Commentary

Role of reference values in making medical decisions

In this issue of the Indian Journal of Medical Research, Aggarwal and colleagues discuss the applicability of Caucasian spirometry reference values to Indian patients. They address the important issue of selecting and using appropriate reference values and provide strong evidence that reference values based on Caucasian subjects are not transferable to Indian patients even when the fixed 10 per cent adjustment often recommended as an acceptable adjustment for ethnic differences is made.

This paper also provides an opportunity to briefly review the role of reference values in clinical decision making. The concepts and the evolution of reference values are discussed in detail by Solberg and Grasbeck.

Physicians make and analyze hundreds of clinical observations every day using patient histories, examination findings, radiographs, and lab data without thinking that every analysis involves reference comparisons. A simple example of the process is illustrated in the Fig. Let us say you are listening to a patient’s heart and you hear a murmur that is not ‘normal’. You just made a reference comparison (what you heard compared with your understanding of sounds from a healthy heart). You then compare the murmur to your memory of sounds made by different valve abnormalities (illustrated as diseases A-D in the Fig.). You have just made four more reference comparisons though they may not be the formal comparisons you would use in interpreting a lung function test. Your ability to make the correct diagnosis hinges on the accuracy of your observations and the reference comparisons you made. Failure at any step could lead to an error in diagnosis.

Comparisons of numerical data can be made with risk based numbers (listed as ideal in the Fig.) or population based reference values (Fig.). Comparison with risk based reference values can be illustrated with cholesterol levels. A cholesterol level of 220 mg/dl in a 65 yr old American man would probably be well within the range of values measured on healthy middle aged American men and by that comparison would be ‘normal’. But if you compare the observed values to values associated with an increased risk for cardiovascular events, you might prescribe a change in lifestyle and a medication. When the patient returns and a follow up cholesterol level is obtained, you will likely compare it to both the earlier one (comparison to self) and to the risk-based reference information. These illustrations make the point that our success in all medical decision making depends as much on selecting and properly using reference values and their limits - the boundaries that lead to changes in action - as it does on getting the measurements correct.

What is in a name? In interpreting reference values for spirometry, we typically compare a patient’s measured values with reference values drawn from population studies and labeled ‘normal’ values. The lower limit of the ‘normal’ range is most commonly defined as the lower 95 per cent confidence interval. Patient values above that demarcation are often arbitrarily labeled ‘normal’ while those below are labeled ‘abnormal’. The terms ‘normal’ and ‘abnormal’ are problematic because they may inaccurately imply health or disease. The shape of the distribution is also important. Decision limits for lung function are usually calculated assuming that the
distribution of the data is Gaussian. This assumption is usually correct for traditional values including FEV$_1$ and forced vital capacity (FVC) but is incorrect for the instantaneous and mid flows (e.g., FEF$_{25-75\%}$).

The picture is further compounded because errors in interpretation will increase with the number of tests applied and when the prior probability of disease is low (e.g., screening asymptomatic, low risk individuals). Vedal & Crapo$^4$ pointed out that the false positive rate was 24 per cent when a full set (14 comparisons) of pulmonary function tests was applied to healthy individuals.

Choosing what limit of the reference range to use is an important issue. Using only a lower limit is appropriate for spirometry and diffusing capacity since the clinical question being asked is if the measured value is too low. However, using a different reference comparison, the laboratory technician should respond when measured values exceed 130-140 per cent of predicted. Townsend$^5$ reported that unusually high measured values suggest a measurement error often due to a malfunctioning flow sensor. This reference comparison should cause the technician to check the instrument.

Upper and lower limits are appropriate for lung volumes where the clinical question may involve a value that may be either too high or too low.

What are the best reference values for spirometry? For a single individual, the best reference would be the patient’s own measurements obtained at a time when she/he was healthy. Most reference values have a distribution that is roughly ± 20 per cent (a 40% range) of predicted about a mean of 100 per cent. A person who started at 120 per cent of predicted would have to lose 33 per cent of his/her lung function before test results would fall outside the normal range. Once a ‘healthy’ level has been established for an individual, intra individual variability about this value may be as little as ±5 per cent and decline is more easily detected. It is obviously impractical to obtain spirometric measurements on everyone. It is, however, quite reasonable to obtain them on individuals at risk of lung injury from toxic or industrial exposures.

Pulmonary function laboratories should select reference values using the following principles$^6$.

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**Fig.** This figure illustrates the variety of reference comparisons that might be made for a single observed value. The most common comparison is with data based on healthy subjects. Other reference comparisons include comparisons to a variety of diseases, previous values, and values that convey risk (ideal comparison) even when they would pass the healthy subject comparison.
Methodological criteria: Instruments and procedures used to generate the reference values should meet current standards. The reference population should be well defined, of reasonable size and the limits of the reference range should be well defined.

Epidemiologic criteria: The reference values should be biologically appropriate to the clientele you serve with attention to age, height, gender, and ethnic characteristics. Some cautions in using reference equations include: (i) Reference equations should not be extrapolated beyond the reported ranges of the age and stature of the reference population, this is especially important when testing young children; (ii) appropriate limits of the reference range should be used and 80 per cent of predicted is not one of them; and (iii) one should be more cautious in the interpretation when the measured value is close to a threshold, the situation where errors are more likely to occur. When possible, clinical information should be used to make these ‘close calls’.

The need for appropriate reference values may appear to be settled but there are at least two areas that cry out for further exploration. The first centers on how data are displayed. The way measured data, reference values, and reference limits are presented can either contribute to interpretative errors or help minimize them. Clinical chemistry laboratories have begun to work on this2,8 but, to my knowledge, it has not been formally addressed in pulmonary function test reports. Improving the way reports display measured values, reference values, and their appropriate limits will reduce interpretative errors.

The other, more difficult but perhaps more useful, area of inquiry for pulmonary medicine is in developing a means of establishing clinical prior probabilities of respiratory disease to assist in interpretations. These would be most helpful when values are near thresholds. An algorithm such as that used to diagnose pulmonary embolism might be a good model.

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