# Xenon-129 MRI detects ventilation deficits in paediatric stem cell transplant patients unable to perform spirometry

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**Hyperpolarised $^{129}$Xe MRI detects regional lung ventilation abnormalities in paediatric stem cell transplantation patients, including in patients with normal spirometry and in patients unable to perform reliable spirometry** http://ow.ly/1T2030nGGQ1

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ABSTRACT

**Background:** Early detection of pulmonary morbidity following haematopoietic stem cell transplantation (HSCT) remains an important challenge for intervention, primarily due to the insensitivity of spirometry to early change, and in paediatrics, patient compliance provides additional challenges. Regional lung ventilation abnormalities in paediatric HSCT patients were quantified using hyperpolarised xenon-129 ($^{129}$Xe) magnetic resonance imaging (MRI) and compared to spirometry.

**Methods:** Medically stable, paediatric allogeneic HSCT patients (n=23, ages 6–16 years) underwent an outpatient MRI scan where regional ventilation was quantified with a breath-hold of hyperpolarised $^{129}$Xe gas. Ventilation deficits, regions of the lung that ventilate poorly due to obstruction, were quantified as a ventilation defect percentage (VDP) and compared to forced expiratory volume in 1 s ($FEV_1$), $FEV_1$/forced vital capacity (FVC) ratio, and forced expiratory flow at 25–75% of FVC ($FEF_{25–75\%}$) from spirometry using linear regression.

**Results:** The mean±SD $^{129}$Xe VDP was 10.5±9.4% (range 2.6–41.4%). $^{129}$Xe VDP correlated with $FEV_1$, $FEV_1$/FVC ratio and $FEF_{25–75\%}$ ($p \leqslant 0.02$ for all comparisons). Ventilation deficits were detected in patients with normal spirometry (*i.e.* $FEV_1$ >80%), supporting the sensitivity of $^{129}$Xe MRI to early obstruction reported in other pulmonary conditions. Seven (30%) patients could not perform spirometry, yet ventilation deficits were observed in five of these patients, detecting abnormalities that otherwise may have gone undetected and untreated until advanced.

**Conclusion:** Lung ventilation deficits were detected using hyperpolarised $^{129}$Xe gas MRI in asymptomatic paediatric HSCT patients and in a subgroup who were unable to perform reliable spirometry. $^{129}$Xe MRI provides a reliable imaging-based assessment of pulmonary involvement in this potentially difficult to diagnose paediatric population.

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## Introduction

Pulmonary complications following allogeneic haematopoietic stem-cell transplantation (HSCT) are a significant source of morbidity and mortality, affecting up to 60% of all HSCT patients, with the highest prevalence in patients with graft *versus* host disease (GVHD) [1, 2]. These complications may arise early or later post-transplantation (*i.e.* >100 days) and may stem from bacterial or fungal infections or from non-infectious sources such as pulmonary oedema or drug-related toxicity related to immunosuppression and chemotherapy [2, 3]. Bronchiolitis obliterans syndrome (BOS), the most common and severe later-onset pulmonary complication following HSCT, is an obstructive lung condition resulting from a combination of immune-mediated inflammation and fibrosis in the small airways. BOS is associated with precipitous declines in pulmonary function, high respiratory morbidity and eventual mortality. Commonly, BOS is an irreversible process, and while there are limited therapies available to stabilise lung function, the only treatment for end-stage lung disease is lung transplantation, which is also associated with BOS and poor prognosis.

Routine pulmonary function testing (PFT) such as spirometry is traditionally the first line of detection of lung abnormalities. The primary clinical parameter from spirometry is the forced expiratory volume in 1 s ($FEV_1$), but generally the diagnosis of BOS is made only after significant consistent decline in $FEV_1$. The clinical symptoms of BOS include chronic nonproductive cough, wheezing, exercise intolerance and dyspnoea on exertion; patients with these symptoms often already have moderate to severe $FEV_1$ declines [4]. Trajectories of $FEV_1$ following HSCT have shown the steepest decline in the 6 months prior to BOS diagnosis followed by stabilisation after diagnosis and intervention [5]. A multicentre, retrospective study of adult HSCT patients in the UK showed that 10% had significant decline in $FEV_1$ and forced vital capacity (FVC) at 12 months post-HSCT compared to pre-transplantation [6], and in another study, Uhlving *et al.* [7] reported that 62% of their paediatric HSCT cohort had reductions in lung function of >10% in the first 3–9 months post-transplantation. Early detection of lung abnormalities is paramount for intervention to conserve pulmonary capacity and improve outcomes [5, 8, 9]. While spirometry is clinically ubiquitous and easy to deploy, there are known limitations, including a poor sensitivity to early disease [10, 11]. Even though routine spirometric screening of HSCT patients is recommended [12, 13], Prais *et al.* [14] suggest that protocols and fulfillment vary greatly across centres as evidenced by many retrospective studies of PFTs in HSCT patients with varying amounts of data and patients at each time point. Furthermore, in the paediatric population, compliance with the effort-dependent spirometry may be challenging. Loeb *et al.* [15] assessed the acceptability and repeatability of spirometry in paediatric subjects and reported that only 50% of subjects at the age of 6 years could perform acceptable repeatable spirometry, which rose to 85% by 10 years.

In addition to spirometry, clinical imaging such as chest radiography computed tomography (CT) may be pursued to detect lung disease. The characteristics of BOS on high-resolution chest CT include mosaic patterning, bronchiectasis, atelectasis and in later stages, severe air trapping [16]; however, these features are typically subtle in early disease. Concerns for exposure to ionising radiation in the paediatric population require judicious use of chest CT, limiting its application for routine screening of asymptomatic patients. While there are efforts to minimise ionising radiation exposure, including modern low-dose CT protocols and expiration-only CT protocols [17], a more sensitive, non-ionising imaging modality would allow for more frequent assessment of lung disease progression or therapeutic response.

Over the past 20 years, the sensitivity and specificity of hyperpolarised-gas magnetic resonance imaging (MRI) to detect early lung obstruction in asymptomatic patients has been demonstrated across a wide variety of pulmonary conditions including cystic fibrosis [18, 19], asthma [20–22], interstitial lung disease [23] and chronic obstructive pulmonary disease [21, 24, 25]. In hyperpolarised xenon-129 ($^{129}Xe$) MRI techniques, the signal of $^{129}Xe$ gas is enhanced many orders of magnitude over thermal equilibrium *via* spin exchange optical pumping, such that the gas may be inhaled and imaged *via* MRI during a single breath-hold (*i.e.* generally $\geqslant$5 s). Regions of the lung that ventilate appear bright in the $^{129}Xe$ images, and regions that are partially or fully obstructed appear relatively or completely dark, respectively, due to the inability of $^{129}Xe$ gas to fill those obstructed airspaces. These deficits in lung ventilation can be quantified, and the repeatability and stability of hyperpolarised-gas ventilation deficits have been demonstrated [26–28], supporting outcomes from $^{129}Xe$ MRI as biomarkers for obstructive lung disease. Indeed, hyperpolarised-gas MRI has been reported in lung transplantation; in a preliminary report of helium-3 ($^{3}He$) MRI in six adult lung-transplantation recipients, McAdams *et al.* [29] found that the extent of $^{3}He$ ventilation defects correlated with the severity of BOS. Gast *et al.* [30] used $^{3}He$ ventilation and oxygen-sensitive MRI methods to investigate normal lung grafts and those with BOS and found that normal grafts had fewer ventilation defects and BOS patients had more heterogeneous intrapulmonary oxygen distribution.

We hypothesised that $^{129}Xe$ MRI could detect ventilation abnormalities in a paediatric HSCT population, including in children who could not perform reliable spirometry, and that quantitative $^{129}Xe$ ventilation

would be sensitive to lung abnormalities post-HSCT before changes *via* traditional spirometry (*i.e.* $^{129}$Xe ventilation deficits would be present in HSCT patients with normal spirometry), providing a means of early detection and intervention. Portions of this work have been presented previously in abstract form [31, 32].

## Methods

### *Subjects and $^{129}$Xe gas preparation*

23 paediatric allogeneic HSCT recipients were recruited for the $^{129}$Xe MRI study with institutional review board approval following United States Food and Drug Administration (US FDA) investigational new drug (IND) approval (IND number 123 577). Inclusion criteria included age ⩾6 years (lower limit of the IND) and ability to perform a breath-hold. Table 1 summarises the demographics for this cohort. In addition to standard MRI exclusion criteria (*e.g.* claustrophobia, incompatible implants), additional exclusions included symptoms of current respiratory infection (loose or productive cough or wheeze), chest tightness within the previous week, baseline pulse oximetry <95% and/or positive pregnancy test (if applicable). All subjects were medically stable outpatients at the time of imaging. Isotopically enriched Xe gas (86% $^{129}$Xe) was polarised to ∼20% using a commercial polariser (Polarean Imaging, Durham, NC, USA) and dispensed into a Tedlar delivery bag ( Jensen Inert Products, Coral Springs, FL, USA) equipped with Tygon tubing, plastic hose clamp and a mouthpiece (Epsilon Medical Devices, Penang, Malaysia).

### *MRI procedure*

After screening, subjects were placed supine in a Philips (Best, the Netherlands) 3 Tesla Achieva MRI scanner with a homebuilt $^{129}$Xe saddle coil tuned to 35.3 MHz. Standard three-plane, hydrogen-1 ($^{1}$H) localisation scans were performed first to ensure optimal field of view for lung imaging. Next, a conventional $^{1}$H gradient-echo scan was performed with a practice breath-hold of room air. For all breath-holds (*i.e.* $^{1}$H and $^{129}$Xe), the gas administrator instructed the subject to fully inhale and exhale twice before gas inhalation beginning at functional residual capacity. The maximum scan duration was 16 s for all scans requiring a breath-hold, and the subject was in the MRI scanner for ∼15 min for hyperpolarised $^{129}$Xe MRI. Due to the non-renewable, hyperpolarised nature of the $^{129}$Xe gas, practice breath-holds with room air were repeated if necessary to ensure compliance for the $^{129}$Xe scans.

First, a small calibration dose of ∼250 mL of hyperpolarised $^{129}$Xe gas was administered during a brief 2-s breath-hold to optimise the *in vivo* flip angle for the $^{129}$Xe ventilation images. For $^{129}$Xe ventilation imaging, the $^{129}$Xe gas dose was one-sixth of a subject's predicted total lung capacity as calculated from plethysmography-based predictive equations using a subject's sex and height [33]. $^{129}$Xe ventilation was acquired using a gradient-echo scan (9–12° flip angle, repetition time=8 ms, echo time=4 ms, nine to 15 slices depending on subject's size, and voxel size ≈3×3×15 mm$^3$ [34]).

$^{129}$Xe gas was administered in the presence of a medical professional (*i.e.* registered nurse or physician), and a minimum of 2 min elapsed between consecutive $^{129}$Xe breath-holds. Subject blood oxygenation (arterial oxygen saturation measured by pulse oximetry ($S_{PO_2}$)) and heart-rate were monitored throughout the $^{129}$Xe breath-holds using a magnetic resonance-compatible pulse oximeter (InVivo Corporation, Orlando, FL, USA), and changes in vitals were compared to baseline resting values using paired t-tests with a p-value ⩽0.05 considered significant. Adverse events were assessed during the $^{129}$Xe MRI procedure and *via* follow-up phone call at day 1 and day 30 (±7 days).

### *$^{129}$Xe ventilation analysis*

$^{129}$Xe ventilation images were analysed using custom software in MATLAB (MathWorks, Natick, MA, USA). Lung masks were generated using $^{1}$H MRI to define the edges of the lungs excluding large airways and vasculature. The $^{129}$Xe ventilation defect percentage (VDP) was calculated using a threshold of <60% of the mean whole-lung $^{129}$Xe signal and quantified as a percentage of the total lung volume. VDP calculated in this manner is a well-established, reproducible outcome measure in the hyperpolarised-gas MRI literature [35–39]. This 60% threshold has been used previously to best separate healthy paediatric controls from those with lung obstruction in cystic fibrosis [40]. $^{129}$Xe VDP was compared to a cohort of age-matched control subjects (n=10; seven males and three females) with a mean±SD age of 12±3 years (range 6–16 years) and $FEV_1$ % predicted of 102±9% (range 89–115%), which were published previously [40]. Ventilation deficits were considered present if $^{129}$Xe VDP was >6%, which is the upper limit typical of our control subjects. $^{129}$Xe image results were compared to measures from $FEV_1$, $FEV_1$/FVC ratio and forced expiratory flow at 25–75% of FVC ($FEF_{25–75\%}$) from spirometry when available using linear regression and Pearson's correlations. Clinical spirometry reports were collected from patient medical records if within 6 months of the MRI. If no recent clinical spirometry was available, spirometry was attempted on the day of the MRI visit.

TABLE 1 Patient demographics

| | |
|---|---|
| **Age years** | 11 (6–17) |
| **Sex** | |
| Female | 14 (61) |
| Male | 9 (39) |
| **Diagnosis** | |
| Bone marrow failure | 11 (48) |
| Primary immune deficiency | 8 (35) |
| Malignancy | 4 (17) |
| **Conditioning regimen#** | |
| Campath/FLU/MELPH | 7 (29) |
| ATG/BU/CY/FLU | 5 (21) |
| ATG/BU/CY | 4 (17) |
| BU/FLU/TT | 2 (8) |
| ATG/CY | 1 (4) |
| ATG/FLU/TT/treosulfan | 1 (4) |
| Campath/FLU | 1 (4) |
| FLU | 1 (4) |
| Campath/FLU/BU+TBI | 1 (4) |
| ATG/CY+TBI | 1 (4) |
| **Donor source/HLA status#** | |
| Related | |
| Matched (8/8, 10/10) | 5 (21) |
| Unrelated | |
| Matched (8/8, 10/10, 12/12) | 10 (42) |
| Mismatched (7/8, 8–9/10) | 9 (38) |
| **Stem-cell source#** | |
| Bone marrow | 15 (63) |
| PBSC | 8 (33) |
| Bone marrow/cord blood | 1 (4) |
| **GVHD prophylaxis#** | |
| CSA/PRED | 7 (30) |
| CD34 selection | 6 (25) |
| CSA/MTX | 4 (17) |
| CSA/MFF | 3 (13) |
| ATG/CSA/maraviroc/PRED | 1 (4) |
| CSA/maraviroc/PRED | 1 (4) |
| Abatacept/PRED | 1 (4) |
| Tacrolimus/sirolimus | 1 (4) |
| **Acute GVHD n/N (%)** | 8/23 (35) |
| Skin (grade 1–3) | 6 |
| Gastrointestinal (grade 2–3) | 3 |
| **Chronic GVHD n/N (%)** | 8/23 (35) |
| Skin (limited–extensive) | 6 |
| Lung | 4 |
| Vagina | 3 |
| Eyes | 2 |
| Mouth | 2 |
| Gastrointestinal | 1 |
| Liver | 1 |

Data are presented as mean (range), n (%) or n, unless otherwise stated. FLU: fludarabine; MELPH: melphalan; ATG: antithymocyte globulin; BU: busulfan; CY: cyclophosphamide; TT: thiotepa; TBI: total body irradiation; HLA: human leukocyte antigen; PBSC: peripheral blood stem cell; GVHD: graft *versus* host disease; CSA: cyclosporine; PRED: prednisone; MTX: methotrexate; MFF: mycophenolate mofetil. #: n=24 transplantations, as one subject underwent two haematopoietic stem cell transplantations.

## Results

The $^{129}$Xe MRI procedure was well tolerated and completed by all subjects. Table 2 summarises the changes in $S_{pO_2}$ and heart rate during the calibration and ventilation imaging doses of Xe gas. As anticipated, there was a small, short decrease in $S_{pO_2}$ associated with the ventilation dose of gas, a mean decrease of ~8% from baseline (compared to ~6% decrease reported for paediatric cystic fibrosis patients and healthy controls [34]). Of the 19 subjects who had a decrease in $S_{pO_2}$, the duration of this nadir was <10 s and $S_{pO_2}$

TABLE 2 Blood oxygenation and heart rate changes during xenon-129 magnetic resonance imaging

| | Flip-angle calibration dose | | | Ventilation-imaging dose | | |
|---|---|---|---|---|---|---|
| | Baseline | At nadir of $S_{pO_2}$ | 2 min post-procedure | Baseline | At nadir of $S_{pO_2}$ | 2 min post-procedure |
| **$S_{pO_2}$ %** | 97.4±1.5 (95–100) | 93.5±4.2 (86–104) | 97.5±1.7 (93–100) | 97.2±1.4 (94–100) | 89.3±5.2 (74–97) | 98.0±1.6 (94–100) |
| p-value | | 0.0018 | 0.74 | | $1\times10^{-6}$ | 0.009 |
| **Heart rate beats·min$^{-1}$** | 92±14 (74–109) | 93±11 (82–121) | 92±13 (70–116) | 92±13 (68–124) | 96±13 (66–123) | 90±15 (67–125) |
| p-value | | 0.80 | 0.54 | | 0.33 | 0.33 |

Data are presented as mean±SD (range), unless otherwise stated. $S_{pO_2}$: arterial oxygen saturation measured by pulse oximetry.

was restored for all subjects with normal breathing of room air. There were no related adverse events and no adverse events during the study visit that required medical intervention, in agreement with previously published safety assessments of $^{129}$Xe MRI in paediatric [34] and adult subjects [25, 41].

The $^{129}$Xe ventilation pattern varied widely across subjects, as demonstrated in figure 1, including across patients with similar FEV1 % pred values (figure 1b,c). Ventilation deficits were apparent (*i.e.* VDP >6%) in 11 (48%) subjects. The mean±SD $^{129}$Xe VDP was 10.5±9.4% in all HSCT patients (range 2.6–41.4%), which was elevated relative to controls [40] (6.3±2.8%), but did not reach statistical significance (p=0.06). A $^{129}$Xe VDP threshold between 60% and 70% provided the maximum separation between HSCT subjects with BOS and control subjects. The wide individual variation in ventilation was apparent especially when $^{129}$Xe VDP was plotted against FEV1 % pred, FEV1/FVC ratio and $FEF_{25–75\%}$ (figure 2), as subjects with similar spirometry values had large differences in VDP. Reliable spirometry data were available for 16 out of the 23 subjects, and the mean±SD days between spirometry and $^{129}$Xe MRI was 46±43 days (range 0–137 days). $^{129}$Xe VDP correlated with FEV1 % pred with a p-value of 0.02; Pearson's coefficient −0.56, with FEV1/FVC ratio ($p<10^{-6}$, Pearson's coefficient −0.92), and $FEF_{25–75\%}$ (p=0.0005 and Pearson's coefficient −0.78).

Importantly, seven (30%) out of 23 subjects in this study were unable to perform reliable post-transplantation spirometry due to technique; however, all subjects were able to complete the $^{129}$Xe MRI protocol. As anticipated, the subgroup without reliable spirometry included primarily the youngest subjects, with an average age of 8±3 years (range 6–13 years). In this group the $^{129}$Xe VDP was 11.4±8.4% (range 3.3–28%) and $^{129}$Xe ventilation deficits were apparent (*i.e.* VDP >6%) in five out of seven subjects. Reliable pre-transplantation FEV1 % pred was available for only eight subjects, and post-transplantation FEV1 was available for six of these subjects with an average decrease of 8% (range 0–32%) at the time of $^{129}$Xe MRI. Patients with reliable spirometry (n=16) were significantly older (average 12±3 years, range 6–17 years; p=0.008) and the $^{129}$Xe VDP was 10.2±10.3% (range 3–41.4%; nonsignificant). There was no significant difference in $^{129}$Xe VDP between patients with known chronic GVHD of any system (n=8, average $^{129}$Xe VDP 10.6±7.8%) and those without chronic GVHD (10.5±10.4%). In the four patients with clinically diagnosed lung GVHD, $^{129}$Xe VDP ranged from 5.5% to 24% (average 13.7±9.1%), which was not statistically different from patients with other forms of chronic GVHD or from patients without chronic GVHD.

To evaluate early and late ventilation abnormalities after HSCT, $^{129}$Xe VDP was compared to the number of days post-HSCT (figure 3a). Ventilation deficits were identified early and late after HSCT, but in the subgroup of 13 patients who had MRI within the first year post-HSCT (figure 3b), seven (54%) patients had obvious ventilation deficits and $^{129}$Xe VDP >6%, including several of the patients who were unable to perform reliable spirometry and one patient with normal FEV1 (figure 1c).

## Discussion

To our knowledge, this is the first demonstration of hyperpolarised $^{129}$Xe MRI in the HSCT population. $^{129}$Xe MRI detected a wide range of lung ventilation abnormalities in paediatric HSCT patients. Ventilation deficits *via* $^{129}$Xe MRI were detected in asymptomatic HSCT patients with normal FEV1 (*i.e.* >80% predicted, *e.g.* figure 1c), which is in agreement with previous studies of $^{129}$Xe MRI in other pulmonary diseases with mild obstruction [19, 36, 38, 40]. These results are in agreement with a case study of lung scintigraphy of an adult HSCT patient with relatively unremarkable chest CT who was diagnosed with bronchiolitis obliterans by the presence of matched ventilation–perfusion deficits on scintigraphy, supporting the diagnostic value of functional lung imaging in the HSCT population [42]. Longitudinal

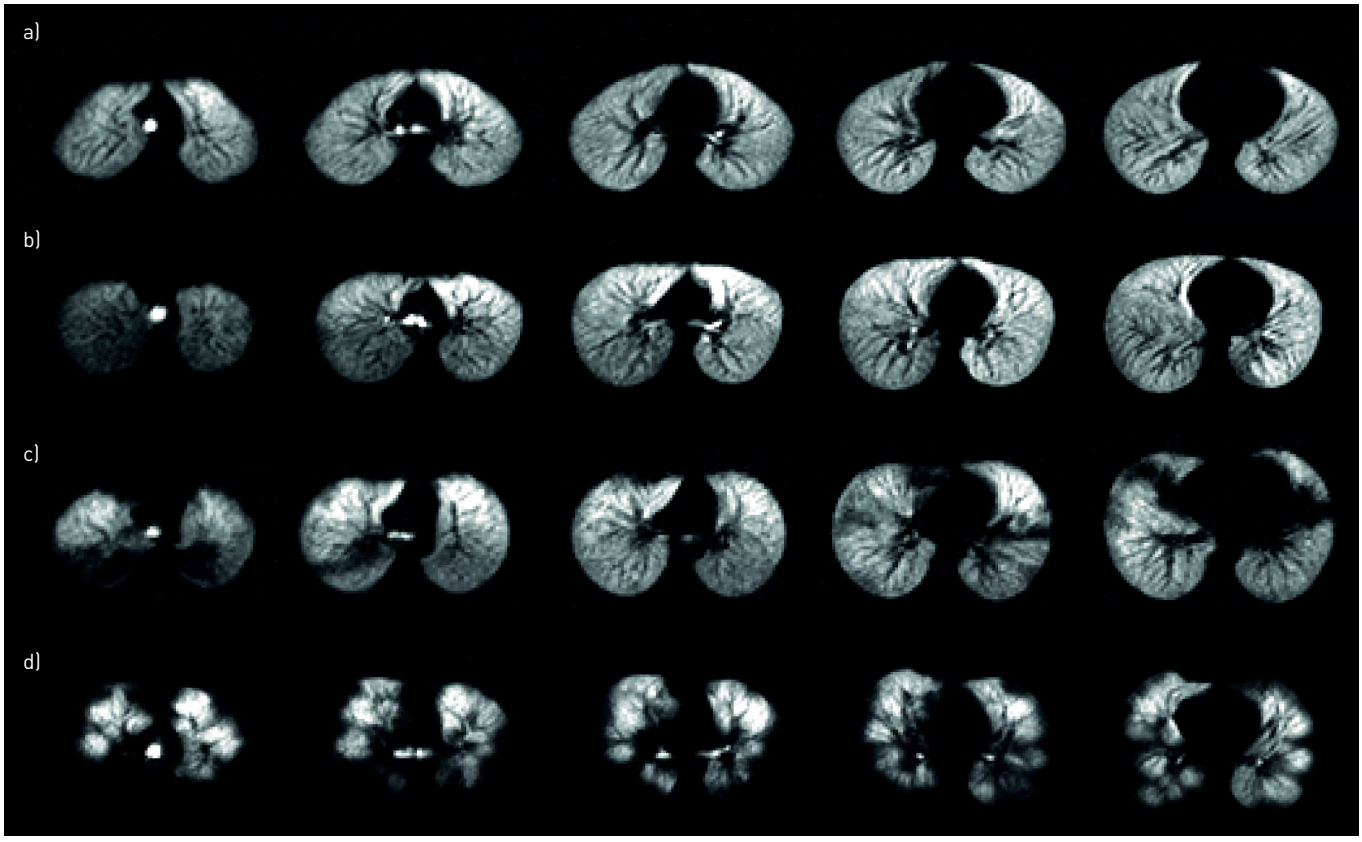


FIGURE 1 Representative axial xenon-129 ($^{129}$Xe) ventilation magnetic resonance images from four haematopoietic stem cell transplantation (HSCT) patients demonstrating the range of $^{129}$Xe ventilation patterns seen in this study. a) 15-year-old female, 145 days post-HSCT, forced expiratory volume in 1 s ($FEV_1$) 108% predicted, $^{129}$Xe ventilation defect percentage (VDP) 3.0%; the subject has high $FEV_1$ % pred, ventilation is homogenous and the $^{129}$Xe VDP is correspondingly low. The sensitivity of $^{129}$Xe MRI to mild lung abnormalities is demonstrated in the subjects in b) (15-year-old female, 3 years post-HSCT, $FEV_1$ 81% pred, $^{129}$Xe VDP 2.6%) and c) (13-year-old female, 93 days post-HSCT, $FEV_1$ 81% pred, $^{129}$Xe VDP 20%), both of whom have similar high $FEV_1$ % pred, yet the subject in c) has large focal deficits (*e.g.* posterior left and right lungs near apexes, anterior right lung near the base) and higher VDP. d) 13-year-old female, 9 years post-HSCT, $FEV_1$ 52% pred, $^{129}$Xe VDP 41.4%. $^{129}$Xe ventilation is very heterogeneous with large deficits and correspondingly high $^{129}$Xe VDP and low $FEV_1$ % pred.

studies to understand how $^{129}$Xe MRI may play a role in screening bone marrow transplant patients for future BOS risk are needed; however, this small, cross-sectional study demonstrates hyperpolarised $^{129}$Xe MRI as a safe, feasible and sensitive modality in paediatric HSCT patients, even relatively soon (*i.e.* 100 days) post-transplantation, and even in children who are unable to perform reliable spirometry, a vastly underevaluated population.

While $^{129}$Xe VDP correlated with $FEV_1$, it is important to note that $FEV_1$ is known to be somewhat insensitive to early obstruction [43, 44]. Consistent with this were two HSCT subjects who had normal $FEV_1$ but >6% VDP, suggesting that $^{129}$Xe MRI is sensitive to early lung involvement in asymptomatic subjects. The correlation between $^{129}$Xe VDP and $FEV_1/FVC$ ratio ($p<10^{-6}$) was stronger than the correlations between $^{129}$Xe VDP and $FEV_1$ ($p=0.02$) and $FEF_{25-75\%}$ ($p=0.0005$); this is in agreement with Kirby *et al.* [38], who reported a stronger correlation between $^{129}$Xe VDP and $FEV_1/FVC$ ratio than with $FEV_1$. While $FEV_1$ is the gold standard for assessing lung disease and reductions in $FEV_1$ are associated with obstruction, it represents just one functional component of lung disease. $FEV_1/FVC$ ratio is a more specific marker for early airway involvement; this is consistent with the stronger correlation with VDP.

It has been reported that lower pre-transplantation $FEV_1$ is associated with increased risk of pulmonary complications following HSCT [45]; however, this baseline is not always obtainable in paediatric subjects, which severely limits surveillance following transplantation. Without a reliable metric for surveillance, complications may go undetected and untreated, as was seen in this study, in the five subjects who could not perform spirometry, yet $^{129}$Xe ventilation deficits were detected. Without pre-transplantation assessment *via* PFTs or imaging, it is unknown whether these ventilation abnormalities were pre-existing and reflective of underlying lung disease or occurred after HSCT, and this is one shortcoming of this study, in addition to the lack of same-day spirometry and $^{129}$Xe MRI assessment. While spirometry is easily deployable, the paucity

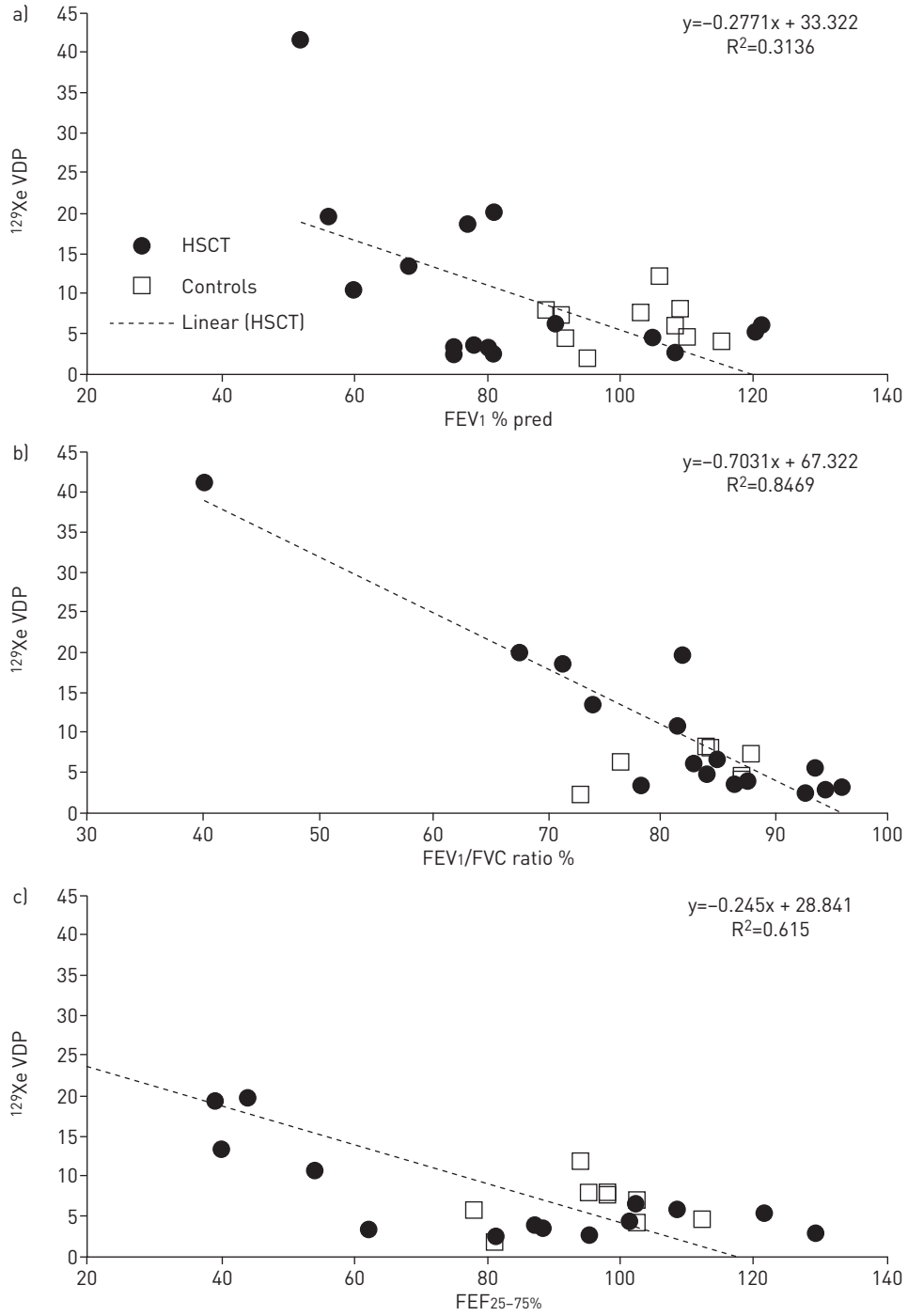


FIGURE 2 Xenon-129 ($^{129}$Xe) ventilation defect percentage (VDP) *versus* a) forced expiratory volume in 1 s ($FEV_1$) % predicted; b) $FEV_1$/forced vital capacity (FVC) ratio; c) forced expiratory flow at 25–75% of FVC ($FEF_{25–75\%}$). HSCT: haematopoietic stem cell transplantation.

of reliable spirometry data in this study reinforces the notion that more robust and sensitive metrics for assessing paediatric lung disease are needed. Indeed, emerging PFTs such as lung clearance index *via* multiple-breath washout and impulse forced oscillometry have shown promise as being less effort-dependent and easier for paediatrics; however, these techniques have not yet been reported in the paediatric HSCT population. Hyperpolarised $^{129}$Xe MRI can address this need while providing additional spatial resolution which may be leveraged for targeted evaluations such as bronchoscopy and lung biopsy.

Currently hyperpolarised $^{129}$Xe gas is regulated by the US FDA as an investigational drug, so its use is limited to research centres with expertise and specialised equipment. However, as the high translational

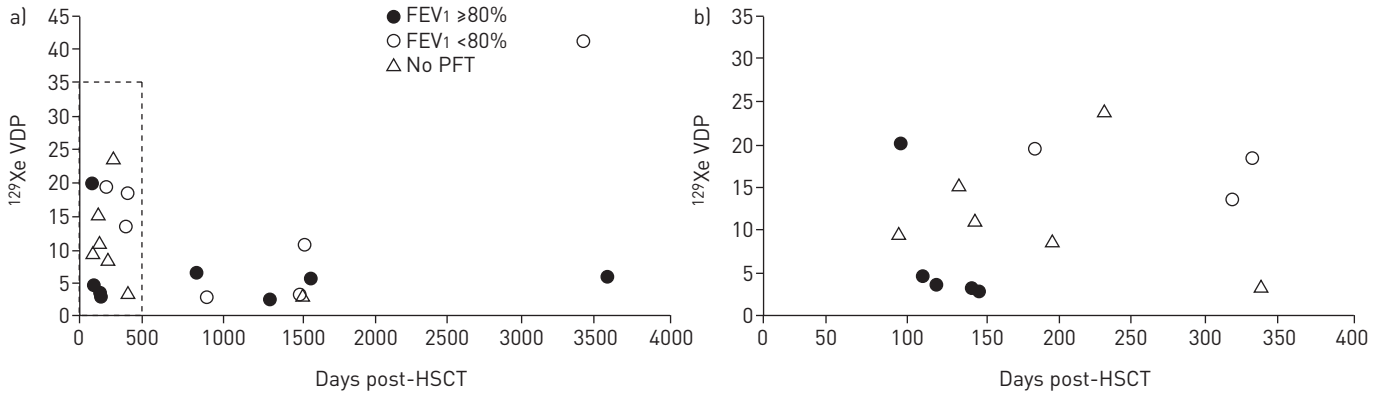


FIGURE 3 a) Xenon-129 ($^{129}$Xe) ventilation defect percentage (VDP) plotted against the number of days post-haematopoietic stem cell transplantation (HSCT); b) subjects imaged within the first year (dashed box in a)) $FEV_1$: forced expiratory volume in 1 s; PFT: pulmonary function test.

potential of $^{129}$Xe MRI continues to be demonstrated across the spectrum of pulmonary disease and patient populations, availability of $^{129}$Xe MRI will probably improve. Alongside other known risk factors such as chronic GVHD [46, 47], ventilation deficits on $^{129}$Xe MRI may inform an algorithm for routine pulmonary screening of HSCT recipients, and as a non-ionising imaging modality, $^{129}$Xe MRI is may be used for serial evaluation in this radiation-sensitive paediatric population. In addition to the need for multisite trials of $^{129}$Xe MRI with larger study cohorts, future longitudinal studies demonstrating the sensitivity and robustness of $^{129}$Xe MRI to early treatment response for individual HSCT patients are in development.

In conclusion, lung ventilation abnormalities following HSCT were quantified using hyperpolarised $^{129}$Xe MRI, providing a means of spatially mapping regional lung function without ionising-radiation exposure. While $^{129}$Xe VDP was correlated with $FEV_1$ % pred, $FEV_1$/FVC ratio and $FEF_{25–75\%}$ from spirometry, there was wide variation in ventilation patterns between subjects with similar spirometric parameters, supporting $^{129}$Xe as a regional biomarker for individualised assessment of lung abnormalities. There is strong translational potential for $^{129}$Xe MRI to personalise treatment approaches for individual HCST patents with pulmonary complications, especially in underevaluated populations such as children who are unable to perform reliable spirometry. $^{129}$Xe ventilation MRI may identify asymptomatic patients who should undergo more frequent screening, pre-emptive anti-inflammatory treatment, or be considered for intervention such as bronchoscopy, where the spatial resolution of $^{129}$Xe MRI can be leveraged to guide the procedure. The sensitivity of $^{129}$Xe to ventilation deficits in asymptomatic HSCT patients with intact spirometry is critical for early intervention to prevent or stabilise disease progression, conserve pulmonary capacity, and ultimately improve outcomes.

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This manuscript is dedicated to our late colleague Javier El-Bietar, who touched the lives of many patients.

Author contributions: All authors contributed to the design of the research project, performed the research, and performed the data analysis and interpretation of the results. Javier El-Bietar died in December 2017. All other authors contributed to drafting and approval of the manuscript.

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