patients with cancer. Our results reinforce the importance of timely palliative care among patients with advanced lung cancer.

Study limitations include misclassification bias for COD; however, the SDR is a comprehensive database specifically designed to capture COD. Depression before cancer diagnosis was included in the Functional Comorbidity Index; however, confounding by other comorbid psychiatric conditions was not studied. Suicides, not suicide attempts, were studied. Palliative care delivered by nonspecialists (e.g., primary care clinicians) was not measured. Alcohol and illicit drug use are associated with suicide, but reliable estimates were unavailable. Higher health care use could confound the relationship between palliative care and suicide; however, lung cancer treatments received were similar between groups. The potential for immortal time bias exists as patients had to live long enough to receive a palliative care encounter.

Veterans with advanced lung cancer are at substantially increased risk for suicide. Palliative care is associated with a decreased risk of suicide, and elements of this patient-centered approach may inform enhanced suicide prevention and treatment efforts, which are urgently needed. This study adds to the literature in support of timely palliative care among patients with lung cancer.

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Donald R. Sullivan, M.D., M.A., M.C.R.*
Oregon Health and Science University
Portland, Oregon

and
Veterans Affairs Portland Health Care System
Portland, Oregon

Christopher W. Forsberg, M.S.
Sara E. Golden, M.P.H.
Veterans Affairs Portland Health Care System
Portland, Oregon

Linda Ganzini, M.D., M.P.H.
Steven K. Dobscha, M.D.
Christopher G. Slatore, M.D., M.S.
Oregon Health and Science University
Portland, Oregon

and

Veterans Affairs Portland Health Care System
Portland, Oregon

ORCID ID: 0000-0003-3266-3389 (D.R.S.).

*Corresponding author (e-mail: sullivad@ohsu.edu).

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Prominent Bronchopulmonary Vascular Anastomoses in Fatal Childhood Asthma

To the Editor:

Despite advances in understanding of disease pathobiology and improvements in clinical care, asthma-associated deaths in young patients remain a persistent problem. Risk of death in childhood asthma is associated with the overuse of short-acting β -agonist

drug therapy, poor drug compliance, reduced symptom perception with the onset of asthma exacerbations, past history of the need for intensive care unit care, and delayed or poor care coordination related to socioeconomic issues (1). Fatal asthma attacks in children are characterized by significant variability in time course, and a subset of these children die suddenly and unexpectedly without clear explanation (2). Individuals with asthma who die suddenly often do not show a progressive increase in respiratory distress with wheezing or other clinical signs of severe airway obstruction or apparent increases in refractory responses to asthma therapies. In contrast to cases with slower onset and disease progression over days to weeks, nearly 50% of fatal cases are of acute onset with rapid progression of symptoms and death within hours. These patients have been described and referred to as having sudden-onset fatal asthma, for which there is limited understanding of underlying pathomechanisms (1–4).

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Table 1. Relevant clinical and pathologic information

Patient	Death Circumstance	Age at Onset of Asthma	Number of Prior Hospital Visits	Medications	Comorbid Conditions	Right Ventricular Hypertrophy	Airways with Plug	Inflamed Airways	Loose Mucus in Airways	Basement Membrane Thickening	Open IBA	PA Muscular Hypertrophy	BA Remodeling
1	Morning wheezing treated with nebulizer, during last treatment developed cardiorespiratory arrest leading to severe anoxic brain injury on the first day, support withdrawn on the fourth day of hospitalization	Unknown	2	Unknown	None	No	3 in 73 (4%)	3 in 73 (4%)	5 in 73 (7%)	Present	Present	Mild	No
2*	No previous symptoms, found unresponsive 10 min after dinner in the bathroom, death within 10 h	4 mo	9	*Prednisone, fluticasone-salmeterol, albuterol, montelukast	None	No	3 in 69 (4%)	0 in 69 (0%)	8 in 69 (11%)	Present	Present	Moderate-severe	Marked
3	5-d history of cold symptoms, could not awaken from sleep, cardiorespiratory arrest, death within 3 h	3 yr	8	Albuterol, fluticasone	Esophageal reflux	Mild	4 in 159 (2%)	9 in 159 (6%)	9 in 159 (6%)	Present	Present	Mild-moderate	Mild

Definition of abbreviations: BA = bronchial artery; IBA = intrapulmonary bronchopulmonary anastomosis; PA = pulmonary artery.

Clinical information and cardiac pathology data extracted from charts and autopsy reports are displayed. Quantification of airway-related microscopic pathology was done by reviewing all sampled lung tissues and counting all airways, including bronchi and bronchioles. Age-matched control was a 6-year-old girl with unexplained sudden death with a remote history of idiopathic cardiomyopathy.

*Patient 2 did not take these prescribed medications prior 5 months, owing to insurance issues.

Figure 1. (A) Lung histologic sections from three cases of sudden death in children with asthma demonstrate open intrapulmonary bronchopulmonary anastomosis (IBA) between bronchial arteries (BAs) and pulmonary arteries (PAs). (B) This connection is confirmed by computerized three-dimensional image reconstruction. (C) Bronchial arteries, veins, and microvessels are prominent and markedly congested (arrows), whereas (D) the PAs are markedly thickened and remodeled. Mild inflammation around an airway (Aw) (A) and loose intraluminal mucus material within an airway (D) are seen.

Histopathology of fatal asthma in children is predominantly characterized by striking mucus plugs, increased inflammatory cells including eosinophilia, thickening of the subepithelial basement membrane, and increased airway smooth muscle (4). Sudden deaths in asthma are characterized by the time of onset of symptoms before death as either short (<3 h) or long (>8 h) courses, which have different inflammatory profiles (4). Among reports of autopsy findings of lung histology in fatal asthma, there has been little description of the bronchial or pulmonary circulation.

In the lung, the bronchial vasculature is highly responsive to β -agonist drugs and has been shown to be hypertrophied in asthma, which may be due to recruitment of preexisting anastomoses between the pulmonary and bronchial arteries, as observed in diverse airway-related pathologic conditions, including inflammation, infection, neoplasm, and chronic obstructive pulmonary disease, but not in healthy lungs (5). Such anatomical changes in the bronchial vasculature have not been reported in asthma, however. Recently, prominent intrapulmonary bronchopulmonary anastomoses (IBAs) have been demonstrated in a variety of severe lung disorders in neonates, children, and adults that are characterized by disorders of compromised microvascular growth with hypoxemia, including alveolar capillary dysplasia, bronchopulmonary dysplasia, congenital diaphragmatic hernia, idiopathic pulmonary artery hypertension, and Down syndrome (6). The physiologic roles of IBA in these settings are uncertain, but IBAs may contribute to intrapulmonary shunt, hypoxemia, and perhaps death. Whether prominent IBAs are present in children with sudden-onset fatal asthma is unknown.

We hypothesized that in addition to structural changes in the bronchial and pulmonary circulation, prominent IBAs are present in a subset of children who die suddenly and unexpectedly with asthma. Through retrospective review of 20 years of autopsy cases, we identified three children with clinically established asthma who died suddenly and unexpectedly. We gathered clinical and epidemiologic data and examined lung and heart tissues to determine the presence of IBA to assess cardiac, pulmonary, and bronchial vascular pathology and the degree of airway disease. Standard histology with hematoxylin and eosin staining and serial sectioning of areas involving IBA was performed. Computerized imaging software (Free-D; Philippe Andrey) was used to create three-dimensional image reconstructions as we previously described (6).

All three patients developed sudden asthma attacks and died shortly thereafter. Two were receiving short-acting β -agonists, one was receiving a long-acting β -agonist, and none had more than 10 hospital visits for asthma attacks. At autopsy, mild right cardiac enlargement but no significant right ventricular hypertrophy was detected to suggest undiagnosed pulmonary hypertension. Microscopically, we found evidence of IBA in each of the three patients (Figure 1A), which was confirmed by three-dimensional reconstruction (Figure 1B). All patients had markedly dilated and congested bronchial arteries, veins, and microvessels (Figure 1C). Hypertensive pulmonary artery remodeling was variably present, with one lung showing changes compatible with moderate to severe changes (Figure 1D). In one patient, the bronchial arteries were markedly remodeled, as characterized by fibrointimal proliferation and wall thickening. The majority of airways were normal;

a few showed low-grade inflammation and/or loose luminal mucous material (Figures 1A and 1D); and rare airways ($\leq 4\%$) demonstrated inflammation with mucus plug (Table 1). An age-matched control lung did not show IBA or vascular remodeling.

Overall, our findings provide anatomical evidence of remodeled pulmonary and bronchial vasculature with prominent IBAs in children with sudden death related to fatal asthma. The sudden opening of intrapulmonary vascular anastomotic pathways has been suggested as a cause of death in a subset of patients with sudden infant death syndrome (7). β -Agonist drugs are critical for asthma management; however, at least some of the increase in asthma mortality has been linked to the overuse of these drugs, β_2 -receptor dysfunction, and genetic polymorphisms (8, 9). Mechanisms that lead to prominent IBAs and their actual physiologic contribution to asthma pathophysiology and sudden death remain uncertain.

However, IBAs can contribute to intrapulmonary shunting in normal individuals at rest, especially in response to catecholamine infusions. β -Agonist drugs are known to often worsen gas exchange during acute asthma exacerbations in some individuals, and this phenomenon is poorly explained by worsened ventilation-perfusion mismatch owing to increased flow to poorly ventilated lung regions (10). Withdrawal of β -agonist treatment during an acute asthma exacerbation has been shown to improve oxygenation and decrease right-to-left shunting (11). It is possible that the combination of relatively increased pulmonary vascular resistance and hypoxia- or catecholamine-induced vasodilator effects on bronchial arteries may lead to intrapulmonary shunting through IBAs, with increased regional blood flow bypassing alveolar capillaries and worsening gas exchange. In combination with airway inflammation and rare airway plugs, marked hypoxemia and sudden death may follow.

The small sample size and the lack of comparative data are limitations of this study. These data should be viewed as exploratory, pending replication in a larger cohort. However, these observations suggest that the recruitment of IBAs with pulmonary and bronchial vascular remodeling may have a contributory role in the pathophysiology of asthma, and they suggest the need for future studies.

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Csaba Galambos, M.D., Ph.D.*
University of Colorado Anschutz Medical Center
Aurora, Colorado

Outcomes of the First Three Years of a Lung Cancer Screening Program at a Veterans Affairs Medical Center

To the Editor:

Lung cancer is common and has a poor prognosis with more than 50% 1-year mortality (1) and less than 20% 5-year survival (2). The National Lung Screening Trial (NLST) demonstrated a 20% relative reduction in lung cancer mortality among at-risk patients with

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Melissa L. Bates, Ph.D.
University of Iowa
Iowa City, Iowa

Douglas Bush, M.D.
Icahn School of Medicine at Mount Sinai
New York, New York

Steven H. Abman, M.D.
University of Colorado Anschutz Medical Center
Aurora, Colorado

ORCID ID: 0000-0002-8940-6650 (C.G.).

*Corresponding author (e-mail: csaba.galambos@childrenscolorado.org).

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low-dose computed tomography (LDCT) of the chest (3). Although national guidelines have recommended lung cancer screening (LCS) (4), it remains controversial with barriers to implementation (5) and uncertainty concerning its generalizability to other populations (6).

Veterans may be a target population for LCS with higher age-adjusted incidence of lung cancer, younger age at diagnosis (7, 8), and higher rates of tobacco use and other exposures (9, 10), but published data in Veterans Affairs medical centers (VAMCs) have shown mixed results (11–13).

Here we describe the outcomes of the first 3 years of LCS at a single VAMC.

Methods

This retrospective cohort study was approved by the Providence VAMC Institutional Review Board (EXP#2-2014-041). Need for informed consent was waived.