Exhaled Nitric Oxide (eNO) Measurements With the New evernoa Device Are Valid and Reproducible Through an Extended Range of eNO Levels

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Exhaled nitric oxide (eNO) is a biomarker that is suggestive of type 2 airway inflammation, with potential applications in respiratory allergic diseases, including diagnosis of asthma, patient phenotyping to ensure a good response to specific biologics and corticosteroids, and assessment of adherence [1,2]. Although numerous publications analyze clinical uses of eNO, few studies provide data on whether measurements performed with different devices are valid and comparable [3]. The aim of this study was to compare the usability and the clinical validity, accuracy, reproducibility, and degree of agreement of FeNO measurements made with the NIOX VERO device (Circassia), which is the reference technique and performs very well in comparison with the more accurate measurements provided by electrochemiluminescence [4], and the evernoa eNO analyzer (Eversens). Both devices are based on electrochemical sensors and follow the recommendations of the American Thoracic Society/European Respiratory Society [5], although recording of measurements with evernoa makes the measurements simpler, since previous inhalation through the device is not necessary. A more accurate description of these devices can be found in the Supplementary material.

We performed a single-center, cross-sectional study based on randomized measurements. The study population comprised 196 patients (18 to 74 years old). Most (76%) had an allergic asthma phenotype, 10% had a nonallergic eosinophilic phenotype, and only 4% had noneosinophilic asthma. The remaining patients (10%) had allergic rhinitis. Half of the asthmatics were being treated with inhaled corticosteroids.

To investigate the greater variability in measurements at a higher concentration of eNO, the population was selected according to 2 groups and 3 classes: Group 1, Class 1, patients with FeNO values <20 ppb; Group 1, Class 2, patients with FeNO values 20-50 ppb; Group 2, Class 3, patients with

FeNO values >50 ppb. The average of the measurements made with NIOX VERO were considered the true reference value. All participants underwent two randomized determinations with each of the devices and in accordance with the recommendations of the American Thoracic Society/European Respiratory Society [5], with intervals of 1 minute between them. The number of attempts needed to obtain the measurements was recorded, as was the patient rating of the simplicity and general experience with both devices. The correlation between the measures (Pearson r) was determined, as was the ability of the device to classify values below or above the clinical cut-off point of 50 ppb (κ index). We also estimated the degree of concordance between the devices, the repeatability of the devices based on the Bland-Altman test, and the bias at 50 ppb [6]. Finally, the concordance analysis was extended by means of a Deming regression, which considers the measurement error introduced by both devices estimated from a reproducibility study of the measurement systems [7].

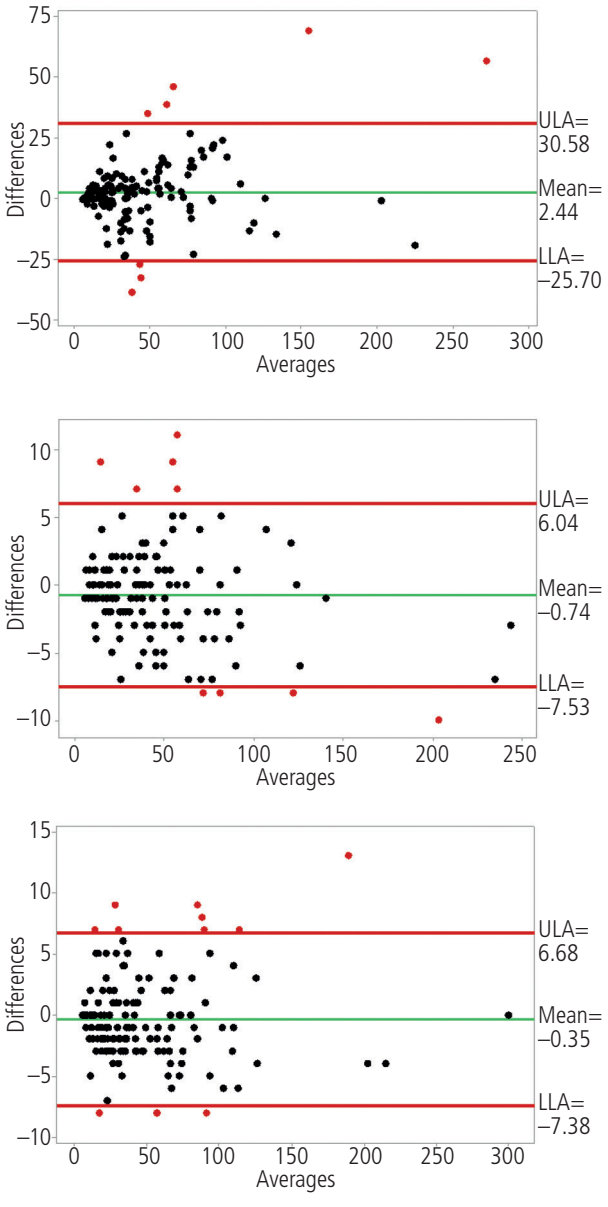

Figure. Analysis of agreement between measurements (Bland-Altman plot). Differences between measurements performed with each device (y axis) vs means of both measurements (x axis). A, evernoa vs NIOX VERO. B, Reproducibility of evernoa. C, Reproducibility of NIOX VERO. ULA indicates upper limit of agreement; LLA, lower limit of agreement.

The measurement range for both devices was between 5 and 300 ppb. eNO was >50 ppb in 30% of cases and >100 ppb in 9%. Despite lacking previous experience, 99% of users successfully tested with evernoa compared with 96.6% of users using NIOX VERO for the first time [8]. A more detailed description of the usability aspects of the equipment is found in the Supplementary material.

The correlation between the measurements with both devices was excellent (Pearson r, 0.943; $P<.001$). The classification capacity of the evernoa device with respect to that of NIOX VERO to classify the subjects into Group 1 or 2 (greater or less than 50 ppb) was also very good (κ, 0.7610). Concordance between the devices was excellent (Bland-Altman test), with an average difference of 2.44 ppb. This was homogeneous throughout the range of measurements (Figure, A). The reproducibility of evernoa showed concordance limits of 6.04 and –7.53 ppb compared with 6.68 and –7.38 ppb for NIOX VERO, thus suggesting that the reproducibility of evernoa is slightly better (Figure, B and C).

A balanced Deming regression [7] was carried out with a value of the measurement error ratio (λ) estimated from 2 studies of the reproducibility of data obtained with the devices. The slope of the regression was 0.904 (95%CI, 0.851-0.956) and the ordinate at the origin was 2.71 (95%CI, –1.182 to 5.523); the results obtained with evernoa were slightly lower than those of NIOX, although there was a high degree of concordance between the 2 devices (Supplementary material). The bias for the level of greatest clinical relevance (50 ppb) was –2.634 ppb, which is within the specifications of evernoa (±3 ppb) and is considered suitable for use in the diagnosis of asthma [9].

To conclude, our results highlight the ease of use and the quality of the measurements obtained with evernoa in terms of diagnostic accuracy, repeatability, reproducibility, validity, and concordance with the reference equipment, which indicates its suitability for the measurement of eNO.

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Conflicts of Interest

A Olaguibel, M Oleaga, A Iraola, L Ruete, and A Botas report grants from Fondos FEDER and grants from Gobierno de Navarra during the conduct of the study.

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R Cortaberria, A Tabar, and MJ Álvarez Puebla declare that they have no conflicts of interest.

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