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EDITORIAL

Measuring bronchial responsiveness in epidemiology

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The standard measure of bronchial responsiveness is the dose or concentration of a provocative agent, such as methacholine or histamine, that causes a 20% decrease in forced expiratory volume in one second ($PD_{20}FEV_1$ or $PC_{20}FEV_1$). In a chest clinic even high doses can be applied, as emergency situations that may occur in patients with a large decrease of their FEV_1 can be handled appropriately. In population studies, the information that can be collected by challenge testing is limited. For safety reasons, subjects with poor pulmonary function are excluded from testing, although they might be subjects with increased bronchial responsiveness. Safety considerations and side-effects, particularly those of histamine, limit the maximal dose that can be applied. Thus, quantitative information is restricted to the 15–25% subjects with a measurable PD_{20}, whereas in the majority of cases the information is purely qualitative: responsive or not. No results are obtained from those subjects who were excluded from testing. This situation is known as censoring. Censoring limits the possibilities for statistical analyses, such as ordinary linear regression.

The criterion of a 20% fall in FEV_1 was chosen because the random error in the measurement of FEV_1 is 3–5%. To differentiate between a random decrease and a meaningful decrease of FEV_1, a change of 10% [1] and, later on, of 20% [2] was considered appropriate, and was included in standard protocols. Random error may be a problem in clinical situations, where one has to make decisions concerning diagnosis of patients as asthmatics and subsequent treatment. In epidemiological studies, random error causes loss of precision and weakens associations, but it does not introduce bias. For this reason, the choice of the criterion of 10 or 20% decrease may be less relevant in population studies.

In 1987, O'Connor *et al.* [3] proposed a simple index of responsiveness in population studies, the dose-response slope. This is calculated as the percentage fall in FEV_1 from the post-saline value to the FEV_1 at the total cumulative dose, divided by the total cumulative dose. This simple two points slope solves, at least in part, the problem of incomplete information, by providing a measure of slope for all subjects that performed a challenge test, and also for subjects with a decrease of FEV_1 of less than 20%.

Dose-response curves may be linear, exponential, hyperbolic, or logarithmic [4]. The dose-response slope according to O'Connor *et al.* [3] is, by definition, linear and thus may not always be representative of the real dose-response curve. Subjects may have different sensitivity and reactivity to provocative agents [5]. In the case of high sensitivity and low reactivity, the dose-response slope will provide a reasonable representation, but this will not be true in the case of low sensitivity and high reactivity. In general, it will be impossible to express both the shape and the position of the dose-response curve by a single index, such as PD_{20} or slope [6]. Ideally, when considering the dose-response curve challenges should be continued until the maximal response plateau has occurred [7]. In most cases, this will not be possible in an epidemiological study, although it may yield important additional information [6, 8]. Theoretically, the maximal response plateau may have any value between 0 and 100%, and may be reached at a very low or at an extremely high dose. For many patients the challenge test is terminated before the maximal response is reached. Even in the case of a ≥20% decline of FEV_1, neither PD_{20} nor dose-response slope gives information on the maximal response. If the highest dose of the protocol has been given without a fall in $FEV_1 \geq 20\%$, the maximal possible response may have been less than 20% (and may be unnoticed!), or remains uncertain.

If a 20% decrease of FEV_1 was not achieved at the highest dose, one might calculate a PD_{20} value by extrapolation from the dose-response curve. However, this is strongly discouraged, even if the extrapolation was not extended beyond one doubling dose. Because the dose-response slope is based on the same limited number of measurements, it is unlikely to provide additional or more reliable information than extrapolation of PD_{20} values. In a random population sample, extrapolated PD_{20} and dose-response slope had similar distributions, and distinguished equally well between subjects with and without symptoms [9]. Recently, Peat *et al.* [10] reported a reanalysis of the Busselton data, using dose-response slope as an index of responsiveness, elaborating the associations of various factors with bronchial responsiveness. To the extent that this was additional information on the basis of extrapolation, it should be interpreted with some caution.

Assessing dose-response slopes provides a measure of responsiveness for all subjects. Additionally, the measure is continuous and, at first sight, these slopes are easy to compute. However, the distribution of the measurements should be approximately normal to allow their use in regression analyses. In the case of dose-response slopes this requires log-transformation, with or without the reciprocal. A constant has to be added to all slope values, because there are always zero and negative values of slopes, and this is not allowed when taking the log.

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This makes calculations somewhat more complicated. Furthermore, the use of different constants in different studies or surveys may prohibit comparison of results from different investigators. However, the most serious disadvantages are that coefficients are hard to interprete and the necessity for recalculation of all results into a standard form, *i.e.* percent decrease in FEV_1 per dose of provocative agent.

Dose-response slopes calculated by more sophisticated methods, as described by CHINN *et al.* [11] in the current issue of the ERJ, essentially offer similar problems. Another way to overcome the problem of censored data is the assessment of regression methods for censored data that allow analysis of PD_{20} as a continuous variable. The paper by CHINN *et al.* [11] provides an evaluation of dose-response slope, least-square slope and PD_{20} using a regression method for censored data. Repeatability, normality, stability of variance, applicability, and interpretability of the various measures are discussed. These authors conclude that there is little to gain by assessing dose-response slope, compared to the use of PD_{20} with assessment of techniques for censored data. They base their conclusion mainly on statistical considerations.

Intuitively, it seems unlikely that any of the above discussed measures of bronchial responsiveness will provide additional insight about responses to doses or concentrations that have not been administered. Therefore, methodological, statistical, computational or practical considerations may direct the decision for a specific measure. In general, it will be important to know whether different measures of bronchial responsiveness or different analytical methods applied to the same dataset reveal similar relationships between various risk factors and responsiveness. More than one measure of responsiveness should be used in the analyses. For instance, in addition to responsiveness as a censored variable, dose-response slope and/or a binary variable should be applied. Advocating one of these measures as the single best is a position that is not tenable.

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