PATIENTS WITH PAEDIATRIC STEM CELL TRANSPLANTS WHO CANNOT PERFORM SPIROMETRY ARE DETECTED BY XENON-129 MRI

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Abstract

Because spirometry is insensitive to early changes following haematopoietic stem cell transplantation (HSCT), The detection of pulmonary morbidity remains a major challenge for intervention, and patient compliance presents additional challenges in paediatrics. The An investigation of regional lung ventilation abnormalities is being carried out in children undergoing HSCT by ^{129}Xe hyperpolarized MRI and spirometry. An MRI was performed on 20 paediatric allogeneic HSCT patients (aged 5–15 years) after breath-holding hyperpolarized ^{129}Xe gas. In lungs with poor ventilation, a ventilation defect percentage (VDP) was used to quantify ventilation deficits caused by obstruction. A forced expiratory volume in one second (FEV1), a force expiratory volume to forced vital capacity ratio (FVC), as well as forced expiratory flow measured by spirometry (FEF25–75%) were also used.According to the results of ^{129}Xe, VDP had a median and standard deviation of 10.4±9.4% (range 2.6–41.4%). According to ^{129}Xe VDP, there is an inverse correlation between FEV1, FEV1/FVC ratio, and FEF_{25-75}%. It has been reported that ^{129}Xe MRI can detect early obstruction in patients with normal spirometry (FEV1 >80%). Two patients will have ventilation deficits, so abnormal conditions that would otherwise have gone undetected and untreated cannot be detected and treated. Five patients will be unable to perform spirometry, but five others will have ventilation deficits.Patients with asymptomatic paediatric HSCT and those who could not perform reliable spirometry were found to have lung ventilation deficits using hyperpolarised ^{129}Xe gas MRI. A reliable method of assessing the involvement of the lungs in children is the ^{129}Xe MRI.

Keywords: MRI, Xenon-129, haematopoietic stem cell transplantation. forced vital capacity ratio

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INTRODUCTION

The graft versus host disease (GVHD) that occurs after allogeneic haematopoietic stem cell transplant (HSCT) can result in pulmonary complications in up to 60% of patients [1, 2]. Bacteria, fungi, or drug-related toxicities may cause infectious complications following transplantation (i.e. >100 days later) such as lung oedema or immune-suppression-related toxicities [2, 3]. BOS is the most severe obstructive lung complication that occurs after HSCT. It is caused by inflammation and fibrosis in the small airways mediated by the immune system. In addition to rapid deterioration of respiratory function, BOS is related with a risk of respiratory mortality and

morbidity. A BOS diagnosis is generally irreversible and has a poor prognosis, despite limited treatment options to stabilize lung function.

Spirometry is traditionally taken to detect lung abnormalities in routine pulmonary function tests (PFTs). Forced expiratory volume in 1 second (FEV1) is the primary clinical parameter from spirometry, but BOS generally can only be diagnosed when FEV1 declines significantly and consistently. In BOS, symptoms include exercise intolerance, chronic non-productive coughing, wheezing, anddyspnoea when exerting. Moderate to severe declines in FEV1 may already be present in these patients. [4]. In HSCT patients, FEV1 declines steepest six months before BOS diagnosis, before stabilizing following diagnosis and treatment [5]. As a result of HSCT, 10% of adult patients with FEV1 and forced vital capacity (FVC) declined significantly after the procedure [6], according to a retrospective study conducted across multiple UK hospitals [7]. There were significant reductions in lung function of >10% among 62% of the paediatric HSCT cohort in the first three to nine months following transplantation. An early detection of lung abnormalities is crucial for lung capacity conservation and improved outcomes[5, 8, 9]. Despite its widespread clinical use and ease of deployment, spirometry has drawbacks, including a low sensitivity to early disease [10, 11]. It is recommended that HSCT patients undergo routine spirometry screening [12, 13], however Prais et al. PFT protocols and fulfilment differ widely between centres according to the results of many retrospective studies of HSCT patients. It might also be more difficult to comply with effort-dependent spirometry in the paediatric population. At the age of 6 years, only 50% of paediatric subjects could perform repeatable spirometry that was acceptable to them, but by the age of 10 years, 85% could do it.

To detect lung disease, clinical imaging including chest radiography and computed tomography (CT) may be utilized in addition to spirometry. BOS typically presents with bronchiectasis, atelectasis, mosaic patterning, and in later stages, severe air trapping [16]. Early disease is often subtle with these features. Radiation exposure concerns in the paediatric population limit routine screening of asymptomatic patients with chest CT due to concerns about ionising radiation exposure.The development of a non-ionising, more sensitive imaging mode would enable more frequent monitoring of lung disease progression and treatment response despite efforts to reduce ionising radiation exposure [17].

Hyperpolarised-gas magnetic resonance imaging (MRI) has been shown to be highly sensitive and specific in detecting early lung obstructions in asymptomatic patients in asthma cystic fibrosis [18, 19], interstitial lung disease, and chronic obstructive pulmonary disease. It is possible to inhale ^{129}Xe gas and obtain MRI images of it in a single breath hold thanks to spin exchange optical pumping (>five seconds). As a result of ^{129}Xe gas' inability to fill obstructed airspaces, ventilating lung regions appear bright on the ^{129}Xe image, while partially or completely obstructed lung regions appear relatively or completely dark on the ^{129}Xe image. ^{129}Xe MRI has demonstrated the potential for quantifying and stabilizing hyperpolarised-gas ventilation deficits, supporting the use of ^{129}Xe MRI as an obstructive lung disease biomarker. In children with HSCT who cannot perform reliable spirometry, ^{129}Xe MRI can detect ventilation abnormalities, while ^{129}Xe ventilation may detect lung abnormalities before traditional spirometry can detect them. (i.e. When HSCT patients have normal spirometry, ^{129}Xe ventilation deficits will exist, providing an opportunity to detect and intervene early.

Methods

Subjectsand ^{129}Xe gas preparation

In the ^{129}Xe MRI study, 20 paediatric allogeneic HSCT recipients were enrolled. As part of the inclusion process, recipients had to be at least 6 years old (younger than the lower limit of the IND) and able to perform a breath-hold test. As shown in Table 1, this cohort has a variety of demographic characteristics. Furthermore, in addition to exclusion criteria for standard MRIs (including claustrophobia and incompatibility of

implants), Chest tightness within the previous week, coughing or wheezing symptoms from current respiratory infections, as well as a pulse oximetry threshold of 95% or higher (if applicable) were excluded. Each subject was medically stable when imaging was performed. Through a commercial polariser, isotopically enriched Xe gas (86% ^{129}Xe) was polarized to 20% by a Tedlar bag equipped with Tygon tubing, hose clamps, and mouthpieces.

MRIprocedure

The subjects were placed supine in a home-built ^{129}Xe saddle coil tuned to 35.3 MHz in a Philips 3 Tesla Achieva MRI scanner (Best, the Netherlands). Optimal field of view for lung imaging was achieved first after performing three-plane hydrogen-1 (1H) localization scans. With practice breaths of room air followed by a 1H gradient-echo scan. All breath-holds (1H and ^{129}Xe) were initiated at functional residual capacity after the subject inhaled and exhaled twice. MRI scans requiring a breath-hold were limited to 16 seconds, and hyperpolarised ^{129}Xe MRIs were limited to 15 minutes. Repeated breath holding practice with room air ensured compliance since ^{129}Xe gas is non-renewable.During a brief 2-s breath-hold, 250 mL of hyperpolarized ^{129}Xe gas was administered for calibration to optimize in vivo flip angle for the ^{129}Xe ventilation images. A ^{129}Xe gas dose equivalent to one-sixth of the predicted total lung capacity was predicted using plethysmography-based predictive equations [33A gradient echo scanner was used to obtain this data (9–12° flip angle, repetition time=8 ms, echo time=4 ms, 9-15 slices, depending on the size of the subject and voxel size 3-3-6-15 mm^3). [34]).

Medical professionals (e.g., registered nurses or physicians) administered the ^{129}Xe gas, and no more than 2 minutes passed between consecutive breath-holds. Using a magnetic resonance-compatible pulse oximeter, blood oxygenation and heart rate were monitored throughout the ^{129}Xe breathholds. In the paired t-test, changes in vitals were compared to baseline resting values with a p-value <0.05 considered significant. A follow-up phone call was made on days 1 and 30 of the year following the ^{129}Xe MRI to assess any adverse events which occurred during the procedure.

^{129}Xeventilationanalysis

We used MathWorks' MATLAB custom software to analyze^{129}Xe ventilation images. The edges of the lungs were defined using 1H MRI, excluding large airways and vessels. VDP (ventilation defect percentage) was calculated as a percentage of the total lung volume using a threshold of 60% of the whole-lung ^{129}Xe signal. The hyperpolarised-gas MR literature has long established a reproducible, well-established method to calculate VDP. Cystic fibrosis patients with lung obstruction have been distinguished from healthy paediatric controls at this 60% threshold. We compared ^{129}Xe VDP with an age-matched control cohort of 10 subjects (n = 10; seven males and three females) ±SD age of 12±3 years (range5–15 years) and FEV1 % predicted of 102±9%, which were published previously. When ^{129}Xe VDP was above 6%, which is typical for our control subjects, ventilation deficits were considered present. An analysis of the ^{129}Xe image results was conducted in comparison with FEV1, FEV1/FVC and forced expiratory flow measurements. Spirometry FEF25-75 percent should be analysed using linear regression and Pearson's correlations. Medical records were reviewed for patients who had an MRI within six months of a spirometry report. If clinical spirometry was not available, MRI was performed.

RESULTS

Each subject completed the ^{129}Xe MRI procedure without any complications. This table shows changes in SpO_2 and heart rate during calibration and ventilation with Xe gas. An 8% decrease in SpO_2 from baseline was observed as expected after gas ventilation. With normal breathing of room air, the average SpO_2 was restored for all 15 subjects who experienced a decline in SpO_2. As previously reported, there were no adverse events associated with ^{129}Xe MRI in pediatric or adult subjects that required medical intervention.Patients with similar FEV1 % pred values displayed a wide variation in ^{129}Xe ventilation pattern. A ventilation deficit was found in 11 subjects (VDP >6%).The mean ± SD ^{129}Xe VDP was 10.4±9.5% in all HSCT

patients , which was elevated relative to controls (6.3±2.8%), but did not reach statistical significance (p<0.06). The maximum separation between HSCT subjects with BOS and controls was provided by ^{129}Xe VDP thresholds between 60% and 70%. In subjects with similar spirometry values, the ^{129}Xe VDP is significantly different from the FEV1/FVC ratio and FEF25–75%. A mean of 46 days passed between spirometry and ^{129}Xe MRI in 15 out of 20 subjects. ^{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 FEF25–75%(p=0.0005 andPearson'scoefficient −0.78).

TABLE1:Variety of demographic characteristics

Ageyears	
Sex	
Female	12
Male	8
Diagnosis	
Bonemarrowfailure	10
Malignancy	4
Primaryimmunedeficiency Malignancy	6
Conditioningregimen	
ATG/BU/CY/FLU	4
Campath/FLU/MELPH	6
BU/FLU/TT	1
ATG/BU/CY BU/FLU/TT	3
ATG/FLU/TT/treosulfan	1
ATG/CY	1
FLU	1
Campath/FLU	1
ATG/CY+TBI	1
Campath/FLU/BU+TBI	1
Donorsource/HLAstatus	
RELATED	
MATCHED(8/8,10/10)	2
UNRELATED	
MATCHED(8/8,10/10,12/12)	8
MISMATCHED(7/8,8–9/10)	10
Stem-cellsource	
PBSC	5
BONEMARROW	12
BONEMARROW/CORDBLOOD	3
GVHDprophylaxis	
CD34selection	4
CSA/PRED CD34selection	5
CSA/MFF	3
CSA/MTX	3
ATG/CSA/maraviroc/PRED	2

CSA/maraviroc/PRED	1
TACROLIMUS/SIROLIMUS	1
ABATACEPT/PRED	1
ACUTE GVHD N/N (%)	8/20
SKIN (GRADE 1–3)	7
GASTROINTESTINAL (GRADE 2–3)	2
CHRONIC GVHD N/N (%)	8/20
LUNG	3
SKIN (LIMITED-EXTENSIVE)	5
EYES	2
VAGINA	3
MOUTH	3
GASTROINTESTINAL	2
LIVER	1

FLU:fludarabine;BU:busulfan; ATG:anti-thymocyteglobulin; TT: thiotepa; HLA: human leukocyte antigen; GVHD:graft *versus*host disease PBSC: peripheral blood stem cell;CSA: cyclosporine; CY: cyclophosphamide; PRED: prednisone; MTX: methotrexate; GVHD:graft *versus*host disease; MFF: mycophenolatemofetil; MELPH:melphalan; TBI: total body irradiation. Despite technical difficulties, seven out of 20 participants were able to perform reliable post-transplant spirometry, but all completed the ^{129}Xe MRI protocol. Most of the subjects without reliable spirometry belonged to the youngest subgroup, with an average age of 8±3 years. 5 of 7 subjects showed ^{129}Xe ventilation deficits (VDP greater than 6%). Based on reliable pre-transplantation and post-transplantation FEV1 % pred data, ^{129}Xe MRI revealed an average 8% decrease in FEV1. In the 16 patients with reliable spirometry (n=16), there was a significant difference in age (average 12 3 years, range 6 17 years; p =0.008) and the ^{129}Xe VDP was 10.3 10.3% (range 3 41.4%; nonsignificant). Chronic GVHD patients (n=8) showed no significant difference from those without chronic GVHD (10.1±10.4%). In four patients with chronic GVHD and four without, there was no statistical difference.

To assess the early and late effects of HSCT on ventilation, ^{129}Xe VDP was compared with days post-HSCT. As early as two weeks after HSCT, ventilation deficits were identified,one patient with normal FEV1 and another unable to perform reliable spirometry were included in the subgroup of 13 who underwent MRI within one year of HSCT.

TABLE2: **Xenon-129 magnetic resonance imaging changes blood oxygenation and heart rate**

FLIP-ANGLE CALIBRATION DOSE					VENTILATION-IMAGINGDOSE	
	Baseline	Atnadir of S_pO_2	2minpost-procedure	Baseline	Atnadir of S_pO_2	2minpost-procedure
S_pO_2%	93.5±1.5	94.5±4.5	98.5±1.5	97.5±1.5	89.5±5.5	97.0±1.8
	(95–100)	(86–104)	(93–100)	(94–100)	(74–97)	(94–100)
p-value		0.0015	0.75		1×10^{-6}	0.008
Heartratebeats-min^{-1}	92±14	93±11	92±13	92±13	96±13	90±15
	(74–109)	(82–121)	(70–116)	(68–124)	(66–123)	(67–125)
p-value		0.80	0.54		0.33	0.33

DISCUSSION

^{129}Xe hyperpolarisation MRI for the HSCT population is the first time it has been demonstrated. Paediatric HSCT patients were found to have a wide range of lung ventilation abnormalities on ^{129}Xe MRI. ^{129}Xe MRI has been used in previously reported studies of pulmonary disease with mild obstruction [19], which revealed ventilation deficits in asymptomatic HSCT patients with normal FEV1. Functional lung imaging after HSCT successfully diagnosed bronchiolitis obliterans with matched ventilation–perfusion deficits in an adult with relatively unremarkable chest CT.

An analysis of long-term ^{129}Xe MRI screening for bone disease. However, the small, cross-sectional study demonstrates that hyperpolarized ^{129}Xe MRI can be used to monitor paediatric HSCT patients for future BOS risk, even relatively soon after transplantation (100 days), as well as children who cannot perform reliable spirometry, a population that is understudied in general.In spite of the fact that ^{129}Xe VDP correlates with FEV1, relatively early obstruction is unknown to affect FEV1. ^{129}Xe MRI was sensitive to early lung involvement in asymptomatic subjects who had normal FEV1 but >6% VDP. Kirby et al. reported that FEV1 and FEF25–75% have greater correlations than FEV1/FVC ratio (p|<0.02). A closer relationship between ^{129}Xe VDP and FEV1/FVC ratio is found. Reduced FEV1 also indicates obstruction in addition to being a gold standard for assessing lung disease. As evidenced by the stronger correlation with VDP, FEV1/FVC is a better indicator of early airway involvement.

HSCT has been shown to increase pulmonary complications in patients with lower pre-transplant FEV1; however, in paediatric patients this baseline is not always available, which severely limits follow-up following transplantation. The spirometer was inaccessible to five subjects, yet ^{129}Xe ventilation deficits were detected despite the lack ofan effective surveillance metric, leading to complications going untreated and undetected. Pre-transplantation ventilation abnormalities were not assessed in this study via PFTs or imaging, so it is unclear if they were underlying lung diseases or after HSCT.. Additionally, ^{129}Xe MRI and same-day spirometry assessment were not available in this study. In spite of spirometry's ease of use, the lack of reliable spirometry data in this study supports the idea that better spirometry metrics are needed for the assessment of paediatric lung disease. Pulmonary clearance index and impulse oscillometry in pediatrics are emerging PFTs, which are less effort-dependent and easier to perform. Unfortunately, there are no reports involving paediatric HSCT yet. As well as providing additional spatial resolution, hyperpolarised ^{129}Xe MRI can be used to evaluate the lungs in more detail after bronchoscopy and lung biopsy, for example.

The US FDA currently regulates hyperpolarized ^{129}Xe gas as an investigational drug, so it can only be used in research centers with special expertise and equipment. While ^{129}Xe MRI may improve availability in the future as it continues to demonstrate high translational potential across a wide spectrum of pulmonary diseases and patient populations, availability may be limited for a while because of its high translational potential. A routine pulmonary screening algorithm for HSCT recipients may be informed by ventilation deficits on ^{129}Xe MRI, in addition to other known risk factors like chronic GVHD. This radiation-sensitive population can benefit from ^{129}Xe MRI, a non-ionizing imaging modality. We are developing future longitudinal studies to demonstrate how ^{129}Xe MRI is sensitive and robust to early treatment response in HSCT patients, in addition to multisite trials with larger cohorts.

CONCLUSION

We conducted quantitative lung ventilation analysis using hyperpolarised ^{129}Xe MRI after HSCT, allowing spatial mapping of A non-ionising method of regional lung function. It appears that ^{129}Xe VDP has a correlation with FEV1 percent pred, FEV1/FVC ratio, and FEF25–75%, but ventilation patterns vary widely among subjects with similar spirometric parameters, suggesting that ^{129}Xe may serve as a regional biomarker that allows individualisation of lung abnormalities. Understudied populations, such as children

who cannot perform reliable spirometry, can benefit from 129Xe MRI for HCST patients with pulmonary complications. Patients who undergo ^{129}Xe ventilation MRI may be identified as being asymptomatic and need more frequent screening, treatment of inflammation pre-emptively, or even consideration for surgery, such as bronchoscopy that may benefit from the spatial resolution of ^{129}Xe ventilation MRI. Asymptomatic HSCT patients with intact spirometry need immediate treatment to slow or stop disease progression and preserve pulmonary capacity to improve outcomes.

References

1. SakaidaE,NakasekoC,HarimaA,etal.Late-onsetnoninfectiouspulmonarycomplicationsafterallogeneic stem cell transplantation are significantly associated with chronic graft-*versus*-hostdisease and with the graft-*versus*-leukemia effect. Blood 2003; 102: 4236–4242.
2. KotloffRM,AhyaVN,CrawfordSW.Pulmonarycomplicationsofsolidorganandhematopoieticstemcell transplantation. AmJRespirCritCare Med2004;170: 22–48.
3. Fidler MM, Reulen RC, Bright CJ, et al. Respiratory mortality of childhood, adolescent and youngadultcancer survivors. Thorax2018; 73: 959–968.
4. WilliamsKM.HowItreatbronchiolitisobliteranssyndromeafterhematopoieticstemcelltransplantation. Blood 2017; 129: 448–455.
5. Cheng GS, Storer B, Chien JW, et al. Lung function trajectory in bronchiolitis obliterans syndromeafter allogeneic hematopoietic cell transplant. Ann Am ThoracSoc 2016; 13: 1932–1939.
6. Dharmagunawardena RT, Pearce RM, Lee J, et al. S135 A retrospective multi-centre study of theeffectsofallogeneichaematopoieticstemcelltransplantationonpulmonaryfunction.Thorax2011;66:Suppl.4, A62.
7. Uhlving HH, Bang CL, Christensen IJ, et al. Lung function after allogeneic hematopoietic stem celltransplantation in children: a longitudinal study in a population-based cohort. Biol Blood MarrowTransplant2013; 19: 1348–1354.
8. Cooke KR. A “window of opportunity” for patients with late-onset pulmonary dysfunction afterallogeneichematopoieticcelltransplantation.BiolBloodMarrowTransplant2014;20:291–292.
9. PalmerJ,WilliamsK,InamotoY,etal.PulmonarysymptomsmeasuredbytheNationalInstitutesofHealth lung score predict overall survival, nonrelapse mortality, and patient-reported outcomes inchronic graft-versus-host disease. Biol Blood Marrow Transplant 2014; 20: 337–344.
10. GustafssonPM,DeJongPA,TiddensHA,etal. Multiple-breath inert gas washout and spirometry *versus* structural lung disease incysticfibrosis.Thorax2008;63:129–134.
11. Horsley AR, Gustafsson PM, Macleod KA, et al. Lung clearance index is a sensitive, repeatableandpracticalmeasureofairways diseasein adultswithcysticfibrosis.Thorax2008; 63:135–140.
12. CarpenterPA,KitkoCL,EladS,etal.NationalInstitutesofHealthconsensusdevelopmentprojectoncriteriaforclinicaltrialsinchronicgraft-versus-hostdisease:V.The2014AncillaryTherapyandSupportiveCareworkinggroupreport.BiolBloodMarrowTransplant2015;21:1167–1187.
13. Majhail NS, Rizzo JD, Lee SJ, et al. Recommended screening and preventive practices for long-termsurvivorsafterhematopoieticcelltransplantation.BoneMarrowTransplant2012;47:337–341.
14. Prais D, Sinik MM, Stein J, et al. Effectiveness of long-term routine pulmonary functionsurveillancefollowingpediatrichematopoieticstemcelltransplantation.PediatrPulmonol2014;49: 1124–1132. LoebJS,BlowerWC,FeldsteinJF,etal.AcceptabilityandrepeatabilityofspirometryinchildrenusingupdatedATS/ERScriteria.PediatrPulmonol2008;43:1020–1024.
15. Gazourian L, Coronata AMF, Rogers AJ, et al. Airway dilation in bronchiolitis obliterans afterallogeneic hematopoietic

stem cell transplantation. Respir Med 2013; 107: 276–283. TogniFilho PH, Casagrande JLM, Lederman HM. Utility of the inspiratory phase in high-resolution computed tomography evaluations of pediatric patients with bronchiolitis obliteransafterallogeneicbonemarrowtransplant:reducingpatientradiationexposure. RadiolBras2017;50: 90–96.

16. ThomenRP,WalkupLL,RoachDJ,etal.Hyperpolarized^{129}Xeforinvestigationofmildcysticfibrosislung diseasein pediatrics.JCyst Fibros2017; 16:275–282.
17. KanhereN,CouchMJ,KowalikK,etal.Correlationoflungclearanceindexwithhyperpolarized^{129}Xe magnetic resonance imaging in pediatric subjects with cystic fibrosis. Am J RespirCritCareMed2017; 196: 1073–1075.