mediators, and the fact that some factors are surly both, is one of the many reasons why the results of large trials are more reliable than the retrospective analyses.

Raghunathan *et al.* suggest using calendar time as an instrumental variable for clinician decision making on HES usage in an environment of changing Food and Drug Administration regulations. Study patients' had noncardiac surgeries between January 2005 and September 2012; during this time period, regulatory changes might have affected overall HES usage. Therefore, we intentionally propensity-matched patients on the year of surgery to make sure most of the times we compared surgeries close in time to each other. Although, among nonmatched patients, the proportion of those receiving HES decreased in years 2011 and 2012 compared to previous years.

Ertmer and Van Aken are also concerned that unadjusted confounding may have contributed to our conclusion that 6% HES 670/0.75 promotes acute renal injury, which would suggest that the product is actually safe. Curiously, they then express surprise that high-molecular-weight starches, which they claim to be "unsuitable for modern perioperative care," are still used at the Cleveland Clinic. It is not just at the Clinic. The high-molecular-weight starch we used remains by far the most commonly used plasma expander in the United States, even after Food and Drug Administration approval of low-molecular-weight starches in December 2007.

Continued use of 6% HES 670/0.75 is hardly unreasonable. There is little previous evidence that the intraoperative use is harmful and there has never been a large trial comparing high- and low-molecular-weight starches. Ertmer and Van Aken cite a meta-analysis to support their assertion that low-molecular-weight starches are safer than higher-molecular preparations.[2] However, that study did not compare low-molecular-weight starches to 6% HES 670/0.75, the preparation we used. In fact, a more recent meta-analysis in cardiac surgical patients who presumably are at high risk for acute kidney injury concludes that "no reliable analysis for separate hetastarch generations compared to albumin, gelatin, or crystalloids was possible."[3]

In summary, retrospective analyses are complicated by factors that are not clearly confounders or mediators. As illustrated by the comparison between our primary and sensitivity analyses, the distinction matters and can profoundly influence conclusions—and is one reason why randomized trials are so important. No large study has compared high- and low-molecular-weight starches; whether one is safer than the other for perioperative use thus remains unclear. In the mean time, the conclusion that 6% HES 670/0.75 is "unsuitable for modern perioperative care" seems premature.

Competing Interests

The authors declare no competing interests.

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References

1. Kashy BK, Podolyak A, Makarova N, Dalton JE, Sessler DI, Kurz A: Effect of hydroxyethyl starch on postoperative kidney function in patients having noncardiac surgery. Anesthesiology 2014; 121:730–9
2. Martin C, Jacob M, Vicaut E, Guidet B, Van Aken H, Kurz A: Effect of waxy maize-derived hydroxyethyl starch 130/0.4 on renal function in surgical patients. Anesthesiology 2013; 118:387–94
3. Jacob M, Fellahi JL, Chappell D, Kurz A: The impact of hydroxyethyl starches in cardiac surgery: A meta-analysis. Crit Care 2014; 18:656

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Tracheal Tube Obstruction Assessed by Computed Tomography

To the Editor:

In a very elegant bench-to-bedside investigation, Mietto *et al.*[1] studied the secretion-induced cross-sectional area (CSA) reductions of tracheal tubes (TTs) in intensive care unit patients. Using *ex vivo* high-resolution computed tomography (CT) scans, extubated TTs showed a minimum CSA 25 ± 4% lower than new and nonused TTs; using *in vivo* standard clinical chest CT scans of selected patients, 6 of 20 intubated TTs showed measurable secretions with a CSA reduction of 24 ± 4% and an absolute reduction of 1.5 ± 0.4 mm in the anteroposterior diameter of TTs.

One main finding in the *ex vivo* CT scans was that CSA progressively decreased from oral to lung end of used TTs, suggesting that increases in the resistance to airflow that could result in higher ventilatory pressures and greater work of breathing are mainly caused by retained secretions at that end of TTs. However, TTs may bend and even "kink" in the part located in the neck and oral region, depending on the tube quality and the number of days it is in use, among other factors. Although this by itself could reduce the inner diameter of TTs, it will certainly increase the impact of secretions on resistance to airflow at this part of TTs. Because of design of the study, the *in vivo* CT scans did not allow Mietto *et al.* to review the extrathoracic part of TT, as neck and oral cavity were not included in the standard clinical chest CT scans.

I agree with the authors that the impact of retained secretions within the TT lumen is of greater clinical importance than often recognized and that CT scanning could be a useful tool for early detection of secretion-induced CSA reductions. But then we may need to deviate a little from the standard clinical chest CT scan by including the neck and oral cavity.

This letter was sent to the author of the original article referenced above, who declined to respond.

Competing Interests

The author declares no competing interests.

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Reference

1. Mietto C, Pinciroli R, Piriyapatsom A, Thomas JG, Bry L, Delaney ML, Du Bois A, Truelove J, Ackman JB, Wojtkiewicz GR, Nahrendorf M, Kacmarek RM, Berra L: Tracheal tube obstruction in mechanically ventilated patients assessed by high-resolution computed tomography. Anesthesiology 2014; 121:1226–35

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Can the Continuous Hemofiltration Control Ebola-induced Systemic Inflammatory Response Syndrome?

To the Editor:

The Ebola virus (EBOV) causes a serious hemorrhagic fever with mortality rates of 50 to 90%. During the clinical evolution, there is a sudden appearance of a multiple organ dysfunction syndrome, which leads to a state of multiple organ failure.[1]

The immune system is incapable of detecting the virus during the early stages of its replication. Indeed, the inflammatory response is inadequate and immunoparalysis supervenes. However, the specific immune response of survivors is capable of developing antibodies at an early stage.[1] Yet later, there is a massive activation of monocytes and macrophages and, in the final phases, destruction of endothelial cells with coagulopathy due to the interaction of the released cytokines.[1]

EBOV produces a systemic inflammatory response syndrome (SIRS) that can be defined as severe viral sepsis. The viral glycoproteins (GPs) (*N-linked high-mannose oligosaccharides*) intervene in a process in which the expression of the adhesion molecules of the endothelial glycocalyx and immune cells is inhibited, and this triggers the release of the cytokines as described above (fig. 1).

Advanced Ebola infection causes a profound acidosis: the replication of the virus is enhanced and the GPs are activated.

If severe SIRS does not develop, or if it is controlled and immunoparalysis is reversed, there may be sufficient time and capacity to generate individual immunity to the virus. This situation is comparable with severe bacterial sepsis,[2,3] and if SIRS and multiple organ dysfunction develops, death may occur due to multiple organ failure.

Hemofiltration and EBOV

We propose a strategy to remove inflammatory mediators and virus components based on convection and adsorption[3] that avoids "dialytrauma."

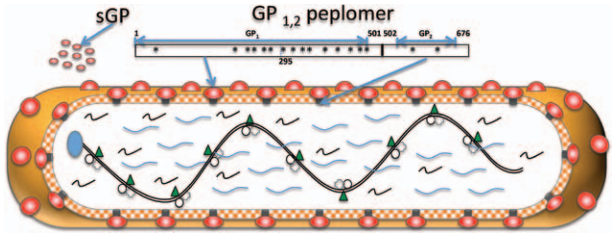

Fig. 1. Schematic illustration of the Ebola virus. The glycoprotein (GP) gene of the virus is translated in to structural GPs, $GP_{1,2}$, and mainly in a small soluble GP (sGP; 41 kDa) that shares its first 295 residues with the glycoprotein 1,2 ($GP_{1,2}$) (indicated by *dotted lines* in the $GP_{1,2}$). The maturation of the GP involves posttranslational splicing. This gives rise to glycoprotein 1 (GP1) and glycoprotein 2 (GP2) fragments that are linked by disulfide bonds. The surface GPs, $GP_{1,2}$, trigger the release of the cytokines by infected monocytes. sGP is also highly glycosylated (not shown) and is secreted in big quantities as a homodimer by the infected cells and fulfills an as yet controversial role. * Potential sites for *N*-glycosylation on the $GP_{1,2}$ molecule.

The size of soluble glycoprotein is 41 kDa, which can be filtered by convection using a membrane with a pore size of 60 kDa. Viral GPs have a negative electric charge, the intensity of which depends on the number of disulfide bonds facilitating adherence to the polyethyleneimine (PEI (+)) in the AN69-ST heparin-coated hemofiltration membrane. $GP_{1,2}$ may also show electrical affinity for the PEI (+).

The virus would be eliminated if the virus-free fraction was large, and because the virus has a size of 267 kDa, the pores of the membrane should be large (*plasmafilter*). To control albumin loss, a slow dialysis method would be used, which would mean a reduction of convective capacity against inflammatory mediators. Another possibility is a hemoperfusion system with the adsorption capacity to eliminate GPs rich in mannose sugars. In this way, we would eliminate the plasma viral load, to be able to continue with the convective treatment.

The AN69-ST heparin-coated membrane has the ability to adsorb negatively or positively charged molecules (endotoxins or inflammatory mediators), owing to its layered composition (sulfonate groups (–) and PEI (+)).[3]

Such hemofiltration is an approach sometimes used in serious sepsis SIRS of infectious. The indication is immunomodulatory, and in the case of Ebola, the disposal bags could be sterilized by sodium hypochlorite.

Possible Application

Possible application includes EBOV infection and signs of instability or organ dysfunction. The duration of the therapy might be based on the time survivors have taken to generate specific immunity.

Hemofiltration Proposal

- Technique: continuous venous hemodiafiltration.
- Catheter: 13.5- to 14-French × 24-cm femoral vein catheter.