Differences in lung clearance index and functional residual capacity between two commercial multiple-breath nitrogen washout devices in healthy children and adults

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ABSTRACT Multiple-breath nitrogen washout (MBNW) and its clinical parameter lung clearance index (LCI) are gaining increasing attention for the assessment of small airway function. Measurement of LCI relies on accurate assessment of functional residual capacity (FRC). The EasyOne Pro LAB (nbd) and Exhalyzer D (EM) are two commercially available MBNW devices. The aim of the study was to compare these two devices in vitro and in vivo in healthy subjects with regard to FRC, LCI and secondary outcome parameters and to relate FRCMBNW to FRC measured by body plethysmography (pleth) and helium dilution technique. MBNW measurements were performed using a lung model (FRC between 500 and 4000 mL) in vitro and in 38 subjects aged 6-65 years followed by helium dilution and pleth in vivo using fixed and relaxed breathing techniques. In vitro accuracy within 5% of lung model FRC was 67.3% for ndd, FRC was >5% higher for EM in all tests. In vivo, FRCpleth ranged from 1.2 to 5.6 L. Mean differences (limits of agreement) between FRCpleth and FRCMBNW were −7.0%, (−23.2 to 9.2%) and 5.7% (−11.2 to 22.6%) using ndd and EM, respectively. FRCndd was consistently lower than FRCEM (−11.8% (−25.6 to 2%)). LCI was comparable between the two devices (−1.3% (−21.9 to 19.3%)). There was a difference of >10% in LCI in 12 of 38 subjects. Using the most recent software updates, both devices show relevant deviations in FRC measurement both in vitro and in vivo and individual differences in LCI in a significant proportion of subjects. The devices are therefore not interchangeable.

MBNW measurements with the Exhalyzer D and EasyOne Pro LAB cannot be used interchangeably for FRC and LCI measurements. FRC measured on both devices showed deviations from in vitro and in vivo measurements. https://bit.ly/2xyyUuJ

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Introduction

Lung diseases such as cystic fibrosis (CF) and asthma may have their onset in the small airways [1–3]. Therefore, considerable interest exists in measuring small airways dysfunction, using the multiple-breath nitrogen washout (MBNW) technique. The lung clearance index (LCI) is its most straightforward outcome parameter. The LCI has increasingly gained attention as a sensitive marker of small airways dysfunction and ventilation inhomogeneity in patients with lung disease, especially in CF [4–10]. The reliability of the LCI depends directly on correct measurement of functional residual capacity (FRC), because LCI is calculated as the number of lung volume turnovers (cumulative exhaled volume/FRC) required to lower the tracer gas concentration to 1/40 of the initial concentration [11].

Currently, two commercially available devices are used for MBNW using N₂ as an inert tracer gas: the EasyOne Pro LAB ("ndd"; ndd Medical Technologies, Zurich, Switzerland) and the Exhalyzer D ("EM"; Eco Medics AG, Duernten, Switzerland). In previous studies, these devices have been compared in vitro using a lung model and to other techniques to measure FRC such as the helium dilution technique (FRC_{He}) and body plethysmography (FRC_{pleth}) [12–19]. The results from these studies suggest that the ndd measures significantly lower FRC values compared to body plethysmography, whereas EM measures similar to significantly higher FRC values compared to body plethysmography. Limitations of these studies were: use of only one of the two devices [12, 13, 15, 16], inclusion of a limited range of FRC by measuring either children or adults and/or use of an old software version of the ndd [14, 16–20]. Therefore, in this study we directly compared both devices with each other with the most recent software version of ndd and included both healthy children and adults.

The effect of breathing pattern on LCI and FRC is not well examined. Relaxed steady tidal breathing has historically been used for measuring the LCI. To derive other indices, such as parameters derived from (normalised) slope III (SnIII) analysis to distinguish between global ventilation inhomogeneity and specific location of ventilation inhomogeneity, a fixed tidal volume is advocated in the European Respiratory Society (ERS)/American Thoracic Society (ATS) statement [11, 21–23]. A tidal volume (Vₜ) between 950 and 1400 mL·kg⁻¹ for adults and between 10 and 15 mL·kg⁻¹ for children is mandatory as a compromise between maintaining physiological breathing and having sufficient phase III to gain SnIII data [11]. It is not exactly known how these different breathing patterns influence the outcome of FRC and LCI. Previous studies that investigated the influence of the breathing pattern on MBNW outcome parameters did not use the volumes recommended by the ATS/ERS statement, and none investigated both adults and children [24, 25].

The aim of the present study was to compare two currently available commercial MBNW devices (ndd and EM), using FRC and LCI as the main outcome parameters in healthy volunteers aged 6–65 years. Additionally, we evaluated the influence of fixed and relaxed tidal breathing patterns on FRC and LCI results.

Methods

Detailed description of randomisation, recruitment and inclusion criteria, study protocol, software versions, power calculation and statistical analysis are provided in the online supplementary material.

Study design

This is a cross-sectional randomised study of in vitro and in vivo MBNW measurements.

In vitro MBNW testing

A lung model setup (Soloplex, Tidaholm, Sweden) based on the model used by Singer et al. [13] was used to conduct in vitro experiments. With one modification: continuous CO₂ was not added to the model. To simulate different breathing patterns, a positive airway pressure ventilator with volume-controlled mode (Breas PV 501, Breas Medical AB, Mölnlycke, Sweden) was connected to the lung model. All measurements were performed by two operators (AZ and LR). To compare lung volume ranges and breathing patterns observed in subjects aged 6–65 years the target FRC of the lung model was set between 500 and 4000 mL, with a respiratory rate between 10 and 30 per min and Vₜ between 300 and 1000 mL. All tests were performed in triplicate, in randomised order of target FRC on both devices.

In vivo MBNW testing

Setting and participants

Healthy volunteers aged between 6 and 65 years were enrolled between April 2016 and April 2017 to conduct MBNW at the lung function department of the Beatrix Children’s Hospital, University Medical Centre Groningen (Groningen, the Netherlands). The study was approved by the local ethics committee (METc 2015.417). Written informed (parental) consent from all participants was obtained.
Protocol
The MBNW devices used were the ndd and EM devices. N₂ was used as a tracer gas. Randomisation took place for the order of the MBNW device used (ndd or EM) and the pattern of breathing. Breathing pattern (fixed or relaxed) was defined in agreement with the ATS/ERS consensus statement (figure 1) [11].

After the MBNW measurements lung function tests were performed in a fixed order: helium dilution technique (MasterScreen PFT System, CareFusion, USA), spirometry (MasterScreen pneumo-spirometer, CareFusion, USA) and pleth (MasterScreen Body Plethysmography, CareFusion, USA) (figure 1). All tests were performed according to the ATS/ERS guidelines and consensus statement [11, 26, 27].

Acceptable limits and statistical analysis
Minimal within-test repeatability of FRC measured by He, pleth and MBNW is defined as 10%, 5% and 10%, respectively [11, 27]. FRC measured using pleth includes the physiological amount of trapped gas, therefore FRC may be up to 10% higher than FRC measured by gas washout [28, 29]. Taking these two facts into account, we defined acceptable differences between $F_{RC_{MBNW}}$ and $F_{RC_{pleth}}$ as within the limits of $-10\%$ to $5\%$, and $F_{RC_{MBNW}}$ and $F_{RC_{He}}$ as within the limits of $-10$ and $10\%$.

Statistical analysis was performed using SPSS 23.0 for windows (IBM SPSS Statistics, version 23.0, Armonk, NY, USA). Statistical significance was set at $p<0.05$.

Accuracy of in vitro data was assessed according to the consensus statement: at least 95% of measured FRC should be within 5% of the lung model FRC [11]. The agreement between the devices, and different

![Flow diagram study design](https://doi.org/10.1183/23120541.00247-2019)
breathing manoeuvres was assessed using the method by Bland and Altman [30]. According to the consensus statement on MBNW, relaxed tidal breathing was used to compare the FRC\textsubscript{ndd} and FRC\textsubscript{EM} with the other lung function tests that measure FRC [11].

**Results**

**In vitro MBNW testing**

Thirty-four tests, each in triplicate, were performed per MBNW device. Mean difference between FRC measured using ndd compared to FRC\textsubscript{lung model} was 4\% (p=0.78, limits of agreement of −8.5 to 12.7\%). The accuracy rate of 5\% between FRC\textsubscript{ndd} and FRC\textsubscript{lung model} was reached in 67.6\%. For FRC\textsubscript{EM}, mean difference was 14.3\% (p≤0.01) with limits of agreement of −2.2 to 30.8\% (figure 2, table 1). All FRC\textsubscript{lung model} measurements with EM were >5\% higher and did not reach the defined accuracy rate. The *in vitro* coefficient of variation of FRC was 0.7\% using the ndd and 1.2\% using the EM.

**In vivo MBNW testing**

A total of 44 healthy volunteers were enrolled between April 2016 and May 2017; 23 children (6–17 years) and 21 adults (18–65 years). Five children, aged 6 to 10 years, were excluded: four were not able to perform acceptable MBNW tests and one showed signs of obstruction on spirometry and had a bronchodilator response of 18\%, without respiratory complaints. One adult was not able to perform the

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**FIGURE 2** Bland-Altman plots of *in vitro* MBNW FRC measurements of a) ndd (EasyOne Pro Lab) and lung model and b) EM (Exhalyzer D) and lung model in absolute values and c) ndd and lung model and d) EM and lung model in relative values. Data are plotted as measured FRC minus lung model FRC, expressed as absolute and relative difference versus mean of measured and lung model FRC values. The middle line represents the mean difference and the upper and lower (dashed) lines the upper and lower limits of agreement (mean difference ± 1.96 SD).
fixed tidal breathing protocol and was excluded. After exclusion, a total of 38 participants were eligible for analysis, their characteristics are outlined in table 2.

Comparison of ndd and EM: FRC, LCI and secondary outcome parameters

FRC_{ndd} was significantly lower than FRC_{EM}, mean difference $-11.8\%$ (p $\leq 0.01$, limits of agreement $-25.6$ to $2\%$) (figure 3, table 3).

The LCI was comparable between the two devices, mean difference $-1.3\%$ (p=0.31, limits of agreement $-21.9$ to $19.3\%$) (figure 3). LCI differed $>10\%$ in seven (39%) children and five (25%) adults between the two devices. Within-test repeatability of LCI was good in both devices; mean coefficient of variation (SD) 4.2 (3.1) using ndd and 3.8 (2.7) using EM.

Cumulative expired volume (CEV) was lower for both, children and adults when measured by ndd in comparison to EM. Respiratory rate was significantly higher using ndd in both groups, $V_T$ was significantly lower in children on ndd compared to EM and a trend was seen towards a lower $V_T\cdot kg^{-1}$ in children on ndd (table 3).

Comparison of FRC measurements between MBNW, body plethysmography and helium dilution technique

FRC_{ndd} was significantly lower than FRC_{pleth} with a mean difference $-7.0\%$ (p $\leq 0.01$ limits of agreement $-23.2$ to $9.2\%$) (table 4, figure S1).

Mean difference between FRC_{EM} and FRC_{pleth} was 5.7\% (p $\leq 0.01$, limits of agreement $-11.2$ to $22.6\%$) (figure S1). FRC_{EM} did not significantly differ from FRC_{pleth} in children in contrast to adults (table 3).

Mean FRC_{ndd} and FRC_{He} did not significantly differ, mean difference 2.1\% (p=0.46, limits of agreement $-10.6$ to $43.2\%$) (figure 3, table 3).

### TABLE 1 Mean difference between measured FRC and FRC lung model

| FRC lung model | ndd          | EM          |
|----------------|--------------|-------------|
| All            | Absolute     | Relative    |
|                | $-4$ (−34−26) | 212 (166−259) |
| <1000 mL       | Absolute     | Relative    |
|                | 59 (35−84)   | 100 (71−128) |
| >1000 mL       | Absolute     | Relative    |
|                | $-39$ (−76−2) | 274 (219−329) |
|                | $-1.0$ (−2.2−0.3) | 11.2 (9.8−12.6) |

Data are presented as mean (95% CI). Absolute measurements are in millilitres, relative in percentage. FRC: functional residual capacity; ndd: EasyOne Pro LAB; EM: Exhalyzer D.

### TABLE 2 Patient characteristics

|                | Child (n=18) | Adult (n=20) |
|----------------|--------------|--------------|
| Age years      | 12.5 (6.1−17.1) | 37.5 (18.8−64.9) |
| Male           | 7 (38.9)     | 12 (60)      |
| Height cm      | 156.8 (124−184) | 179.9 (167−192) |
| Weight kg      | 47.6 (25−78) | 74.1 (53−103) |
| FEV₁           | 0.08 (−2.0−1.5) | 0.17 (−1.6−1.3) |
| FVC            | 0.13 (−2.2−1.4) | 0.17 (−1.4−1.7) |
| FEV₁/FVC       | −0.16 (−2.0−1.2) | −0.07 (−1.6−1.3) |
| MEF₂₅          | −0.07 (−1.2−1.2) | 0.24 (−1.3−1.4) |
| FRC_{pleth} L  | 2.1 (1.2−4.2) | 3.8 (2.8−5.6) |
| FRC_{He} L     | 1.9 (1.0−3.8) | 3.6 (2.7−4.7) |

Data are presented as mean (range) or n (%). FEV₁, FVC, FEV₁/FVC and MEF₂₅ are expressed as z scores. #: n=17; 1 child was not able to perform He test due to technical problems. FEV₁: forced expiratory volume in 1 s; FVC: forced vital capacity; MEF₂₅: maximal expiratory flow at 25% of vital capacity; FRC: functional residual capacity; pleth: body plethysmography; He: helium dilution technique.

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Relaxed versus fixed tidal breathing
Mean FRC and LCI (p-value, limits of agreement) were $-1.8\%$ ($p=0.45$, $-32.1$ to $28.6\%$) and $-1\%$ ($p=0.37$, $-22.5$ to $20.5\%$) using ndd and $-1.4\%$ ($p=0.33$, $27.8$ to $25.0\%$) and $-1.5\%$ ($p=0.17$, $-18.7$ to $15.7\%$) using EM, respectively (figure S2). Overall, 11 (61%, ndd) and 10 (56%, EM) of the children and 6 (30%, ndd) and 6 (30%, EM) of the adults had a relaxed tidal breathing pattern that fulfilled the ATS/ERS criteria for fixed tidal breathing. In children, only a significant difference was seen in a lower respiratory rate on EM during fixed tidal breathing (see Table S1 online supplementary materials). In adults, respiratory rate was significantly lower on ndd during fixed tidal breathing. $V_T$ and $V_T\cdot kg^{-1}$ were significantly higher on both devices during fixed tidal breathing (see Table S1 online supplementary materials).

Discussion
Our study demonstrates that for MBNW the ndd and EM cannot be used interchangeably in healthy children and adults. $FRCEM$ yielded higher values compared to $FRC_{ndd}$ both, in vitro and in vivo. The LCI was comparable between the two devices; however, there were differences within subjects in almost one-third of measurements. Moreover, both devices showed deviations in FRC measurement in vitro and in vivo compared to pleth as well as the helium dilution technique. $FRC_{ndd}$ was lower compared to $FRC_{pleth}$ in 38% of subjects; $FRC_{EM}$ was higher than $FRC_{pleth}$ and $FRC_{He}$ in 50 and 66% of subjects.

**TABLE 3 Comparison of FRC between the different test methods**

|                  | Absolute (l) | Relative (%) | p-value   |
|------------------|--------------|--------------|-----------|
| **FRC**          |              |              |           |
| $FRC_{ndd}$      |              |              |           |
| $FRC_{pleth}$    | $-0.16$      | $[-0.24; -0.07]$ | $-7.7$ | $[-12.1; -3.4]$ | $<0.005$ |
| $FRC_{ndd}$      | $-0.24$      | $[-0.39; -0.09]$ | $-6.3$ | $[-10.2; -2.4]$ | $0.04$ |
| $FRC_{He}$       | $0.07$       | $[-0.03; 0.17]$ | $3.9$   | $[-1.3; 9.1]$  | $0.15$ |
| $FRC_{EM}$       | $0.01$       | $[-0.17; 0.19]$ | $0.5$   | $[-4.3; 5.3]$  | $0.88$ |
| $FRC_{pleth}$    | $0.08$       | $[-0.03; 0.18]$ | $4.0$   | $[-0.6; 8.5]$  | $0.15$ |
| $FRC_{EM}$       | $0.27$       | $[0.13; 0.42]$ | $7.1$   | $[3.3; 11.0]$  | $<0.005$ |
| **EM versus pleth** | $0.31$       | $[0.19; 0.43]$ | $17.4$  | $[10.3; 24.5]$ | $0.04$ |
| **EM versus He** | $0.52$       | $[0.29; 0.75]$ | $15.3$  | $[8.8; 21.7]$  | $<0.005$ |

Data are presented as mean [95% CI]. The p-value was calculated based on the absolute values of $FRC_{MBNW}$ versus $FRC_{pleth}$ or $FRC_{He}$. FRC: functional residual capacity; ndd: EasyOne Pro LAB; pleth: body plethysmography; He: helium dilution technique; EM: Exhalyzer D.

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respectively. In addition, this study shows that predefined breathing patterns have no significant effect on FRCMBNW and LCI.

In vitro
Neither of the two devices fulfilled the ATS/ERS criteria of >95% of measurements within 5% of FRClungmodel. In contrast to published data, FRCEM was higher than the defined accuracy rate of 5% in all tests [13, 17, 20].

In theory, several factors could explain the differences between FRCMBNW and FRClungmodel. First, the volume of dead space and correction for dead space are different between the two devices. The ndd device has a larger dead space area than EM. FRC is automatically corrected for dead space in both devices. A study investigating the effects of dead space showed that increasing dead space did not have a significant effect on FRC in healthy adults [31]. This suggests that it is unlikely that dead space differences influenced our results. Second, CO2 in exhaled breath might be crucial for accurate calculation of molar mass with the ultrasonic sensor utilised for MBNW in these devices. Unfortunately, simulation of physiological CO2 concentrations during expiration of human breathing patterns is not yet possible in the lung model. One can either choose between no CO2 administration or continuous CO2. It is unlikely that continuous CO2 would affect the comparison of both devices using the lung model.

Third, FRClungmodel was based on the volume of the lung model when the MBNW device was connected. Connection of the devices led to a reduction in FRClungmodel, which can be explained by the internal resistance of the devices. This reduction was more pronounced in the EM device compared to ndd. Previous studies did not describe whether the FRC was measured with or without connection of the MBNW device [12, 13, 17, 20]. Interestingly, a relative volume-dependent difference was seen in FRClungmodel <1000 mL in both devices, suggesting that the devices are less suitable for lower lung volumes. This needs to be explored in further research.

In vivo
FRCEM was significantly higher than FRCndd and not within the limits of clinical acceptability, indicating that the two devices are not interchangeable. The underestimation of FRCndd and the overestimation of FRCEM was consistent in vitro and in vivo and in other studies that investigated the two devices [14, 16, 18, 20].

In agreement with other studies, the EM yielded a slightly overestimated FRC for the group compared to FRCPleth; however, in 50% of subjects measured FRC was overestimated more than can be considered clinically acceptable [14, 15, 17, 18, 20]. In contrast the ndd does underestimate the FRC compared to FRCPleth. These data suggest a systematic measurement error within both devices.

| TABLE 4 Comparison of outcome parameters between EasyOne Pro LAB (ndd) and Exhalyzer D (EM) during relaxed tidal breathing |
|---------------------------------------------------------------|
|                      | ndd          | EM            | p-value |
|-----------------------|--------------|---------------|---------|
| **FRC L**             |              |               |         |
| Child                 | 1.9 (1.5; 2.4) | 2.2 (1.7; 2.6) | <0.005  |
| Adult                 | 3.6 (3.3; 3.9) | 4.1 (3.8; 4.4) | <0.005  |
| **LCI**               |              |               |         |
| Child                 | 7.2 (6.8; 7.5) | 7.1 (6.9; 7.3) | 0.83    |
| Adult                 | 7.3 (6.9; 7.8) | 7.6 (7.1; 8.1) | 0.14    |
| **CEV L**             |              |               |         |
| Child                 | 13.9 (10.7; 17.0) | 16.6 (13.6; 19.7) | <0.005 |
| Adult                 | 26.3 (23.6; 29.0) | 33.5 (29.5; 37.4) | <0.005 |
| **Vt mL**             |              |               |         |
| Child                 | 543 (452; 633) | 653 (513; 792) | 0.04    |
| Adult                 | 862 (717;1006) | 840 (756; 926) | 0.63    |
| **Vt·kg⁻¹ mL·kg⁻¹**   |              |               |         |
| Child                 | 11.6 (10.3; 13.0) | 15.4 (11.5; 16.0) | 0.06    |
| Adult                 | 11.6 (9.9; 13.4) | 11.4 (10.4; 12.4) | 0.72    |
| **RR min⁻¹**          |              |               |         |
| Child                 | 22.5 (19.8; 25.2) | 15.4 (13.0; 17.8) | <0.005  |
| Adult                 | 15.3 (13.1; 17.5) | 11.9 (10.4; 13.3) | <0.005  |

Data are presented as mean [95% CI], unless otherwise stated. FRC: functional residual capacity; LCI: lung clearance index; CEV: cumulative expired volume; Vt: tidal volume; RR: respiratory rate.
In the ndd, the underestimation of FRC was clearly reduced using the new software applying the N₂ algorithm, compared to studies that used older software versions [16–18, 20].

Our data are in agreement with the retrospective data of Tonga et al. [17], who also found an underestimation of FRC\textsubscript{ndd} versus FRC\textsubscript{pleth} of around −10% using the new software. Software changes led to the reduction of underestimation of FRC, by improving delay time correction between flow and gas measurement points and the switch of use of a prototype expirogram derived from the early breaths from the washout to compute N₂ to a point-by-point measurement during the entire expirogram. The change in delay time potentially has a large effect on FRC calculation [32]. However, in almost 40% of the subjects the underestimation of FRC was still not clinically acceptable, which implies the measurement can be further improved.

The mean LCI for the group was comparable, in contrast to previous studies that compared the two devices and showed a significantly higher LCI measured by EM compared to ndd [14, 20]. Nonetheless, in the present dataset there was a wide range and the limits of a clinically acceptable difference of <10% were not met in almost one-third of subjects, as was previously shown by Ponicin et al. [14] using an old software of ndd (version 3.37) [18]. Since the LCI is calculated as CEV/FRC, it can be expected that differences in CEV and/or FRC will explain the variability in LCI. Although CEV and FRC measured by EM were consistently higher than ndd, these parameters did not explain the variation in LCI, in contrast to the findings of Ponicin et al. [14].

In contrast to the absence of effect of dead space on the FRC, the difference in dead space correction could have had an effect on LCI in our in vivo measurements [31]. For EM LCI is automatically corrected for the dead space component. This is not the case for ndd, although this option became available in the latest software version as LCI at airway opening (LCI\textsubscript{ao}) (version V3.05.01.07, 03-2019). A post hoc recalculation in LCI\textsubscript{ao-ndd} led to a significantly lower LCI compared to LCI\textsubscript{EM}, mean difference −11.8% (p<0.005, limits of agreement −24.32 to 1.6) and thus led to a decrease in comparability between the two devices.

Breathing pattern

The use of a fixed and relaxed tidal breathing protocol did not result in any systematic difference in FRC or LCI, in contrast to other studies investigating the influence of breathing pattern that showed inconsistent effects on FRC and LCI [24, 25]. The explanation might be that many of our subjects fulfilled the ATS/ERS criteria of fixed tidal breathing during relaxed tidal breathing. Many of our smaller adult subjects experienced difficulties to fulfil the ATS/ERS fixed tidal breathing criteria [11]. Therefore, we advise a standard breathing protocol with relaxed tidal breathing pattern with a minimal breath size of around 8 mL·kg\(^{-1}\) to overcome dead space ventilation.

Changes in breathing pattern, different from the change between a fixed and relaxed tidal breathing protocol, can influence MBNW outcome parameters [11, 24, 25]. Although we did not perform a systematic evaluation of the experience of subjects on both devices, issues that might have influenced relaxed tidal breathing pattern were raised spontaneously by the subjects. For the EM, a feeling of resistance during breathing was reported. This is supported by the previously mentioned reduction of FRC\textsubscript{lungmodel} during connection of the EM in vitro. For ndd, some subjects felt "rushed" by the on-demand oxygen supply, which explains the higher respiratory rate for ndd compared to EM. Improvement could be reached by changing from on demand to a continuous oxygen supply. The effect of these issues would be interesting to explore in future research. Still, if a change of breathing pattern were the explanation for the differences between the devices, we would have expected the in vitro measurements to be more consistent, as the effect of a different breathing pattern was excluded using a standardised ventilator.

Strengths and limitations

This is the first prospective comparative study assessing two MBNW devices both in vitro and in vivo over a broad FRC range (FRC\textsubscript{pleth} varying between 1.2 and 5.6 L) including comparison with plethysmography and helium dilution for both devices.

A limitation of our study is that the power calculation was based on the study of Raaijmakers et al. [20]; at that time the only available study on this topic. According to the data published by Tonga et al. [17], 34 volunteers would have been needed for each group to achieve a power of 80% with a two-sided significance level (α) of 0.05. Therefore, it may be argued that the present study is under powered [14, 17]. Nevertheless, we were able to detect clinically relevant and statistically significant differences.

Conclusion

Numerous studies demonstrated that MBNW is an important tool for assessing early changes in peripheral airways in CF [4, 7, 10, 33, 34]. There is growing interest to support the use of LCI as primary outcome...
parameter in interventional and clinical studies [35–37]. Our study shows that there is room for further improvement of available equipment, given the scientific importance of addressing small airways disease. Based on the present study there is no clear preference for one of the two devices; however, it is essential to choose one device for clinical follow-up of patients as well as in longitudinal research protocols.

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