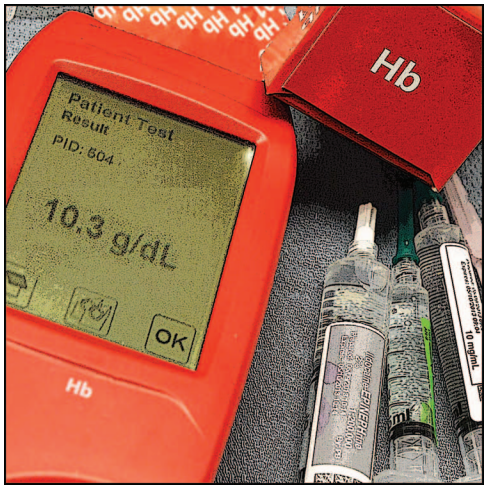
The Great Fluid Debate

When Will Physiology Prevail?

IN this issue of ANESTHESIOLOGY, Konrad *et al.*[1] present a study in pigs in which they compare the renal microvascular oxygenation effects by using either a balanced crystalloid solution or a balanced hydroxyethyl starch 6% 130/0.4 solution (HES) for acute normovolemic hemodilution to a fixed hematocrit of 15%. They have chosen this method to assess the impact of crystalloids and starches on the most sensitive physiological compartment, the microcirculation, of the organ most sensitive to the deleterious effects of fluids, the kidney. Their measurement of kidney microcirculatory oxygen further targets one of the unwanted effects of fluids, namely, the hemodilution-induced reduction of the oxygen-carrying capacity of blood.[2] They, thereby, examine which of the fluid types exerts harm when used in the context of hemodilution; this issue is a key question that is central to the current debate regarding fluid treatments. They conclude that, in their model, more harm is inflicted on the kidney by the use of crystalloids than by a balanced HES 130/0.4 solution.

The advantage of using a physiological model is that one can address several mechanistic aspects of a clinically relevant hypothesis and/or controversy in a controlled manner. In this respect, this study is very timely because several large multicentral clinical trials have been completed comparing the effects of crystalloid solutions with the effects of starch solutions.[3–5*] The great fluid debate appears to be as heated as it has ever been, as studies purporting that starches are harmful,[3,4] clash with other investigations that reach the opposite conclusion.[5*]



"If one is to compare the respective effects of crystalloid solutions and starch solutions … it is essential that a clear hemodynamic endpoint … be applied.... [C]linical trials of these two types of solutions could benefit from adopting a variant of the hematocrit endpoint approach used by the current study."

Furthermore, this debate has been clouded not only by a recent case of inappropriate scientific conduct,[6] but also by the issuance of, in my opinion, premature recommendations into the relative benefits/drawbacks of starches *versus* crystalloids.[7] A physiological approach is useful for addressing this situation because it can deliver clarity regarding the disputed issues, focus on mechanisms, permit studies to be conducted in a controlled fashion, and most importantly, provide guidance for the design of appropriate clinical trials that can generate evidence for clinical recommendations.

In this current study, the authors apply hemodilution to healthy pigs using either a balanced crystalloid solution or a balanced starch solution to reduce the hematocrit to 15% in a stepwise fashion. As they suggest, this procedure is designed to mimic the situation that is encountered in cardiac surgery. This assumption, however, merits critical appraisal because a hematocrit of 15% is rarely encountered during cardiopulmonary bypass. Indeed, the authors' finding that few deleterious functional effects (*e.g.*, deficiencies in creatinine and inulin clearance) from crystalloids occurred at hematocrit values of as low as 20% could

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*Available at: www.clinicaltrials.gov. Annane D: Colloids compared to crystalloids in fluid resuscitation of critically ill patients: A multinational randomized controlled trial: The CRISTAL trial: Clinical Trials.gov Identifier: NCT00318942: 2013. Accessed April 28, 2013.

 Anesthesiology 2013; 119:248-9

be considered to be a more clinically relevant result than the fact that the kidney demonstrated a comparatively worse response to crystalloids than to starches at a hematocrit of 15%. However, the authors did discover a significant reduction in the kidney microcirculatory pO_2 at a hematocrit of 20% with crystalloids but not with starches although they found no deleterious functional consequences. Setting this critique aside, there remain a number of key features of this article that are clearly relevant both to the fluid debate and to researchers who are conducting the clinical fluid trials. The first issue of importance is that the authors chose to use a clearly defined hemodynamic endpoint (in their case, hematocrit) to determine the amount of fluids that they administer; then, they compared the effects of the fluid treatment on functional parameters that are known to contribute to renal failure. They found that significantly more crystalloids than starches (three times as much) are required to reach their chosen endpoint. Indeed, in a clinical microcirculation study, we found that two and a half times more crystalloid solution than a starch solution was needed to reach similar mean arterial and venous pressure resuscitation endpoints in septic-shock patients.[8] The authors' current finding that the greater administration of fluids is associated with a more deleterious effect on renal function is well known from clinical trials.[9] In this context, the often quoted saying by the father of toxicology, Philippus von Hohenheim (Paracelsus; 1493–1541), comes to mind: "All things are poison, and nothing is without poison; only the dose permits something not to be poisonous." This aspect of the study is relevant to the assessment of current recently completed clinical fluid trials, in which crystalloid and starch solutions with different composition, and pharmacological and physiological effects are administered in a blinded fashion. From a physiological point of view, this type of experimental design warrants significant skepticism. Currently, two large clinical trials have been completed concerning the comparison between crystalloid solutions and starch solutions, the 6S trial in Scandinavia[3] and the Crystalloid versus Hydroxyethyl Starch trial in Australia.[4] These studies reported deleterious effects of starches on renal function. Both studies chose a strategy for evaluating the relative benefits or drawbacks of the respective fluids by examining a large number of patients in combination with blinding a clinician to the type of fluid that is being administered. No clear guidelines concerning the dosage of the fluids for individual patients were provided, aside from an upper limit based on the safety restrictions for starches. If one is to compare the respective effects of crystalloid solutions and starch solutions, particularly in the kidney, an organ that is extremely sensitive to the volume and composition of fluids, it is essential that a clear hemodynamic endpoint in the individual administration of these solutions is applied. In this sense, the clinical trials of these two types of solutions could benefit from adopting a variant of the hematocrit endpoint approach used by the current study. Although these clinical trials are to be commended on their impressive undertaking and may indeed hold true under certain circumstances, from a physiological perspective, the results and conclusions of these trials may need to be taken with a pinch of salt.

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