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 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 110,000*g* 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 ± 1.5 mg/dl residual triglyceride (n = 5). Although these residual triglycerides are low, Nadrowitz *et al.*[5] showed that even 0.05% Lipofundin®, containing 10 mg/dl triglyceride, slightly reduced the peak current amplitude of I_{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_{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.

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References

1. Wagner M, Zausig YA, Ruf S, Rudakova E, Gruber M, Graf BM, Volk T: Lipid rescue reverses the bupivacaine-induced block of the fast Na^+ current (INa) in cardiomyocytes of the rat left ventricle. Anesthesiology 2014; 120:724–36
2. Hori K, Matsuura T, Mori T, Kuno M, Sawada M, Nishikawa K: The Effect of Lipid emulsion on intracellular bupivacaine as a mechanism of lipid resuscitation. Anesth Analg 2013;117:1293–301
3. Xiao YF, Sigg DC, Leaf A: The antiarrhythmic effect of n-3 polyunsaturated fatty acids: Modulation of cardiac ion channels as a potential mechanism. J Membr Biol 2005; 206:141–54
4. Lamas JA, Martinez L, Canedo A: Caprylic acid, a medium chain saturated fatty acid, inhibits the sodium inward current in neuroglioma (NG108-15) cells. Neurosci Lett 1995; 198:181–4
5. Nadrowitz F, Stoetzer C, Foadi N, Ahrens J, Wegner F, Lampert A, Koppert W, de la Roche J, Leffler A: The distinct effects of lipid emulsions used for "lipid resuscitation" on gating and bupivacaine-induced inhibition of the cardiac sodium channel Nav1.5. Anesth Analg 2013; 117:1101–8

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In Reply:

We thank Dr. Hori *et al.* for their interest in our article[1] 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 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 Na^+ concentration constant during experiments assessing Na^+ current magnitude. Because the information on the 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 ± 0.05 mM (n = 3, mean ± SD), which we referred to as "approximately 2 mM" in the article, and we therefore included 2 mM Na^+ in the corresponding control solution. Upon receiving your comments, on request to the supplier, we learned that the Na^+ concentration of Lipovenös® is less than 5 mM but may vary from charge to charge. We therefore also measured the Na^+ concentration of Lipovenös® in the second charge we used in our study. The result was 3.18 ± 0.12 mM (n = 3, mean ± SD) and therefore approximately 1 mM higher that 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 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 Na^+ current increase (at V_{Pip} = –40 mV) caused by increasing the Na^+ concentration from 18.2 to 18.3 mM to be 0.7%. We therefore conclude that the measurements of I_{Na} were not disturbed by these marginal differences in 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.[2]

A solution containing 0.05% Lipovenös® appears clear to the eye and therefore it is perfectly possible that our centrifuged emulsions contained approximately 10 mg/dl triglycerides as suggested. Consequently, a part of a "direct lipid effect" may still be present even in the centrifuged emulsions. It should be noted, however, that Nadrowitz *et al.* used Lipofundin® and Intralipid® in their experiments, whereas we used Lipovenös®. Even though Lipofundin® and Lipovenös® contain a similar mixture of triglycerides containing long- and medium-chain fatty acids, presently it is unclear whether the medium-/long-chain fatty acid mixture of Lipofundin® or a different component (that may or may not be present also in Lipovenös®) is responsible for the inhibition of Nav1.5-mediated currents demonstrated by Nadrowitz *et al.* In this regard, it is interesting that although Lipofundin® inhibited Nav1.5-mediated currents, Intralipid® did not. It seems prudent to assume that this is due to differences in lipid content, however, at this point this is a speculation and warrants further exploration.

In our article, to validate the results, we compared the apparent reduction of the bupivacaine concentration as assessed by concentration–response analysis of the patch clamp experiments to the actual reduction of the bupivacaine concentration as assessed by gas chromatography–mass spectrometry. We found that both approaches yielded similar bupivacaine concentrations in the centrifuged lipid emulsions. Consequently, we do not expect that residual triglycerides have significantly affected our results.

Taken together, we do not think that the reasonable concerns raised by Hori *et al.* can explain the "direct lipid effect" as described in our article. Yet, we are grateful for their comment as it clearly points out that the nature of what we have called "direct lipid effect" in our article is, at present, unclear. In fact, it includes every effect that cannot be attributed to the lipid sink. Clearly, we cannot rule out that a part of this effect may be explained by limitations of our experimental approach, but most importantly, more experiments are necessary to explore the nature of this effect.

Competing Interests

The authors declare no competing interests.

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References

1. Wagner M, Zausig YA, Ruf S, Rudakova E, Gruber M, Graf BM, Volk T: Lipid rescue reverses the bupivacaine-induced block of the fast Na^+ current (I_{Na}) in cardiomyocytes of the rat left ventricle. Anesthesiology 2014; 120:724–36
2. Nadrowitz F, Stoetzer C, Foadi N, Ahrens J, Wegner F, Lampert A, Koppert W, de la Roche J, Leffler A: The distinct effects of lipid emulsions used for "lipid resuscitation" on gating and bupivacaine-induced inhibition of the cardiac sodium channel Nav1.5. Anesth Analg 2013; 117:1101–8

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Healthcare Technology: Is It Cost Efficient?

To the Editor:

Your editorial titled "From heroism to safe design: leveraging technology," by Peter J. Pronovost *et al.*,[1] made for interesting reading. The ideas expressed for use of integration of technology to improve patient safety are innovative.

We would like to add a few points:

1. Technology has been described as both part of the problem and part of the solution for safer health care. Healthcare providers can be so focused on data from monitors that they fail to detect potentially important subtle changes in clinical status.[2] If a clinician fails to prescribe a correct narcotic dose and fails to recognize a narcotic overdose, we think there is a lack of clinical acumen.
2. Use of high-end technology in simple clinical decisions would be shunning our responsibility as physicians.
3. Problems may emerge based on the sheer volume and the complexity of new devices.[2]
4. The race for providing healthcare technology is presently market driven dominated by a few multinational companies. There is no focus on making it inexpensive and widely available.[3]
5. Automated patient care systems also face problems of system downtime and data accuracy which further spiral costs of health care.[4]
6. We still have a long way to go till such technology becomes widely available, is used efficiently for patient safety, and becomes truly "productive."

Competing Interests

The authors declare no competing interests.

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References

1. Pronovost PJ, Bo-Linn GW, Sapirstein A: From heroism to safe design: Leveraging technology. Anesthesiology 2014; 120:526–9
2. Powell-Cope G, Nelson AL, Patterson ES: Patient Safety and Quality: An Evidence-based Handbook for Nurses. Rockville, Agency for Healthcare Research and Quality (US), 2008, pp 207–20
3. Kumar RK: Technology and healthcare costs. Ann Pediatr Cardiol 2011; 4:84–6