◆ EDITORIAL VIEWS

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Perfluorochemical "Blood Substitutes"

Indications for an Oxygen-carrying Colloid

IN this issue of ANESTHESIOLOGY, Spahn *et al.* present the first prospective randomized clinical study of a red-cell substitute.[1] Although hemoglobin solutions and perfluorochemical (PFC) emulsions have both been in clinical testing for more than 20 years, this study represents the first comparison of the physiologic effects of a "blood substitute" *versus* volume expansion *versus* blood.

In 1965 Clark performed a simple yet ingenious experiment that spawned an entirely new area of investigation. He was working with a series of compounds known as perfluorochemicals. These 8-10 carbon molecules are formed by replacing the hydrogen atoms with fluorine, resulting in chemically inert liquids that are very heavy (a density of nearly 2 g/ml) and immiscible in water and lipids. At room temperature these liquids have nearly 20 times the solubility for oxygen and other gases as does water, and Clark wondered whether mammals could survive breathing these unusual liquids. He immersed a rat in the liquid, equilibrated 100% oxygen for 20 min, and retrieved it alive.[2] Although PFCs can carry a substantial amount of oxygen, intravenous injection results in a liquid embolus that can arrest the circulation. In 1967, Geyer[3] produced a microemulsion of PFCs in normal saline. Rats underwent complete exchange transfusions (hematocrit < 1%) and survived when breathing 100% oxygen. For the past 30 yr, work has been directed toward the development of a PFC emulsion that could act as a temporary red cell substitute. Because the emulsion droplets of PFCs are approximately a tenth of a micron (1/70 the size of a red blood cell), they may also be able to perfuse and oxygenate tissue more effectively than red cells. Unfortunately, because these droplets are seen as foreign bodies, they are quickly cleared from the circulation by the reticuloendothelial system (with a plasma half-life of approximately 12 h).[4] Once out of circulation, the PFC accumulates in the liver and spleen and then is slowly transported to the lung, where it leaves the body chemically unchanged in the expired gases, with a tissue half-life measured in months.

The first commercial PFC emulsion, Fluosol DA 20%, was tested in humans in the late 1970s and found to have several limitations.[4,5] First, the emulsion was relatively unstable and had to be stored frozen. Second, it could only be made in a 20% solution by mass, that is, 20 g/100 ml of solution (10% by volume); therefore, the product was relatively "anemic." Finally, some patients experienced an acute reaction resulting from the emulsifying agent.[6] In the early 1990s a second-generation PFC emulsion was developed, perflubron.[7,8] Although perflubron is more concentrated and is stable at room temperature, the basic limitations of a short intravascular half-life and the requirement for high inspired oxygen are the same. Therefore, the clinical situations in which PFC treatment may be beneficial are those that require a short duration of supplemental tissue oxygenation in patients with a high arterial oxygen tension (≥ 400 mmHg): acute tissue ischemia, organ preservation, cardioplegia, cardiopulmonary bypass pump prime, cerebral protection, tumor sensitization, and temporary red blood cell substitution.[9,10] Because PFCs also have high solubility for nitrogen, they have been demonstrated experimentally to be useful in the treatment of venous air embolism.[9] Despite the wide variety of potential uses for PFC emulsions in clinical medicine, the primary interest has been as a "blood substitute," more properly described as an oxygen-carrying colloid.

In the clinical study presented in the current issue of this journal, Spahn *et al.* investigated patients undergoing elective orthopaedic surgical procedures. The patients underwent acute normovolemic hemodilution immediately before the surgical procedure and then were randomized into four treatment groups if and when one of four transfusion "triggers" was met. The four treatments were two doses of PFC, colloid and autologous blood transfusion. The authors compare the duration of transfusion-trigger reversal and the percentage of pa-

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tients who reverse their transfusion triggers as primary and secondary endpoints in this trial. Although the transfusion triggers included tachycardia, high cardiac output, and hypotension, it was only the fourth transfusion trigger, decreasing mixed venous oxygen tension (< 38 mmHg), which was achieved in the study. This is consistent with the results of a noncontrolled pilot study.[6] The protocol starts all patients at a 40% inspired oxygen fraction and increases to 100% for patients randomized into either of the PFC-treated groups or the colloid group: Patients treated with autologous blood remain at 40% inspired oxygen. The authors therefore attempt to compare volume therapy with colloid and high arterial oxygen tension with and without PFC to red-cell treatment without high inspired oxygen. Interestingly, the increase in inspired oxygen fraction (which increased arterial oxygen tension by approximately 260 mmHg) caused plasma oxygen content to increase twice as much as the PFC oxygen content in the high-dose treatment group (approximately 0.78 vol% for plasma *vs.* 0.38 vol% for PFC). Nevertheless, the PFC at high arterial oxygen tension did caused the greatest delay in the mixed venous oxygen tension transfusion trigger, in a dose-dependent fashion.

This article presents several questions. First, with respect to study design, should the autologous group have been treated with 100% oxygen also? This may have provided interesting results but would not have answered the question the authors originally posed: That is, is it additional hemoglobin-transported oxygen or dissolved oxygen that supports consumption better in patients with this range of hematocrits. Second, what is the clinical significance of changes in mixed venous oxygen tension that are still within the normal range? Without this variable the results of this study would have been primarily negative, because there were no significant differences with the other three transfusion triggers. Finally, even if one assumes that PFC treatment in conjunction with acute normovolemic hemodilution does reduce the use of allogeneic blood in some patients, is this really the best indication for PFC treatment? With the current HIV risk of the blood supply approaching 1:1,000,000 per unit of blood and the hepatitis C contamination less than 1:100,000, it would appear that the blood supply is impressively safe.[11–13] Currently the clinical experience with PFC is very limited, and there are known adverse effects on platelets, a flu-like syndrome, and concerns regarding its effect on the immune system.[9,14] It would appear more logical to use this oxygenating fluid to treat known disease that is not currently well treated or a problem with a much higher incidence that may benefit from additional tissue oxygenation as described previously.

The implication from this study is that PFC emulsions may be useful in conjunction with acute normovolemic hemodilution to delay and ultimately reduce the amount of allogeneic blood required for elective surgical procedures. The authors state that this conclusion clearly cannot be assumed from this study. The authors should be congratulated on conducting a large multicentered protocol of this complexity. The fact that transfusion triggers themselves are not generally agreed upon makes the task of demonstrating the utility of a product such as perflubron even more difficult.[15] Determination of the definitive clinical effect of PFC-supplemented acute normovolemic hemodilution awaits studies analyzing overall morbidity and mortality rates. Because such a study has only recently been attempted for blood itself, it will be even more challenging to conduct a study comparing a "blood substitute" to this controversial gold standard.[16]

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Auditory Evoked Potentials and 40-Hz Oscillations

An Opportunity To Study Mechanisms of Action of General Anesthetics?

IN this issue of ANESTHESIOLOGY,[1] Dutton *et al.*[1] examine the effects of propofol and desflurane on the 40-Hz activity that is part of the midlatency auditory evoked potential (MLAEP). They show that attenuation of the 40-Hz activity by propofol or desflurane correlates well with the loss of consciousness. Consciousness was defined as responsiveness to simple verbal commands.

Auditory evoked potentials are changes of the electroencephalogram caused by auditory stimuli. *Midlatency* designates the potentials that occur 12 to 50 ms after the stimulus (in awake subjects). The MLAEP consists of thee main peaks: Na, Pa, and Nb, with respective usual latencies near 15, 28, and 40 ms in awake subjects.[2] These peaks represent variation of electrical potential as a function of time. The first letter indicates the polarity of the wave at the vertex; the second, the order of occurrence. Other peaks (Pb and Nc) can sometimes be identified after Nb. The interval from Pa to Nb approximates a one cycle sinusoid with a period of approximately 25 ms (40 − 15 ms), which corresponds to a frequency near 40 Hz. This is the 40-Hz activity contained in the MLAEP (fig. 1).

The article by Dutton *et al.* is an important contribution to the abundant literature on the effects of general anesthetics on MLAEP. General anesthetics produce robust concentration-dependent alterations of MLAEP (increased latency and decreased amplitude) that are remarkably similar for most anesthetics.[3] Some of these alterations, such as the increase of the latency of wave Nb, allow reliable prediction of the presence or absence of consciousness.[4] Madler and Pöppel[5] showed that anesthetic-induced changes of MLAEP reflected loss of 40-Hz activity and suggested that this could explain why identification of sensory events is no longer possible during general anesthesia. Substantial 40-Hz MLAEP activity during surgical anesthesia is frequently accompanied by signs of light anesthesia.[6] Dutton *et al.*[1] provide a much-needed study: one that examines directly the relationship between 40-Hz MLAEP activity and the level of consciousness.

There are at least two reasons to search for neurophysiologic measures of anesthetic effect on the brain: (1) to

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