Antihypotensive agent disrupts the immune system in sepsis

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Patients who go into septic shock are treated with the antihypotensive agent norepinephrine. Researchers from Radboud University Medical Center published results in today's *American Journal of Respiratory and Critical Care Medicine* revealing that its use is not without drawbacks: The drug disrupts the immune system and increases susceptibility to infections. This may have negative consequences for patients. Research into alternatives is therefore justified.

Sepsis is a life-threatening inflammatory response spreading throughout the body due to an infection. One in four patients with sepsis succumbs to it, and it is the No. 1 cause of death around the globe. As such, sepsis was recently designated as a global health priority by the World Health Organization (WHO). Patients with sepsis have a severely dysregulated immune system, which impairs clearance of the infection and leaves the body susceptible to new infections with an increased risk of death. Severe sepsis also often leads to a dangerously low blood pressure called septic shock, which requires treatment with antihypotensive agents. Norepinephrine has been the primary agent of choice to increase blood pressure in this condition since the 1950s.

However, intensive care researchers Roel Stolk and Matthijs Kox have now shown that norepinephrine contributes to the dysregulation of the immune system and thereby impairs the ability to combat infections. They found the first indications in laboratory tests, by exposing white blood cells to norepinephrine in combination with bacterial and viral components to induce an inflammatory response. Norepinephrine proved to suppress the function of these immune cells.

Impaired defense against infections

The researchers then switched to an animal model. Roel Stolk, lead author of the study, says, "We replicated an infection in mice by injecting them with endotoxin, a bacterial cell-wall component. If mice were administered norepinephrine, their immune response was strongly suppressed."

Furthermore, in mice with an actual bacterial infection, infusion of norepinephrine led to increased bacterial growth in the spleen, liver, and blood, again indicating a weakened immune system. "We also studied the effect of vasopressin, an alternative antihypotensive agent, on white blood cells and mice," Stolk says. "Interestingly, in contrast to norepinephrine, this drug has no effects on the immune system or defense against infections."

Healthy volunteers

"Next, we wanted to know whether the effects of norepinephrine also apply to humans," said Matthijs Kox, head of the study. "We infused either norepinephrine, vasopressin, or a placebo in three groups of healthy volunteers. We then administered a low dose of endotoxin to these volunteers. Once again, we observed clear differences. Compared to the placebo group, blood concentrations of proinflammatory proteins decreased in the group that received norepinephrine, while levels of anti-inflammatory proteins increased. With vasopressin, we once again observed no effects on the immune response. Those results confirmed the previous data that norepinephrine suppresses the immune system."

Two hundred sepsis patients

Stolk and Kox also examined a group of nearly 200 patients with septic shock, all of whom were treated with norepinephrine. In these patients, they found that the balance between proinflammatory and anti-inflammatory proteins in the blood tipped towards the anti-inflammatory side in patients who were treated with higher dosages of norepinephrine. They also showed that these adverse effects of norepinephrine on the immune system were less

pronounced in patients who used beta-blockers for their heart condition or blood pressure.

Further research

Based on this study, the researchers conclude that the use of antihypotensive agents in patients with sepsis should be reevaluated, preferably in a large group of patients. Kox: "Compare the effects of norepinephrine with those of vasopressin, for example, as we have shown the latter to have no adverse effects on the immune system. Further research is also required into the effects of beta-blockers in sepsis patients treated with norepinephrine. Both strategies could improve defense against infections in these patients, which may lead to improved treatment of this serious condition."

More information: Roeland Stolk et al, Norepinephrine Dysregulates the Immune Response and Compromises Host Defense During Sepsis, *American Journal of Respiratory and Critical Care Medicine* (2020). DOI: 10.1164/rccm.202002-0339OC

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