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Back to basic physiological questions and consideration of fluids as drugs

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The two articles,[1 2] to be published in the same issue of the *BJA* as this editorial, describe the vascular aspects and the type of fluid therapy used to treat hypovolaemia are full of information, which might be discussed in the light of practical questions such as: (i) What are the goals of giving fluid? (ii) What parameters inform the best on the fluid's efficiency? (iii) How to decide when to stop fluid administration? (iv) Are the available fluids equivalent for achieving the goals? (v) What is the impact of the patient's cardiovascular status on the choice of fluid? The article from Chawla and colleagues[1] summarizes the useful concepts, tries to clarify the questions that are still unsolved, and proposes new research directions. The goal for fluid administration is to improve tissue perfusion, for which systemic haemodynamic improvement is the first step before improving the microvessel perfusion and tissue oxygenation. Often the warning signal for making a decision to give fluid in the clinic is hypotension, especially when symptoms of hypoperfusion are present. The hypothesis made by the clinician is then: the given volume of fluid will increase cardiac output (CO), which in turn will increase arterial pressure (AP) and then tissue perfusion. However, several observations coming from practical experience challenge such a hypothesis. First, for the same volume given, the CO generated varies greatly from patient to patient: the generated CO results from the cardiac pump performance, but also from a forgotten variable called the time for circulation.[3] This aspect is illustrated by many examples: in arterio-venous fistulae,[4] time for circulation is shortened and CO increases, as it does in sepsis when peripheral shunting is significant;[5] in severe diabetic keto-acidosis, a condition with profound hypovolaemia and dehydration, the CO is high; inotrope-induced increased CO relates not only to improved cardiac performance but also to the shortened circulation time;[6] β-blockers in septic shock induce only a moderate decrease in CO.[7] Secondly, the increase in CO does not induce a sustained increase in AP, but more frequently results in vascular dilatation,[8] which motivates the clinician to add vasopressors despite the high CO. Thirdly, microcirculation improvement after fluid administration can result from systemic haemodynamic effects but may also exist when the CO does not change, suggesting that different mechanisms are controlling microcirculation than those controlling the systemic circulation. Fourthly, for the objective to improve the level of capillary oxygen tension, only blood transfusion is efficient when colloid or crystalloid did not, despite similar CO changes after haemorrhagic shock.[9] The listed key questions by Chawla and colleagues concerned the vascular barrier (Vb), vascular content (Vc), vascular tone (Vt), and blood flow (BF), considering the fluid administered as if it were a 'conventional' drug. If most of these issues can be measured with more or less accuracy, very few techniques can be used at the bedside in an emergency context. In addition, if some parameters can be obtained from systemic haemodynamic variables, it becomes difficult to apply them also to the regional haemodynamic situation. Knowing the regional flow and then the vascular tone is important because organ vasomotor regulation may differ and this affects regulation of the systemic circulation.[10] A hypothesis can then be formulated: based on targeting tissue perfusion, the organ BF and microcirculation may be seen as the key factors for tissue oxygenation. As a consequence then, it is reasonable to base decisions related to fluid resuscitation on microcirculatory monitoring as a primary option. Both existing and new tools would be useful if they had a short response time and provided quantitative values, which may help to decide to stop fluid administration earlier, before overloading, and to add other therapies such as vasoactive drugs. This strategy may indicate when the microperfusion is compromised by a systemic haemodynamic problem, by microcirculatory abnormalities, or both.[11] In addition, performing functional testing might help the clinician evaluate small vessel vasoreactivity and disease, helping to design the best therapeutic strategy.

After making the decision to give fluid, the choice of fluid to be given becomes a key decision. The article from Raghunath and colleagues[2] summarizes the views of the authors and the main results from trials testing different types of fluids, with a focus on colloids, especially hydroxylethyl starch (HES). If fluid management is a dynamic process with four phases (rescue, optimization, stabilization, and de-escalation), the choice of fluid is frequently not based on pharmacological properties such as pharmacokinetics, tissue cell function, and immune status, which do not exist for most of the fluids. The classic fluid separation between crystalloids and colloids

(according to their volume-expanding ability) remains adequate only when the vascular barrier is intact, but becomes negligible when this barrier is altered. From the initial concept developed by Starling in 1896,[12] clinicians have used colloids in the hope of better expanding the blood volume with the intent of reducing the amount of volume given to correct hypovolaemia. Some important issues have challenged such an overly simplistic view. First, the Starling equation has to be modified in the light of the realization of the presence and importance of the endothelial glycocalyx.[13] Secondly, in acutely inflamed patients, the oncotic pressure gradient between the intravascular and interstitial spaces almost disappears, the colloids can now cross the compromised vascular barrier. The expansion power argument cannot now be used and more consideration should be given to the interstitial consequences, cellular effects, and functional changes that occur in the micro-environment. Thirdly, some potentially toxic effects have been reported for HES, leading to restrictive recommendations from drug agencies. Fourthly, if crystalloids are the first line of choice, the question on the potential 'toxic' effect of hyperchloraemia becomes an important issue.[14 15] This later point promotes the idea of using so-called 'balanced' fluids to limit the induced hyperchloraemic acidosis.[16] As pointed by Raghunath and colleagues, 'none of the currently used resuscitation fluids have been rigorously evaluated through multiphasic processes that are required for new medications' and 'this was primarily due to the adoption into clinical practice of "historical" fluids'. It seems therefore that fluid therapy is still at the 'primary age' of drug development, and future research should focus on comparing different fluid solutions in randomized placebo controlled trials performed in each clinical condition where i.v. fluids are given in large amount.

Declaration of interest

See supplementary material conflict of interest document.

Supplementary material

Supplementary material is available at *British Journal of Anaesthesia* online.

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