

in table 6 and transfusion was similar between groups. Second, major surgical bleeding may have been responsible for delayed transfusion after the first 24 h. Third, several major articles about antifibrinolytic therapy used a 1-week (or even more) endpoint.<sup>2-4</sup> Indeed, the goal of antifibrinolytic therapy is to decrease transfusion with its related complications, some being life threatening, and cost. Transfusion risk depends on the number of units or donors to which the patient is exposed during his whole hospitalization, not just during day 1. Thus, in our opinion, focusing on the first day is looking through the wrong end of the telescope. If one dose of tranexamic acid does not make a difference compared with another after the intraoperative period, then it is not superior.

Sanfilippo *et al.* asked for some details about postoperative procedures, such as antiplatelet therapy and anticoagulation. In fact, we forgot to mention in the article that postoperative care was adapted to the medical and surgical problems of each patient and did not differ from those usually practiced. It was indeed important for us to evaluate tranexamic acid in a “real-life situation,” once again to be sure to bring out a strong difference.

Finally, Sanfilippo *et al.* asked for the incidence of postoperative renal replacement therapy. Unfortunately, we did not collect these data. We would like to add that hemorrhagic events (pleural and pericardial effusions) after the first 24 h (day 2 to day 28) were rare: 12 in the low-dose group (4.3%) and 8 in the high-dose group (2.8%). The low incidence of such events attenuates the possibility that all these potential flaws may have biased our study.

### Competing Interests

The authors declare no competing interests.

**Stéphanie Sigaut, M.D., Benjamin Tremey, M.D., Marc Fischler, M.D.** Hôpital Foch, Suresnes, France, and University Versailles Saint-Quentin en Yvelines, France (M.F.). m.fischler@hopital-foch.org

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## Lipid Emulsion Increases the Fast Na<sup>+</sup> Current and Reverses the Bupivacaine-induced Block: A New Aspect of Lipid Resuscitation?

### To the Editor:

We read with great interest the article by Wagner *et al.*,<sup>1</sup> in which the authors evaluated the effects of lipid emulsion with bupivacaine on cardiac action potential and fast Na<sup>+</sup> current (I<sub>Na</sub>) in native rat cardiomyocytes. Because lipid emulsion is becoming a standard rescue treatment for intractable fatal arrhythmias resulting from local anesthetic systemic toxicity, it is of great significance to assess the effects of lipid emulsion on cardiac electrophysiology. Of special interest was the result showing a “direct lipid effect” in the presence and absence of local anesthetics on sodium channels, separating a “lipid sink” by ultracentrifugation. In the presence of local anesthetics, a direct lipid effect was clearly shown by subtracting the effect of centrifuged from uncentrifuged lipid solutions. However, we had some concerns in interpreting these results. In our recent study, we also evaluated the lipid sink effect using lipid emulsions and their centrifuged solutions in voltage-gated proton channels.<sup>2</sup> Use of these solutions in proton channels was unimportant because lipid emulsions did not affect proton currents. However, we thought some care should be taken when using these solutions in voltage-gated sodium channels.

Our first concern is in regard to a small amount of sodium ions contained in lipid emulsions. Wagner *et al.* used Lipovenös® MCT 20% (medium-chain triglycerides) (Fresenius Kabi AG, Bad Homburg, Germany), which contains sodium hydrate and sodium oleate, that is, up to 5 mM sodium ions in total.\* These concentrations are low but can slightly increase the driving force of sodium currents. In addition, as the authors described in detail, sodium currents in cardiomyocytes can easily lead to voltage errors. Therefore, the low concentration of sodium in lipid emulsions may increase the I<sub>Na</sub>. Indeed, Wagner *et al.*<sup>1</sup> showed that 10% Lipovenös®-containing solutions without local anesthetics increased the I<sub>Na</sub> by approximately 20% compared with the control solutions. Lipovenös® MCT 20% consists of 50% long-chain triglycerides and 50% MCTs. Some long-chain triglycerides (linolenic acid, linoleic acid, and oleic acid) and caprylic acid in MCT have been shown to reduce I<sub>Na</sub>, whereas other monounsaturated or saturated fatty acids did not.<sup>3,4</sup> Indeed, recent report by Nadrowitz *et al.*<sup>5</sup> indicated that 15% Lipofundin® (B. Braun Melsungen AG, Melsungen, Germany) (50/50 long-chain triglyceride/MCT) significantly reduced I<sub>Na</sub> by 42 ± 4% in human embryonic kidney cells expressing human Nav 1.5. In contrast, Wagner *et al.* first showed the increase of I<sub>Na</sub> by lipid emulsion in native rat cardiomyocytes, which could be the

\* Available at: [http://www.fresenius-kabi.de/files/Fachinfo\\_Lipovenoes\\_MCT20.pdf](http://www.fresenius-kabi.de/files/Fachinfo_Lipovenoes_MCT20.pdf). Accessed April 20, 2014.

new important mechanism of lipid resuscitation. However, we are concerned about the effects of low sodium concentration on this increase and would like to know how the authors think about their results of lipid emulsion different from that of previous reports. How did they adjust  $\text{Na}^+$  content of 10% lipid-containing solution (“approximately 2 mM”)?

Our second concern is regarding the residual triglyceride after removal of lipid emulsion by centrifugation. In our preliminary trial, we centrifuged 10% lipid-containing solution using Lipofundin® 20%, which consists of the similar contents with Lipovenös® MCT 20%. We made the same solution as Wagner *et al.* and centrifuged it similarly at 110,000g for 2 h at 4°C (CP-100α; Hitachi Koki Co., Ltd., Tokyo, Japan) and measured the triglyceride concentrations (Cholestest®TG; Sekisui Medical Co., Ltd., Tokyo, Japan). The centrifuged solutions of 10% Lipofundin® contained  $9.6 \pm 1.5$  mg/dl residual triglyceride ( $n = 5$ ). Although these residual triglycerides are low, Nadrowitz *et al.*<sup>5</sup> showed that even 0.05% Lipofundin®, containing 10 mg/dl triglyceride, slightly reduced the peak current amplitude of  $I_{\text{Na}}$  in human embryonic kidney cells. Thus, the direct lipid effect on sodium channels may not be shown by simply subtracting the effects of centrifuged from uncentrifuged lipid solutions.

We cannot estimate the effects of these two concerns on their results. However, as the sodium contents and residual triglyceride of lipid emulsion can directly affect the  $I_{\text{Na}}$ , we have to carefully analyze the data obtained with lipid emulsions and their centrifuged solutions in experiments using voltage-gated sodium channels. Aside from these concerns, we thank the authors for presenting these very interesting results, providing a new aspect of lipid resuscitation.

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## Competing Interests

The authors declare no competing interests.

**Kotaro Hori, M.D., Ph.D., Miyuki Kuno, M.D., Ph.D., Kiyonobu Nishikawa, M.D., Ph.D.** Osaka City University Graduate School of Medicine, Osaka, Japan (K.H.). k.hori@med.osaka-cu.ac.jp

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## In Reply:

We thank Dr. Hori *et al.* for their interest in our article<sup>1</sup> and their valuable and critical comments. We share their curiosity regarding the “direct lipid effect” described and agree that other explanations for the effect of the lipid emulsion alone should be ruled out before this effect can be regarded as proven. Dr. Hori *et al.* raise two concerns: one regarding possible differences in  $\text{Na}^+$  concentration between the lipid and control groups and the other concerning the presence of residual triglycerides in the centrifuged solutions.

As Dr. Hori *et al.* noted correctly, it is important to keep the  $\text{Na}^+$  concentration constant during experiments assessing  $\text{Na}^+$  current magnitude. Because the information on the  $\text{Na}^+$  concentration of Lipovenös® (Fresenius Kabi AG, Bad Homburg, Germany) provided by the supplier is somewhat vague (up to 5 mM), we measured it ourselves by flame photometry in the initial charge of Lipovenös® used. The result was  $2.06 \pm 0.05$  mM ( $n = 3$ , mean  $\pm$  SD), which we referred to as “approximately 2 mM” in the article, and we therefore included 2 mM  $\text{Na}^+$  in the corresponding control solution. Upon receiving your comments, on request to the supplier, we learned that the  $\text{Na}^+$  concentration of Lipovenös® is less than 5 mM but may vary from charge to charge. We therefore also measured the  $\text{Na}^+$  concentration of Lipovenös® in the second charge we used in our study. The result was  $3.18 \pm 0.12$  mM ( $n = 3$ , mean  $\pm$  SD) and therefore approximately 1 mM higher than the 2 mM used in our control solution. Nevertheless, because the final solution used for experiments contained only 10% of either Lipovenös® or control, the difference in the  $\text{Na}^+$  concentration in our experiments was still marginal: 18.2 mM under control conditions and 18.3 mM in the presence of Lipovenös®. Using the Goldman–Hodgkin–Katz equation, we calculated the expected  $\text{Na}^+$  current increase (at  $V_{\text{pip}} = -40$  mV) caused by increasing the  $\text{Na}^+$  concentration from 18.2 to 18.3 mM to be 0.7%. We therefore conclude that the measurements of  $I_{\text{Na}}$  were not disturbed by these marginal differences in  $\text{Na}^+$  concentration and that the direct lipid effect of Lipovenös® must have a different cause.

We thank Dr. Hori *et al.* for sharing their interesting results regarding the removal of triglycerides by ultracentrifugation of Lipofundin® 20% (B. Braun Melsungen AG, Melsungen, Germany). We are very pleased about their demonstration that by ultracentrifugation it is possible to remove more than 99.5% of the triglycerides from a lipid emulsion. Yet, we were surprised by the results reported by Nadrowitz *et al.* in their elegant and interesting article that even 0.05% Lipofundin® has some effect on Nav1.5-mediated currents.<sup>2</sup>