Study: Fluid buildup in lungs is part of the damage done by the flu

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In a fight against respiratory infections, the body typically produces a little fluid to help the lungs generate a productive cough. But new research suggests that the influenza virus can tip the balance toward too much fluid in the lungs, interfering with the supply of oxygen to the rest of the body.

An immune response ultimately is needed to eliminate the virus, but this research suggests that it's not the presence of the virus alone that does all the harm to a sick person. Instead, the fluid buildup deep inside the lungs might help kill a person infected with the flu, according to the research, which was conducted in mice.

"My take is that when people die of these illnesses, they're dying because they can't breathe," said Ian Davis, assistant professor of veterinary biosciences at Ohio State University and senior author of the study. "If the lungs aren't working well, then it doesn't matter whether a week from now you can make an immune response and clear the virus if you can't survive that long because you just can't get oxygen."

Detailing exactly how flu interferes with fluid clearance in the lungs lays the groundwork for a second phase of related studies to test a new therapy - a drug that is already known to regulate the amount of fluid that builds up in infected lungs.

In the event of a flu pandemic, such a drug, which scientists hope could be inhaled by mouth, might be an important supplement to antiviral

medications and ventilators, Davis said.

The research is published in a recent issue of the *American Journal of Respiratory and Critical Care Medicine*.

Davis and colleagues infected mice with high doses of an influenza A virus to compare oxygen levels and fluid clearance in infected mice to those of healthy mice.

Mice that were infected with the highest doses of flu experienced a steady decline in oxygen in their blood and higher levels of fluid in the lungs. Two days after infection, fluid clearance in these mice was only half as effective as fluid clearance from the lungs of uninfected mice.

Lung infections have been known to cause problems with what is called alveolar fluid clearance, but the effects of the flu on the lungs had not been tested before, Davis said. The alveoli are air spaces deep inside the lungs where oxygen enters the blood in exchange for carbon dioxide to be exhaled.

The scientists used an unusual method to observe the fluid clearance. After being infected, the mice were anesthetized and put on ventilators. The researchers then placed fluid containing protein into one lung of each mouse and tested the fluid 30 minutes later. The amount of protein left in the remaining fluid allowed the investigators to determine whether the infected lung was clearing fluid adequately.

Davis said the study showed that when the flu virus infects cells in the lung, those cells release small molecules, or nucleotides, that are part of the energy-producing and replication machinery of the cell. Those nucleotides then bind to receptors of other cells in a series of events that ultimately shut down the transport of sodium from airways to the blood. All of these interactions take place in the epithelium, the lining of the

airways in the lungs.

Under normal conditions, sodium is absorbed from the lungs into the blood and carried away to be excreted by the kidneys. But in infected lungs, when the sodium channels are damaged, more and more fluid builds up in air spaces instead of being pumped across the airway lining and into the blood.

"A little bit of fluid gives us a way to flush the nasties out of the lung," Davis said. "If you get a bacterial infection and bacteria are all over the lungs and cell surfaces, you release these nucleotides and generate fluid so you can cough up the bacteria and wash them out. The downside is as you build up fluid in the lung, you can't oxygenate as well.

"If the bacteria or virus wins, you get more and more fluid and you get sicker and sicker. But if you can wash it away, then you've won and things go back to normal."

The potential therapy that Davis is investigating was originally used in earlier research to block the generation of these nucleotides to prove the fluid clearance mechanism behind a different viral lung disease. Now that his newer work has shown that influenza A has the same effect on the lungs, Davis is planning to test the therapy's effects against flu infection.

The first studies will involve delivering the drug in aerosol form to mice. Davis also plans to culture human epithelial cells to see whether these cells in humans have the same role as do mouse cells in the fluid clearance mechanism.

Davis noted that the current health-care system can help manage most serious cases of the flu, even if some of the sicker patients require ventilation to help them clear fluid and get oxygen to the blood.

"But if we get into a pandemic situation and there are 200 people with low levels of oxygen in their blood and five ventilators, 195 people are out of luck. We hope to develop something that those people can take by aerosol that might reduce the need for that kind of ventilation," he said.

Source: Ohio State University