

A decade later, some veterans find it hard to breathe

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For military personnel who were deployed to Iraq and Afghanistan in the early 2000s, burn pits—areas where various waste was burned in open pits—were a visceral reminder of that hellish experience.

"A burn pit contained essentially everything a military base produces. They ([military personnel](#)) dig a big hole in the ground and dump everything into that pit," said John Osterholzer, M.D., associate professor of internal medicine in the division of pulmonary and critical care. "That could include excess food from the mess hall, Styrofoam and plastic utensils, tires, computers, medical equipment, electrical items, unused munitions, and even medical, animal, and human waste. After placement in the pit, jet fuel is added and then the material is kept burning with the addition of new material."

For some, the smoke that emanates from a burn pit would seem like the obvious source for any resulting lung disease but burn pit smoke is only one of several concerning sources of inhalational exposures during deployment commonly referred to as "airborne hazards." More than a decade later, many formerly fit military personnel (including veterans) who were exposed to burn pits and other airborne hazards go to their doctors complaining of [shortness of breath](#), only to find that the breathing tests and CT scans often done to assess respiratory symptoms come back either normal or near normal findings. What is clear is that "normal" findings may not tell the whole story.

Osterholzer and his colleagues at the Department of Veterans Affairs Veterans Health Administration are searching for better ways of testing these veterans that will allow physicians to find the physical cause of their life-altering symptoms. To date, the most definitive test available involves a [lung biopsy](#), a surgical procedure to remove [lung tissue](#) and examine it under a microscope. The use of this test to diagnose deployment related respiratory disease stems from a 2011 report published in the *New England Journal of Medicine*. As described in that report, a team led by Robert Miller, M.D., at Vanderbilt University took the unusual step of offering lung biopsies to 49 soldiers experiencing shortness of breath after deployment whose routine test results were mostly normal. Yet all of the biopsy samples were abnormal, with most

showing damage similar to a condition known as constrictive bronchiolitis, or scarring of the small airways.

Pathologists who examined the lung samples "chose constrictive bronchiolitis because, although multiple parts of the lung can be affected, the abnormalities in the small airways stood out and seemed the most likely explanation for their symptoms," said Osterholzer.

The tricky part is that pathologists, healthcare providers who examine tissue samples for evidence of disease, don't always agree on the definition of constrictive bronchiolitis. Furthermore, scientists remain uncertain about what specifically causes the small airway damage.

The Airborne Hazards and Burn Pits Center of Excellence, located at the New Jersey War Related Illness and Injury Study Center recognized this difficulty and is taking steps to better identify the cause of damage. The AHBPCE convened a group of multidisciplinary experts to address the difficulty in achieving consensus around the diagnosis of constrictive bronchiolitis and associated terminology.

An [expert panel](#), including Osterholzer, was brought together that includes 19 pathologists, radiologists, pulmonologists and environmental and occupational medicine physicians across VA, DoD and academia.

Ultimately, the panel reached consensus on the approach to diagnosing and managing constrictive bronchiolitis as well as definitions and agreed upon terminology. Findings from this panel were summarized in a manuscript recently submitted for publication.

Learning from mice

A key element is to understand the pathophysiology of CB and other small airway diseases. To find out, a recent study from the VA Ann

Arbor Healthcare System and University of Michigan Medical School led by Osterholzer and Seagal Teitz-Tennenbaum, used a mouse model to explore how damage to a specific type of cell in the lung, called a club cell, could result in damage similar to deployment-related constrictive bronchiolitis.

Club cells help repair the small airways, or bronchioles, if they get injured.

"They also talk to the immune system and other cells to try and ensure that that part of the lung is working appropriately," explained Osterholzer.

Scientists knew that club cells can get injured when exposed to toxic substances, like sulfur dioxide or mustard gas. When comparing the small airway damage in genetically-modified mice subjected to sustained club cell damage, they found that it caused scarring and inflammation of the small airways that appeared similar to the damaged airways identified in military personnel diagnosed with constrictive bronchiolitis.

Furthermore, the study found that the lungs' immune response to toxic exposures may contribute to the lung damage. They showed this by eliminating the macrophages (white blood cells) in the lungs of the mice subjected to sustained club cell injury and demonstrating that these mice did not develop as much scarring in their airways.

Getting help for Veterans

While the study helps explain how the damage may occur, there's still the challenges associated with making the diagnosis; this can be the point where, more often than not, veterans hit a dead end.

"The stories I've heard are all the same. You have people who were otherwise healthy who went into the military and who have come home and are saying 'I feel old, I'm exhausted when I'm trying to run, I can't catch my breath'," said Rachel Howard, a formerly-deployed Army veteran who is also a research health science specialist working with Osterholzer's team at the VA Ann Arbor.

The challenge comes, she explains, when these veterans are put through the typical battery of lung function tests, they come up normal.

Howard added, "You have this catch-22 where their energy and their exercise ability has decreased due to these unexplained issues. As they stop exercising, they start gaining weight and become deconditioned and finally end up at the doctor, who says 'your BMI is 38 so of course you are out of breath.'"

In 2014, the VA established a national Airborne Hazards and Open Burn Pit Registry (AHPBCE) to try to assess the scope of the health issues facing veterans as a result of exposure to burn pits, sand storms, and other airborne particulates and chemicals. More than 313,000 veterans have registered so far. The registry is managed by AHPBCE. The AHPBCE developed the Post Deployment Cardiopulmonary Evaluation Network comprising a network of clinicians and researchers, including the VA Ann Arbor, which provides extensive, multi-disciplinary evaluations for select veterans on the registry who may have lung conditions related to their deployments.

Working with veterans as part of the PDCEN and the recently formed VA Ann Arbor Post-Deployment Respiratory Health Clinic, Howard says she notices their palpable sense of relief at finally being heard.

To further raise awareness of veterans' respiratory concerns, Alex Rabin, M.D. worked with a team at the Ann Arbor VA, University of Michigan,

and the AHBPCE to write up a "Clinical Problem-Solving" case report, published in the *New England Journal of Medicine*. They describe a 35-year-old formerly-deployed veteran who presented to the VA with shortness of breath and cough who was subsequently diagnosed with constrictive bronchiolitis. The case, they write "underscores the importance of asking about a patient's exposures, including those during military service, and pursuing a more comprehensive evaluation in cases in which initial testing does not yield a diagnosis that adequately accounts for the clinical picture."

New insights

Due to its invasiveness, many clinicians are reluctant to recommend a surgical lung biopsy to patients with unexplained shortness of breath, even if injury to the small airways is suspected. In search of better diagnostic tools, Dr. Osterholzer sought assistance from Craig Galban, Ph.D. in the University of Michigan's Department of Radiology. Galban had previously helped develop and pioneer a novel analytical technique, called Parametric Response Mapping, or PRM, which uses standard, clinically available high resolution CT scans to visualize and quantify the extent of small airways disease in patients suffering from COPD. For PRM to detect small airways disease in a patient, paired CT scans must be obtained while the lungs are fully inflated and deflated. Differences in the lungs' densities at these inflation-levels makes it possible for PRM to differentiate diseased from healthy lung.

"Conceptually, regions of the lung afflicted by chronic bronchiolitis will appear darker than normal on the deflated CT scans as this indicates that the air isn't able to leave the lungs as easily as it should, making it detectible by PRM," explained Osterholzer. Osterholzer and Galban recognized that this technique held promise for finally delivering a more accessible path towards diagnosis for affected veterans.

Assisted by Caroline Davis, M.D., a third-year fellow with the U-M Division of Pulmonary and Critical Care Medicine, Drs. Osterholzer and Galban used CT PRM to compare the CT scan images from soldiers diagnosed with constrictive bronchiolitis to CT scans from healthy subjects and from patients with varying severity of COPD, a chronic lung disease primarily caused by smoking. They found that the military personnel with constrictive bronchiolitis have increased small airways disease relative to healthy subjects; furthermore, the amount of small airways disease was, on average, comparable or worse than patients with mild to moderate COPD.

The findings are important because they may help explain and better diagnose the symptoms of cough and shortness of breath some military personnel experience after military deployment. Furthermore, they also may identify new opportunities to use PRM and related technologies to better define the spectrum of deployment related [lung](#) disease and how it may respond to attempts at treatment.

"Right now, we need to better understand the natural history of the condition, if it gets worse or remains the same." said Osterholzer. "This new approach should help."

Additionally, without a diagnosis, many veterans with these issues can't receive a service connection, disability compensation for injuries acquired during [military service](#). Osterholzer says there are multiple efforts in Congress to try to obtain what are called presumptive service connection to provide resources for veterans with these conditions. Yet acquiring presumptive service connections in the VA isn't always easy.

Recently, VA Secretary Denis McDonough announced support for the historic Sergeant First Class Heath Robinson Honoring our Promise to Address Comprehensive Toxics Act, signed by President Biden in early June.

According to a news release issued by the VA, the PACT Act "would codify many of the ongoing efforts by the department to improve its process for establishment of presumptions of service connection due to toxic exposure, reducing the burden for veterans and increasing transparency."

"These issues are both complex and challenging. As clinicians we want to advocate for our patients, and as researchers we want to be able to do the best science possible. From both perspectives, we want to help the VA to use its resources wisely."

Osterholzer and his team hope that their current and future clinical and research efforts will help veterans get the patient-centered care and benefits they need and deserve.

More information: Seagal Teitz-Tennenbaum et al, Sustained Club Cell Injury in Mice Induces Histopathologic Features of Deployment-Related Constrictive Bronchiolitis, *The American Journal of Pathology* (2021). [DOI: 10.1016/j.ajpath.2021.11.012](https://doi.org/10.1016/j.ajpath.2021.11.012)

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