and children and between men and women (1). Inappropriate application of the regression approach of Toth et al. might lead to the conclusion that these differences were merely "artifacts."

The improper use of measures and statistical methods will give spurious or misleading results, and this occurs more frequently than one would like in the medical literature. Many times a perfectly sound statistical method is used incorrectly, e.g., a t -test on very skewed data. We have attempted to demonstrate that the argument that ratios of physiological function or quantity and body size are inherently inaccurate is not correct and potentially misleading. The problems identified earlier by Tanner (3) and more recently by Toth et al. are not in the ratios themselves but, rather, in the way the information is used.

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