CHEST

Pulmonary Functional MRI and CT in a Survivor of Bronchiolitis and Respiratory Failure Caused by e-Cigarette Use

Rachel L. Eddy, PhD; Hana Serajeddini, MD; Danielle Knipping, RN; Simon T. Landman, MBBS; Karen J. Bosma, MD; Constance A. Mackenzie, MD; Inderdeep Dhaliwal, MD; and Grace Parraga, PhD

Although nearly 3,000 e-cigarette-related hospitalizations have been reported in North America, the long-term outcomes in these patients have not been described. We followed an 18-year-old boy who survived acute critical illness and respiratory failure related to 5 months of e-cigarette use. Chronic irreversible airflow obstruction and markedly abnormal ^{129}Xe MRI ventilation heterogeneity was observed and persisted 8 months after hospital discharge, despite improvement in quality-of-life and chest CT findings. Lung clearance index and oscillometry measures were also highly abnormal at 8 months postdischarge. Although ^{129}Xe MRI ventilation abnormalities were dominant in the lung apices and central lung regions, the pattern of ventilation defects was dissimilar to ventilation heterogeneity observed in patients with obstructive lung disease, such as asthma and COPD. Our findings underscore the long-term functional impacts of e-cigarette-related lung injury in survivors of critical illness; longitudinal evaluations may shed light on the pathophysiologic mechanisms that drive e-cigarette-related lung disease.

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KEY WORDS: CT; e-Cigarettes; MRI; vaping

Hospitalizations related to e-cigarette vaping-associated lung injury (EVALI) have declined since the initial outbreak,[1,2] but the long-term outcomes in survivors of acute critical illness related to e-cigarette use are not well understood. A variety of CT abnormalities have been reported in the acute phase,[2-4] but to our knowledge, there have been no CT or MRI follow-up studies in EVALI patients. ^{129}Xe MRI is noteworthy because it provides a way to sensitively and longitudinally quantify ventilation and acinar duct abnormalities in patients.[5-9]

e-Cigarette use can lead to a variety of respiratory complications, although most well known currently is alveolar damage as reflected in the EVALI epidemic.[2,4] We report CT and ^{129}Xe MRI 8 months after hospital discharge in an 18-year-old boy (17 years old at first

ABBREVIATIONS: EVALI = e-cigarette, or vaping, product use-associated lung injury; LCI = lung clearance index; R = resistance; TAC = total airway count; VDP = ventilation defect percent; X = reactance

AFFILIATIONS: From the Robarts Research Institute (Drs Eddy and Parraga and Ms Knipping), the Department of Medical Biophysics (Drs Eddy and Parraga), and the Divisions of Respirology (Drs Serajeddini, Landman, Mackenzie, Dhaliwal, and Parraga), Critical Care (Dr Bosma), and Clinical Pharmacology and Toxicology (Dr Mackenzie), Department of Medicine, Western University, London, ON, Canada; and the Ontario, Manitoba, Nunavut Poison Centre (Dr Mackenzie), Canada.

The original case was reported up to hospital discharge (Landman et al, CMAJ 2019), and a preliminary version of the post-discharge results were reported in an abstract for the ATS 2020 International Conference (now canceled).

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CORRESPONDENCE TO: Grace Parraga, PhD, Robarts Research Institute, 1151 Richmond St N, London, ON, Canada, N6A 5B7; e-mail: gparraga@robarts.ca

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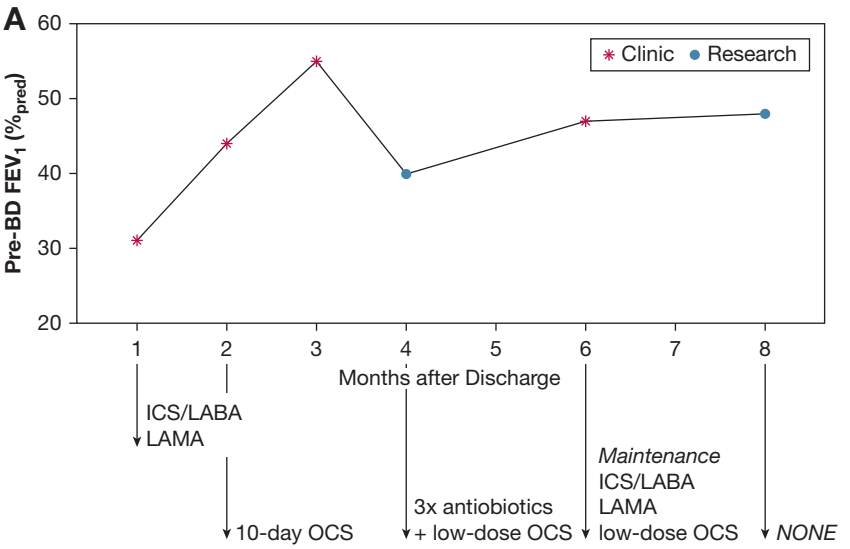

B

Time after discharge	4 mo		8 mo	
	Pre-BD	Post-BD	Pre-BD	Post-BD
FEV_1 L	1.64	1.66	2.03	2.23
FEV_1 L $\%_{pred}$	40	40	48	53
FVC $\%_{pred}$	69	72	75	82
FEV_1/FVC %	49	47	55	55
RV/TLC $\%_{pred}$	193	208	196	167
LCI	15.2	16.8	15.8	16.5
R_5 $cmH_2O{\cdot}s/L$	–	–	5.13	4.34
$R_{5\text{-}19}$ $cmH_2O{\cdot}s/L$	–	–	1.92	1.82
X_5 $cmH_2O{\cdot}s/L$	–	–	–3.08	–2.31

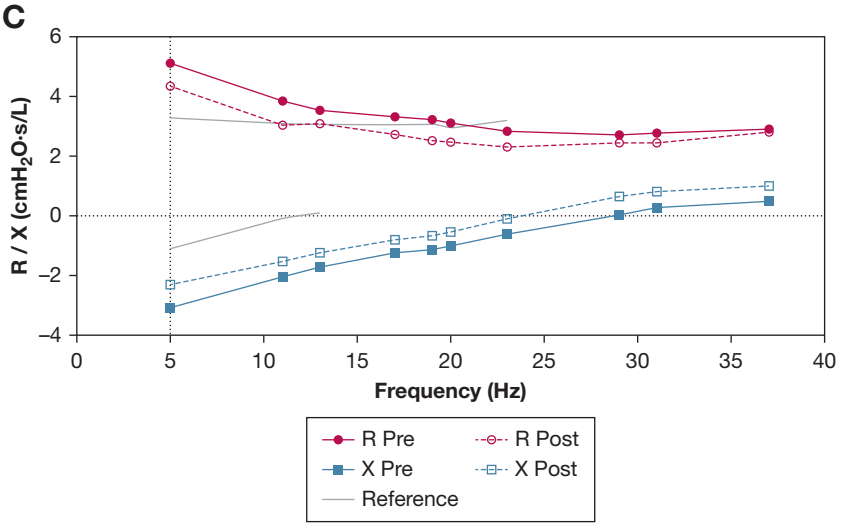

Figure 1 – *Pulmonary function tests following hospital discharge. A, FEV_1 and treatment decisions postdischarge. Blue circles indicate MRI research visits. B, Pre- and post-bronchodilator (BD) pulmonary function 4 and 8 months postdischarge. C, Pre- and post-BD oscillometry plots over 5 to 37 Hz at 8 months postdischarge. Resistance (R) is shown using circles, and reactance (X) is shown using squares. Pre-BD measurements are shown using solid symbols and lines and post-BD measurements are shown using open symbols and dotted lines. Reference lines for this patient are shown in gray. BD = bronchodilation; LABA = long-acting beta-agonist; LAMA = long-acting muscarinic antagonist; LCI = lung clearance index; OCS = oral corticosteroids; R = resistance; RV = residual volume; TLC = total lung capacity; X = reactance.*

presentation to hospital) who experienced near-fatal respiratory failure attributed to a 5-month history of daily e-cigarette use. The clinical case was previously reported[10] as a unique diagnosis of bronchiolitis related to e-cigarette use. To the best of our knowledge, this is the first report of postdischarge imaging findings in a survivor.

Case Report

A 17-year-old boy (at first presentation to hospital; 18 years old during time of postdischarge follow-up) suffered severe acute bronchiolitis associated with e-cigarette use, which required critical care, invasive mechanical ventilation, and extracorporeal membrane oxygenation during 47 days of hospital-based care. Full details of his clinical presentation were previously published.[10] Briefly, the patient was previously healthy, with no preexisting respiratory conditions and had vaped flavored e-liquids and tetrahydrocannabinol daily for 5 months before hospital admission. Flavors included "dew mountain," "green apple," and "cotton candy" purchased through an online Canadian retailer, and he regularly added tetrahydrocannabinol to the e-liquid. On admission, chest CT showed diffuse centrilobular tree-in-bud opacities in the absence of mosaic attenuation, ground-glass opacity, or consolidation. Based on CT findings and negative infectious workup, the patient was diagnosed with bronchiolitis, which differed from previous EVALI reports from the United States.[2] After discharge, the patient was followed up clinically, using spirometry 1, 2, 3, and 6 months postdischarge, and he underwent full-inspiration CT 1 and 7 months postdischarge. He provided written informed-consent to ^{129}Xe MRI (NCT02723500), acquired 4 and 8 months postdischarge. VIDAVision (VIDA Diagnostics Inc) was used to segment the CT airways; MRI ventilation defects were quantified as ventilation-defect-percent (VDP).[11]

Figure 1 shows FEV_1 increased from 31%$_{pred}$ to 55%$_{pred}$, 3 months postdischarge, when the patient's condition was managed using mometasone-formoterol (200/5-µg metered dose inhaler, 2 inhalations twice daily via spacer) and tiotropium (2.5-mg mist-inhaler 2 inhalations once daily) plus salbutamol (100-µg metered dose inhaler 2 inhalations as needed)[10] and a 10-day course of 40 mg oral prednisone. Three months postdischarge, he experienced worsening sinus congestion/cough and sputum purulence without consolidation or pneumonia. He was prescribed two courses of azithromycin (500 mg once daily for 3 days each) and one course of levofloxacin (500 mg once daily for 7 days) as an outpatient, after which he was prescribed daily 10 mg oral prednisone. At 4 months postdischarge, FEV_1 declined to 40%$_{pred}$, whereas at 6 and 8 months postdischarge, FEV_1 remained at 47%$_{pred}$ and 48%$_{pred}$, respectively. The patient was compliant with daily mometasone-formoterol (200/5-µg metered dose inhaler 2 inhalations twice daily via spacer) and tiotropium (2.5-mg mist-inhaler 2 inhalations once daily) inhalers and 10 mg prednisone at 6 months postdischarge, but he chose to stop inhaled and oral medication, 7 months postdischarge.

Figure 1 also shows that FEV_1 was not bronchodilator reversible, and residual volume/total lung capacity remained elevated postbronchodilator; the lung clearance index (LCI) measured using multiple-breath nitrogen-washout was markedly abnormal (LCI = 16.5; upper limit of normal = 7.0 for an 18-year-old boy[12]) and did not improve postbronchodilator. Eight months postdischarge, he was evaluated using oscillometry, concurrent with MRI. Resistance (R) was abnormally elevated (R_5 = 156%$_{pred}$, $R_{5\text{-}19}$ = 945%$_{pred}$), and reactance (X) was abnormally low (X_5 = 279%$_{pred}$). The frequency-dependence of R and X reflected heterogeneously narrowed and stiffened small airways, respectively. Both R and X did not meet the recommended thresholds for positive bronchodilator responses (-40% for R and +50% for X[13]); postbronchodilator, R decreased -16% whereas X increased +24%. St. George's Respiratory Questionnaire scores improved from 57 at 4 months postdischarge, to 8, 8 months postdischarge—an improvement greater than the minimal-clinically-important-difference.[14]

Figure 2 shows CT acquired 1 month postdischarge,[10] which showed incomplete resolution of centrilobular nodules and new mild bronchial dilation. Segmented CT airway trees (yellow) showed a total-airway-count (TAC) of 459 (twofold greater than TAC measured in healthy never smokers[15]), which was likely due to airway dilation and airway wall thickening, which allows CT segmentation of distal airways, thereby increasing TAC. Figure 2 also shows that at 4 months postdischarge, ^{129}Xe MRI ventilation was highly heterogeneous with prominent abnormalities in the apices and central lung (VDP = 21%). At 4 months postdischarge, the patient also underwent postbronchodilator diffusion-weighted ^{129}Xe MRI to measure the apparent diffusion coefficient, an indicator of airspace enlargement.[16] Whole-lung apparent diffusion coefficient was 0.048 cm^2/second, which is similar to values previously reported for healthy volunteers[16,17] and suggests that there was no evidence of airspace enlargement or alveolar damage.

Figure 2B shows CT acquired 7 months postdischarge, which indicated that most of the nodules resolved, whereas TAC diminished to 274, perhaps because of reduced airway dilation compared with CT at 1 month postdischarge. Despite improved CT findings, MRI

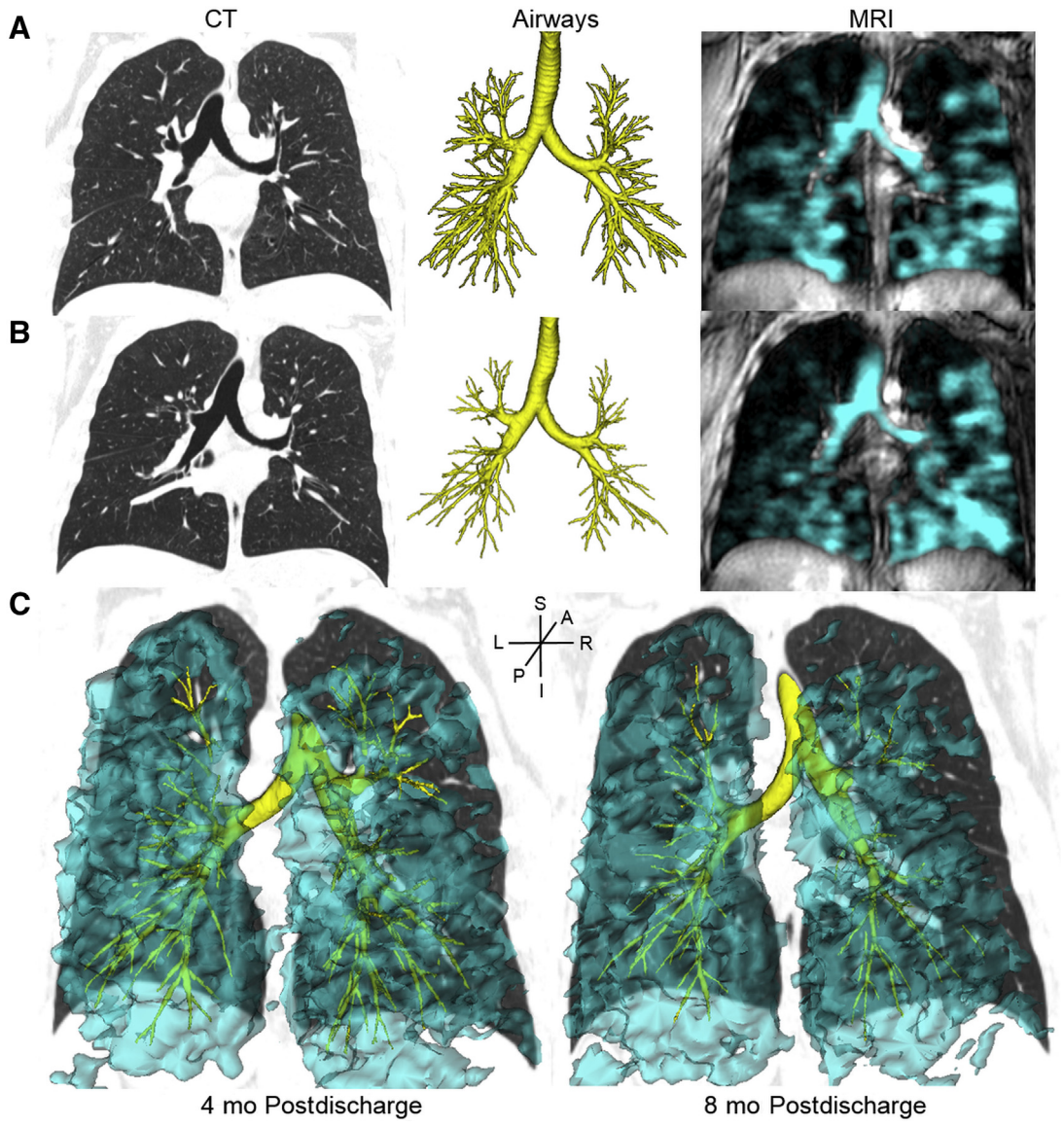

Figure 2 – *CT and MR imaging after hospital discharge. A, thoracic CT and segmented 3D airway tree acquired 1 month postdischarge and coronal center slice ^{129}Xe ventilation (cyan) co-registered to anatomic ^{1}H (grayscale) 4 months postdischarge. B, thoracic CT and segmented 3D airway tree acquired 7 months postdischarge as well as ^{129}Xe MRI acquired 8 months postdischarge. C, coronal reconstructed CT co-registered with MRI to highlight structure-function relationships 4 (left) and 8 months (right) postdischarge.*

ventilation heterogeneity was not improved 8 months postdischarge, and MRI VDP (22%) was still markedly abnormal.

Figure 2C shows MRI ventilation co-registered to CT from a posterior view to highlight structure-function relationships at 4 months and 8 months postdischarge. At both times, airways may be observed proximal to temporally and spatially persistent MRI ventilation defects, especially in the right and left upper lobes.

Discussion

Nearly 3,000 e-cigarette-related hospitalizations have been reported in the United States,[1] but the long-term outcomes in these patients have not been described. In this survivor, there were persistent pulmonary functional effects, 8 months postdischarge. Although CT nodules and patient-reported quality of life improved, there was persistent, chronic, irreversible airflow limitation and gas trapping, despite triple bronchodilator therapy and daily low-dose oral

corticosteroids. Perhaps most alarming was the highly heterogeneous ventilation, prominent in the central lung, which did not improve over time. This abnormal ventilation pattern is novel and dissimilar to ventilation heterogeneity observed in patients with obstructive lung disease.[5,9] In asthma and COPD, ^{129}Xe MRI ventilation abnormalities are typically wedge-shaped and follow the segmental and subsegmental airways to the periphery. Typically, these ventilation defects are also spatially related to abnormally remodeled airways.[18,19] The diagnosis of bronchiolitis in this patient,[10] in contrast to alveolar damage reported in previously published e-cigarette-related cases,[2] may have contributed to this unique and persistently abnormal ventilation pattern.

Our findings underscore the long-term functional impacts of e-cigarette-related lung injury. Longitudinal evaluations in survivors may shed light on pathophysiologic mechanisms that drive e-cigarette-related lung disease.

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