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Short communication

Simultaneous multiple breath washout and oxygen-enhanced magnetic resonance imaging in healthy adults

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ABSTRACT

Lung function testing and lung imaging are commonly used techniques to monitor respiratory diseases, such as cystic fibrosis (CF). The nitrogen (N_2) multiple-breath washout technique (MBW) has been shown to detect ventilation inhomogeneity in CF, but the underlying pathophysiological processes that are altered are often unclear. Dynamic oxygen-enhanced magnetic resonance imaging (OE-MRI) could potentially be performed simultaneously with MBW because both techniques require breathing of 100% oxygen (O_2) and may allow for visualisation of alterations underlying impaired MBW outcomes. However, simultaneous MBW and OE-MRI has never been assessed, potentially as it requires a magnetic resonance (MR) compatible MBW equipment. In this pilot study, we assessed whether MBW and OE-MRI can be performed simultaneously using a commercial MBW device that has been modified to be MR-compatible.

We performed simultaneous measurements in five healthy volunteers aged 25−35 years. We obtained O_2 and N_2 concentrations from both techniques, and generated O_2 wash-in time constant and N_2 washout maps from OE-MRI data.

We obtained good quality simultaneous measurements in two healthy volunteers due to technical challenges related to the MBW equipment and poor tolerance. Oxygen and N_2 concentrations from both techniques, as well as O_2 wash-in time constant maps and N_2 washout maps could be obtained, suggesting that simultaneous measurements may have the potential to allow for comparison and visualization of regional differences in ventilation underlying impaired MBW outcomes.

Simultaneous MBW and OE-MRI measurements can be performed with a modified MBW device and may help to understand MBW outcomes, but the measurements are challenging and have poor feasibility.

1. Introduction

Lung function testing and lung imaging are commonly used techniques to monitor respiratory diseases [2−3]. The nitrogen (N_2) multiple-breath washout technique (MBW) is a pulmonary function test to assess ventilation inhomogeneity [4−7]. The MBW test is more sensitive than conventional spirometry to assess mild lung disease and is increasingly used in clinical trials in CF [2,4]. During N_2MBW testing, a patient continuously breathes 100% oxygen (O_2) to wash out resident N_2 from the lungs until 2.5% of the initial N_2 concentration is reached. The primary outcome is the lung clearance index (LCI), which is the number of lung turnovers (functional residual capacity) needed to wash out N_2 to the target concentration [5]. MBW outcomes, such as LCI are measured at the mouth opening and assess global lung function, but do not allow assessment of the spatial distribution of ventilation defects (i.e., location, size and distribution) [8]. Therefore, it is unclear which underlying pathophysiological processes are altered when MBW outcomes are impaired.

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Pulmonary functional magnetic resonance imaging (MRI) is a non-invasive, radiation-free method suitable for longitudinal monitoring of CF [2,8]. Outcomes from functional lung MRI have been shown to correlate with MBW outcomes and provide direct visualization of the regional differences and defects in the lung associated with changes in MBW outcomes [2,8]. Dynamic oxygen enhanced MRI (OE-MRI) is a method that could potentially be performed simultaneously with MBW because both require breathing 100% O_2. In OE-MRI, the O_2 acts as a weak contrast agent [3]. The inhaled O_2 reaches functioning lung units (i.e., ventilated, perfused and able to exchange gases), diffuses into the pulmonary capillaries and lowers the longitudinal relaxation times (T_1) of blood and consequently of the lung tissue [9]. The decrease in lung T_1 due to breathing 100% O_2 can be measured voxel-wise and dynamically during serial acquisitions with specialized quantitative T_1 MRI acquisitions. Generally, poorly ventilated lung regions need longer O_2 washin time and show slower or no T_1 declines [9].

While MBW assesses N_2 washout, the OE-MRI assesses O_2 washin, and therefore both techniques could be combined, and their results compared if performed simultaneously in the scanner. Measurement of O_2 washin through the MBW device allows for monitoring O_2 delivery and assessment of washin completeness in real-time and direct comparisons between MBW and OE-MRI outcomes at different stages of the washin. Visualising regional ventilation defects and distribution patterns associated with MBW outcomes and washout curve dynamics will help to understand underlying disease. However, simultaneous MBW OE-MRI measurements have not been assessed, possibly due to the technical challenges associated with having the MBW equipment in the MRI scanner. In this pilot study, we aimed to assess whether a commercially available MBW device can be made MR-compatible to perform MBW simultaneously with OE-MRI and we report our first experiences with simultaneous measurements.

2. Methods

A MBW device (MRI-Exhalzyer D and the Spiroware 3.3.0-RESEARCH, Eco Medics AG Druenten, Switzerland) was modified to allow for MRI compatibility and remote control from outside the scanner room (Fig. 1). The Exhalzyer D was equipped with a Faraday cage, and all magnetic device components were distanced from the scanner to provide minimal interference with the magnetic fields. Additionally, the carbon dioxide (CO_2) sensor was built into the Exhalyzer D.

We performed simultaneous MBW OE-MRI in five healthy volunteers aged 25−35 years in a supine position using a mouthpiece and nose clip. The study was approved by the local ethic committee of Bern (KEK-Nr: 2019-01591) and informed consent was obtained. MR imaging during free breathing might lead to inaccurate pulmonary T_1 values due to lung compression/expansion and concomitant density modulations. Therefore, simultaneous measurements included breath holds of 4 s to ensure robust T_1 mapping. MBW data were quality controlled according to established guidelines [10] and post-processed using a custom written python script (LungSim) to improve breath detection, the determination of O_2 and CO_2 concentrations and their offsets, and to correct for the recently revealed sensor crosstalk error in the Exhalyzer D [11].

End-expiratory OE-MRI was performed on a single slice with a 1.5T scanner (MAGNETOM Avanto-Fit, Siemens Healthineers) using an Inversion-recovery ultra-fast balanced steady-state free precession sequence, as previously described, but with one inversion block to reduce scan time (<4 s) [9,12,13].

From simultaneously measured MBW and OE-MRI trials, we obtained and compared the N_2 washout and O_2 washin concentrations. For OE-MRI, these were calculated per voxel by fitting exponential T_1 signal decay (Equation) using the end-expiratory T_1 maps and setting normalized initial/final concentrations to 100% N_2 (0% O_2)/ 0% N_2 (100% O_2), according to the MBW principle of O_2 and N_2 exchange. We used the following T_1 decay equation: $T_1(NB)=(T_{1,NB=0} - T_{1,NB=\infty})*\exp(-NB/\tau)+T_{1,NB=\infty}$. From the T_1 signal decays, we obtained O_2 wash-in time constant (τ in washout breaths) maps, and N_2 maps at 100%, 25%, 10%, 5% and 2.5% of the initial N_2 concentration, respectively.

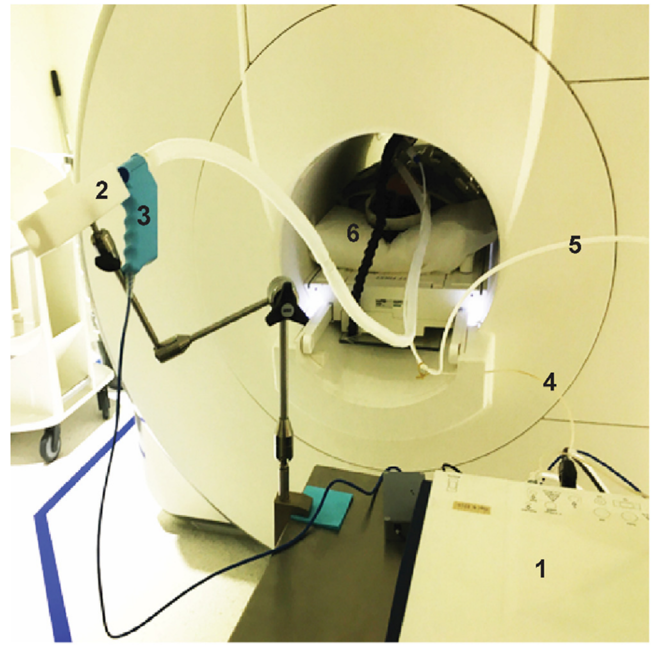

Fig 1. Multiple-breath washout (MBW) equipment modified to be magnetic resonance compatible. The setup has the following components: 1) Exhalzyer D hardware (Eco Medics AG, Druenten, Switzerland), 2) Bypass, 3) Ultrasonic flow measurement device, 4) Tube for gas sampling to assess gas concentration, 5) Room air and oxygen supply tube, 6) Healthy volunteer inside the scanner.

3. Results

We performed simultaneous N_2_MBW and OE-MRI in five healthy volunteers and obtained technically acceptable data in two subjects. Trials were excluded due to MBW technical failures including an absence of MBW signals, inability to save the MBW signals, and premature cessation of MBW data collection resulting from automatic test termination due to incorrect O_2 and CO_2 concentrations offsets and inaccurate breath detection (Fig. 2). There were no technical difficulties limiting OE-MRI. One trial was excluded due to poor imaging quality resulting from restlessness of one healthy volunteer inside the scanner.

Repeated simultaneous measurements were challenging, and participants reported fatigue due to breath holding and discomfort due to immobility inside the scanner (i.e. stiffness, restlessness, jaw pain). Mean duration of the acceptable MBW-OE-MRI trials was seven minutes. Mean (SD) LCI of all acceptable MBW trials was 7.5 (1.2). O_2 and N_2 concentrations from simultaneous MBW and OE-MRI could be plotted against breath number (Fig. 3), and τ-maps and N_2 maps could be obtained. The N_2 maps visualise N_2 concentration for each voxel covering the lungs at different MBW endpoints. Due to the long test duration of simultaneous measurements, OE-MRI was only assessed at one slice position.

4. Discussion

Our results show that a MBW device could be customized to perform MBW simultaneously with OE-MRI, but that the feasibility was low due to technical challenges with the modified MBW device

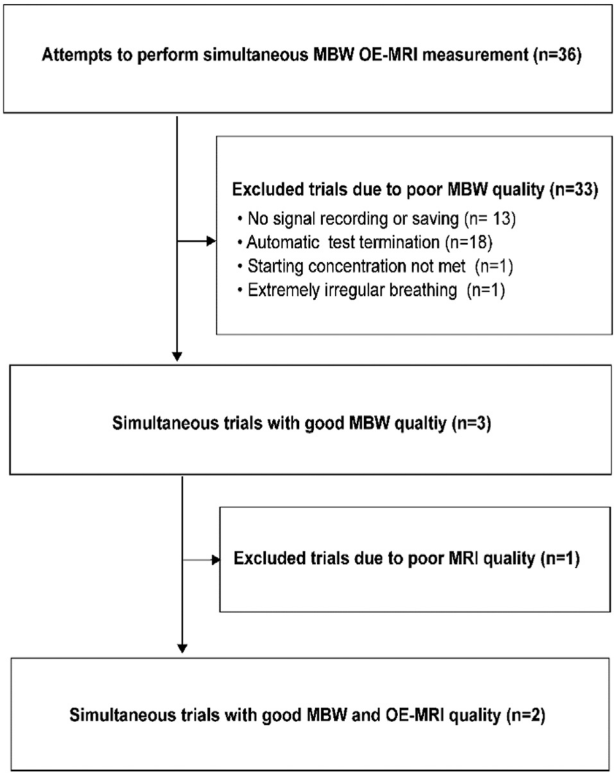

Fig 2. Flow chart presenting trial acceptability of simultaneous nitrogen multiple breath washout (MBW) and oxygen-enhanced magnetic resonance imaging (OE-MRI) in five healthy adult volunteers.

and performing simultaneous assessments. Nonetheless, several simultaneous measurements could be obtained, LCI values were within a realistic range [14], and imaging quality was generally good. Gas concentrations could be obtained from both techniques at the same time providing proof of concept that simultaneous measurement may potentially allow for comparison of the two techniques in time. Further, the τ-maps and N_2 maps suggest that visualisation of N_2 washout, regional differences in ventilation, and distribution patterns of ventilation defects underlying MBW outcomes may be possible in the same posture and physiological state.

Only two out of the five healthy adults delivered evaluable data, which suggests that our set up is not appropriate for further testing in healthy volunteers or patients with lung disease. Future studies may require MBW devices that are specifically designed for simultaneous MBW OE-MRI, shorter or simpler washout analyses, and OE-MRI sequences that allow tidal breathing and multi-slice imaging. While previous publications suggested a complementary role of MBW and MRI in detection and understanding of disease and responses to emerging therapies in CF [19–20].

The limited data in healthy adults did not allow for assessment of signal robustness, outcome reproducibility or discrimination between physiologic processes and artefacts. Consequentially, the data could not be used for calculation of functional lung imaging outcomes relevant for assessment of respiratory diseases or for comparison with alternative MRI methods such as matrix-pencil, contrast-enhanced or hyperpolarized gas MRI in terms of feasibility and results [2,6,15-18].

In summary, we showed that simultaneous MBW and OE-MRI measurements could be performed with a modified commercial MBW device, but that this was technically challenging and had poor feasibility.

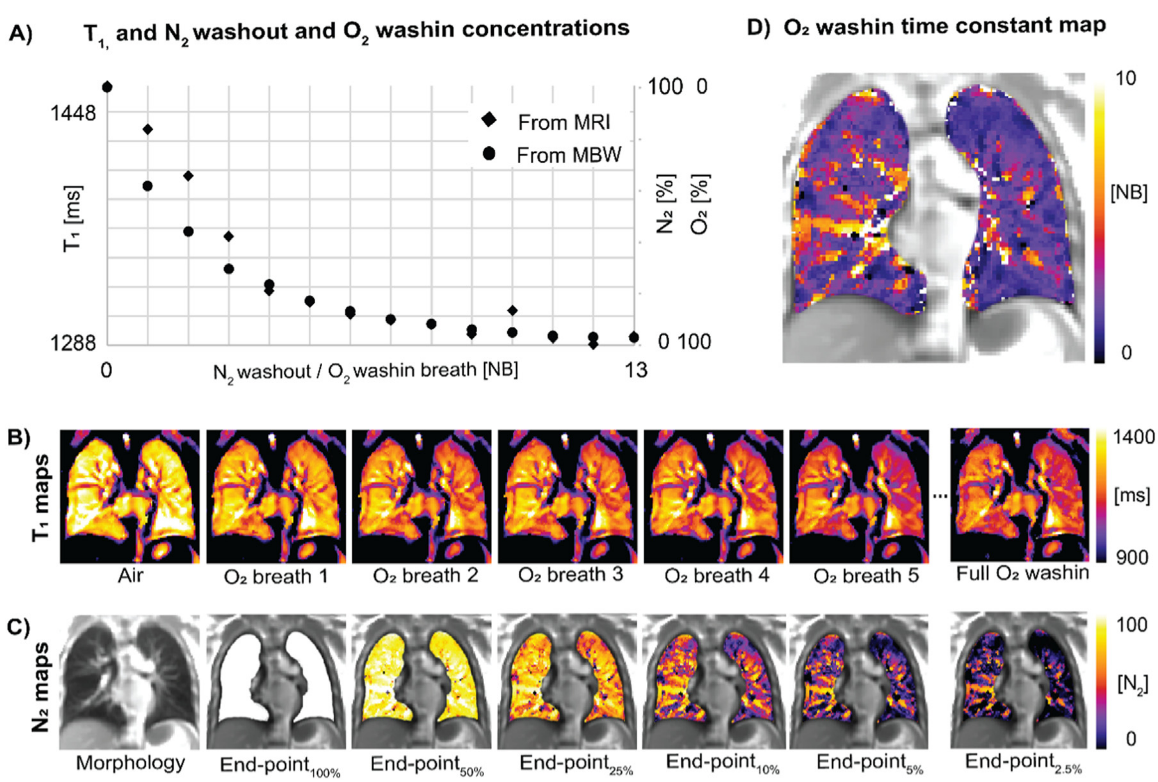

Fig. 3. Results from simultaneous multiple breath washout (MBW) oxygen-enhanced magnetic resonance imaging (OE-MRI) measurements. A) Pulmonary longitudinal relaxation times (T_1), and oxygen (O_2) washin and nitrogen (N_2) concentrations from a simultaneous MBW and OE-MRI trial plotted per oxygen breath (NB) normalized for initial gas concentrations at start of the oxygen delivery. B) End-expiratory T_1 maps during room air breathing, during five oxygen washin breaths, and full O_2 washin. C) N_2 washout maps obtained from OE-MRI data at different washout end-points: 100%, 50, 25%, 10%, 5% and 2.5% of the initial N_2 concentration, respectively. D). O_2 wash-in time constant map in washout breath number (NB).

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Data availability

The data presented in this article is available via the corresponding author upon reasonable request.

Conflict of interest statement

Eco Medics AG (Duernten, Switzerland) produced the customized MBW setup and a research version of their commercial software Spiroware 3.3. A.C. Kentgens is recipient of a Swiss Government Excellence Scholarship from the Swiss Confederation, Federal Department of Economic Affairs, Education and Research (EAER). F. Santini reports research grants from the Swiss National Science Foundation and consulting fees of Hoffmann – La Roche paid to the institution. P. Latzin reports grants from Vertex and OM Pharma paid to the institution; personal payments or honoraria from Vertex, Vifor and OM Pharma; payments or honoraria from Vertex, Vifor and OM Pharma paid to the institution; personal fees for participation on a Data Safety Monitoring Board or Advisory Board from Polyphor, Santhera (DMC), Vertex, OM pharma, Vifor and Sanofi Aventis; and fees for participation on a Data Safety Monitoring Board or Advisory Board from Polyphor, Vertex, OM pharma and Vifor paid to the institution, all outside the submitted work. K.A. Ramsey reports a grant from Vertex paid to the institution. Otherwise, all other authors report no other competing interests.

CRediT authorship contribution statement

Anne-Christianne Kentgens: Conceptualization, Methodology, Investigation, Formal analysis, Data curation, Visualization, Writing – original draft. **Orso Pusterla:** Conceptualization, Methodology, Investigation, Formal analysis, Data curation, Visualization, Writing – review & editing. **Grzegorz Bauman:** Conceptualization, Methodology, Writing – review & editing. **Francesco Santini:** Conceptualization, Methodology, Investigation, Writing – review & editing. **Florian Wyler:** Methodology, Data curation, Writing – review & editing. **Marion S. Curdy:** Methodology, Data curation, Writing – review & editing. **C.Corin Willers:** Conceptualization, Methodology, Investigation, Writing – review & editing. **Oliver Bieri:** Conceptualization, Methodology, Investigation, Writing – review & editing. **Philipp Latzin:** Conceptualization, Methodology, Writing – review & editing. **Kathryn A. Ramsey:** Conceptualization, Methodology, Investigation, Writing – review & editing.

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