subsystems, instead of limiting depth to describing an observed state as somehow more profound in an ill-defined manner. Of course, this is based on an enormous simplification of the nervous system. But even at that, it allows the concept of depth to provide a much more meaningful context for the complexities described by Garcia and Sleigh. It also encourages us to view anesthesia not as a unitary phenomenon, but rather as a suite of altered neurologic functions roughly affiliated with a suite of neurologic regions. And it is this suite of regions, and their interconnections, that provides a substrate of sufficient complexity to encompass all the alterations caused by anesthetics.

Competing Interests

The author declares no competing interests.

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Amendments and Corrections to Mattusch *et al*. (Anesthesiology 2015; 122[5]:1047–59), "Impact of Hyperpolarization-activated, Cyclic Nucleotide-gated Cation Channel Type 2 for the Xenon-mediated Anesthetic Effect: Evidence from *In Vitro* and *In Vivo* Experiments"

To the Editor:

We previously reported that the anesthetic xenon impairs hyperpolarization-activated, cyclic nucleotide-gated cation channel type 2 (HCN2) function and thalamocortical signal propagation in murine thalamocortical slices, and supported by *in vivo* data, we discussed these findings as hypothetical mechanisms that might contribute to the anesthetic property of xenon.[1] Subsequent to this publication, concerns were expressed to the Editor-in-Chief of the journal regarding part of the methodology, as well as the validity of the interpretation of our observations. In that correspondence, the following putative limitations of the *in vitro* and *in vivo* data were expressed:

- Under our experimental conditions, a change in oxygen concentration and/or pH could have occurred during xenon application that confounded interpretation of or even directly elicited the observed effects.
- The concentration of xenon in the *in vivo* experiments was uncertain.
- The observed *in vivo* effects were due to deficits in locomotor activity of the mice secondary to deletion of the HCN2 channel itself.

Within the course of the ensuing communications, discrepancies between the methods employed and their description in the original article were also identified. For this we are indeed grateful, and these mistakes have also been corrected below. These issues prompted the Editor-in-Chief to request that we clarify the methodologic approach used in our original publication and suggested performing additional experiments to confirm that the effects observed were indeed exclusively due to xenon. We thank the Editor-in-Chief for the opportunity to address those concerns here.

In Vitro Results

In the following sections, all data are reported as means ± SD. One of the criticisms focused on the oxygenation of the brain slices and, referring to Mattusch *et al.*,[1] it was claimed that our slices were subjected to very low oxygen levels. In the Materials and Methods section of Mattusch *et al.*,[1] we wrongly indicated that the storage chamber was perfused with artificial cerebrospinal fluid (aCSF) at a rate of 5 ml/min and the recording chamber at a flow rate of 2 to 3 ml/min. Even though many acknowledged experts in the field do in fact perfuse their slices with exactly those rates or only 1.5 to 3 ml/min,[2–8] and some do not even provide any information,[9–15] in our experiments the recording chamber was in fact perfused at a rate of 5 to 8 ml/min. The storage chamber (beaker with a gauze platform for the slices to be kept on) was not connected to a perfusion system but rather aerated directly with carbogen gas (95% O_2/5% CO_2). Insufficient oxygen tension is unlikely to be a confounding variable for the following reasons:

As standardized by almost all research groups performing *in vitro* slice experiments, we aerated the aCSF with carbogen. When aCSF was recirculated at a flow rate of 5 to 8 ml/min, an oxygen-sensitive biosensor (ISO-OXY-2 oxygen sensor; World Precision Instruments, USA) located at the bottom of the recording chamber revealed an oxygen partial pressure of 501 ± 27 Torr (n = 4). The discrepancy between the calculated oxygen pressure (approximately 690 Torr in the laboratory) and our measured pressure level is not

surprising and can well be explained by the constraints of perfusion (*e.g.*, open surfaces in the reservoir and chamber). As such, the commonly used statement "aCSF was saturated with carbogen gas" could, in the strictest formalistic sense, be interpreted by some to be misleading. However, this term is more or less standardized in many publications in the field, and fellow colleagues know precisely what is meant.

Even if according to Ivanov and Zilberter[16] the high rate of perfusion used (5 to 8 ml/min) is still too slow, there is ample evidence that intracellular signaling cascades and synaptic transmission remain unperturbed under these conditions. This is demonstrated by numerous studies[17–23] (including several from our laboratories) that report reliable induction of long-term potentiation over many hours under comparable flow rates, which would not be possible under hypoxic conditions. Thus, the slices perfused with the flow rate used in Mattusch *et al.*[1] were not hypoxic, certainly not to a degree that would have any relevance for interpretation of the results.

For evaluating the neuronal effects of xenon in brain slices in Mattusch *et al.*,[1] xenon was applied within prefabricated gas mixtures consisting of:

- 18% xenon/47% N_2/30% O_2/5% CO_2
- 30% xenon/35% N_2/30% O_2/5% CO_2
- 65% xenon/30% O_2/5% CO_2
- 100% xenon

The composition of these gas mixtures was documented imprecisely in the Materials and Methods section of Mattusch *et al.*[1] These xenon gas mixtures were applied together with carbogen. Co-application of our gas mixture containing 65% xenon together with carbogen at the same flow rate would consequently lead to a calculated gas concentration of 32.5% xenon/62.5% O_2/5% CO_2. Given the nature of electrophysiologic measurements in acute brain slices, the experiments were performed using open perfusion systems. This might lead to a discrepancy between the calculated and the true gas fractions and the resulting partial pressures of dissolved gases in the aCSF. Gas chromatography revealed a concentration of 1.9 mM xenon dissolved in aCSF. We consequently avoided stating that the slices themselves were exposed to 65% xenon in Mattusch *et al.*[1] but reported the effect of 1.9 mM xenon throughout the manuscript. We now see that this lack of clarity in the description of our experimental setting was obviously a cause for serious concern, and for this we apologize.

It was also argued that our experimental procedure led to a simultaneous change of both the oxygen and xenon partial pressure. The change in oxygen partial pressure might interfere with the validity of the results since it could be impossible to distinguish whether the observed effects were either due to xenon or subsequent to the changed oxygen tension (or the combination of both).

To address this issue, we now measured the partial pressure of oxygen and carbon dioxide and monitored pH in the presence of carbogen alone or when co-applied with either a nitrogen gas mixture (65% N_2/30% O_2/5% CO_2) or a xenon gas mixture (xenon 65%/O_2 30%/CO_2 5%). When nitrogen mixture was co-applied with carbogen, the partial pressure of oxygen was significantly reduced from 501 ± 27 to 421 ± 17 Torr (P = 0.011; n = 4) near the bottom of the recording chamber (*i.e.*, at the level where the brain slice would be located). Comparably, oxygen partial pressure was reduced from 531 ± 14 to 466 ± 15 Torr (P < 0.001; n = 5) when the aCSF was aerated with xenon mixture. The pH of the aCSF remained unchanged with either carbogen only (7.43 ± 0.02) or carbogen and nitrogen mixture aeration (7.47 ± 0.01; n = 4; P > 0.05). Similarly, xenon mixture co-application did not affect pH (7.47 ± 0.01 carbogen only *vs.* 7.47 ± 0.02 carbogen + xenon mixture; n = 5; P > 0.05). In summary, we could detect a decrease in oxygen partial pressure of ~80 Torr with nitrogen mixture and ~64 Torr with xenon mixture.

To rule out any potential implications of differences in oxygen tension for the interpretation of our results, we now provide additional results from supplementary voltage-sensitive dye imaging and patch clamp experiments.

Voltage-sensitive Dye Imaging Experiments

First, we tested whether co-application of nitrogen mixture in carbogen-aerated aCSF had any effect on the cortical fast depolarization-mediated signal (FDS) in response to electrical stimulation of the ventrobasal nucleus. aCSF was aerated with carbogen, and under these conditions stable baseline recordings for at least 20 min were performed, following which the nitrogen mixture was co-applied. As shown in figure 1 (A and B), the fractional change in fluorescence (ΔF/F) within the region of interest did not change (carbogen: 1.00 ± 0.08, carbogen + nitrogen mixture: 0.96 ± 0.15; n = 10; P = 0.75). These results clearly demonstrate that the additional application of a gas mixture with an oxygen fraction of 30% (the balance of the admixture being 65% N_2 and 5% CO_2) to aCSF saturated with 95% oxygen does not affect neuronal activity as measured by FDS.

We then re-evaluated the inhibitory effect of xenon on FDS propagation in the thalamocortical slice preparation. Slices were superfused with aCSF aerated with carbogen and nitrogen mixture. After stable baseline recordings of FDS for at least 20 min, we replaced the nitrogen mixture with xenon mixture (applied at the same flow rate and still in the presence of carbogen; fig. 1C). Under these conditions, xenon produced a significant reversible reduction in the FDS to 0.74 ± 0.04 normalized to control (n = 7; P < 0.01; fig. 1D). Taken together, these results indicate that it is xenon *per se* and not a reduction in oxygen tension that produces a decrease in FDS propagation.

Whole Cell Patch Clamp Recordings

Since we observed a slight but significant reduction of the partial pressure of dissolved oxygen in the aCSF during co-application of carbogen with xenon 65% (or nitrogen 65%) gas admixture, we performed subsequent experiments to test whether this decrease in oxygen might compromise

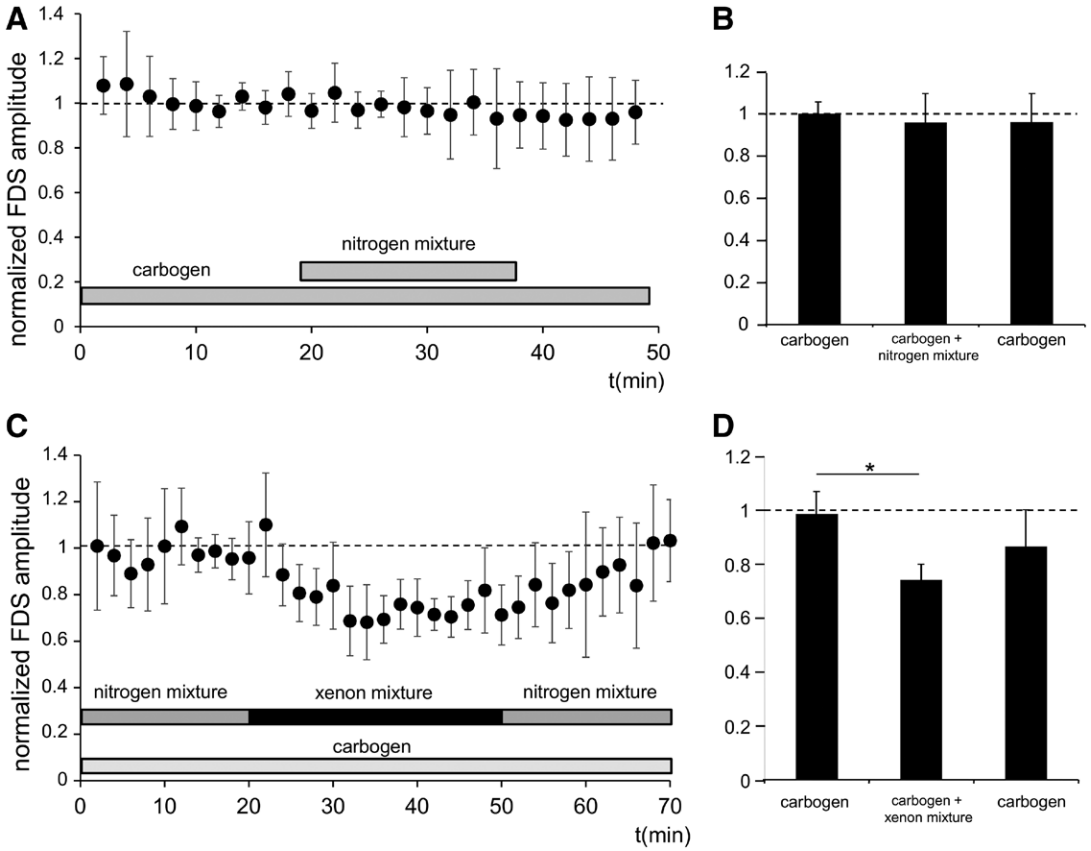

Fig. 1. Co-application of nitrogen gas mixture has no effect on thalamocortical signal propagation, whereas substituting nitrogen gas mixture with xenon gas mixture results in diminished signal propagation. Voltage-sensitive dye imaging was used to assess thalamocortical signal propagation following thalamic stimulation. (*A*) Averaged data plotted *versus* time. Each *symbol* represents the fast depolarization signal (FDS) activity averaged more than 2 min. At the beginning of each experiment, artificial cerebrospinal fluid (aCSF) was aerated with carbogen gas; after obtaining 20 min of stable baseline responses, nitrogen mixture was co-applied to the aCSF for 20 min (as shown). (*B*) Bar diagram showing the mean FDS amplitude recorded during the last 5 min of carbogen, carbogen + nitrogen mixture, and carbogen (washout) aeration. (*C*) Thalamocortical brain slices were perfused with aCSF aerated with carbogen and nitrogen mixture as indicated by the *bars* at the bottom. After stable baseline recordings of FDS activity, nitrogen mixture was replaced by xenon mixture, which reversibly suppressed the FDS. (*D*) Bar diagram showing the mean FDS amplitude recorded during the last 5 min of carbogen + nitrogen mixture, carbogen + xenon mixture, and carbogen + nitrogen mixture aeration. Averaged data indicate that xenon reversibly decreased FDS amplitudes induced by thalamic stimulation to 0.74 ± 0.04 normalized to control (n = 7). *$P < 0.01$.

the validity of the effects of xenon on I_h currents recorded from thalamocortical neurons as originally described.[1] In these newly performed experiments, the carbogen-saturated aCSF was additionally aerated with the nitrogen mixture. Co-aeration of aCSF with carbogen and nitrogen mixture had no effect on I_h amplitude (96.9 ± 21% of control when cells were hyperpolarized to −133 mV, n = 5; $P > 0.05$; fig. 2A), voltage sag (1.18 ± 0.31 relative to control; n = 5; $P > 0.05$; fig. 2B), or rebound delay (0.92 ± 0.20 relative to control; n = 5; $P > 0.05$; fig. 2B) in thalamocortical neurons. Replacing nitrogen with xenon did, however, reduce I_h at hyperpolarized membrane voltages (fig. 2C). In these experiments, the aCSF was co-aerated with carbogen and nitrogen mixture as the control condition, and nitrogen mixture was then replaced by xenon mixture for the experimental condition. We found that xenon significantly reduced I_h amplitude at the most hyperpolarized membrane potential tested (reduction by 0.23 ± 0.18 compared to I_h amplitude under carbogen + nitrogen mixture; n = 5; $P < 0.05$; fig. 2C). This degree of reduction was not significantly different from the effect of xenon described previously (0.33 ± 0.12).[1]

In summary, these subsequent experiments clearly demonstrate that the reduction of oxygen partial pressure by ~64 Torr does not affect neuronal signaling or HCN channel-mediated currents. These observations are supported by further findings that argue against a relevant change in oxygen supply during xenon application:

- Unchanged resting membrane potential under xenon conditions (see fig. 2D in Mattusch *et al.*[1])
- Unchanged AP threshold and AP frequency under xenon conditions (see fig. 2, E and F, in Mattusch *et al.*[1]).

Interestingly, a critique was also raised that xenon affects I_h currents obviously only when cells were hyperpolarized.

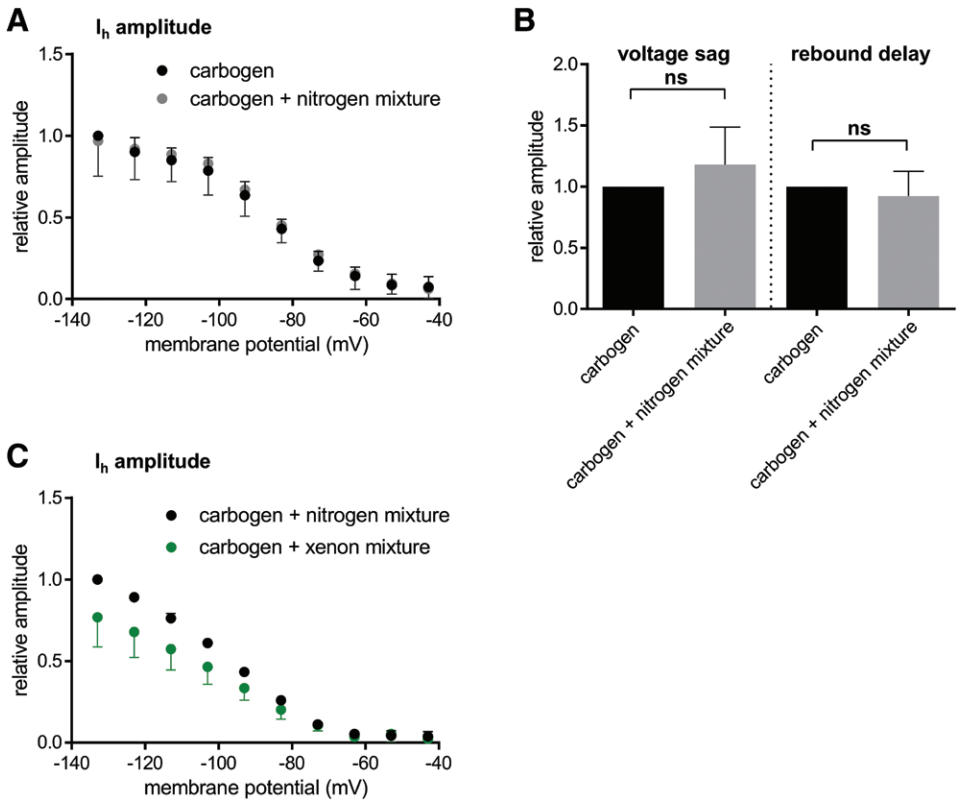

Fig. 2. Co-application of nitrogen gas mixture gas to carbogen gas has no impact on hyperpolarization-activated cyclic nucleotide-gated cation channel-mediated currents (I_h), whereas substitution of nitrogen mixture with xenon gas mixture results in reduced I_h amplitude. (*A*) Hyperpolarization-activated cyclic nucleotide-gated cation channel-mediated currents (I_h) were obtained by hyperpolarization of neurons to the indicated membrane potentials (voltage protocol not shown). Simultaneous aeration of the artificial cerebrospinal fluid with both carbogen and nitrogen mixture had no effect on I_h amplitude (96.9 ± 21% of carbogen saturation only; at membrane potential of −133 mV). (*B*) Hyperpolarization-activated cyclic nucleotide-gated cation channel-mediated voltage sag and rebound burst delay were recorded in current clamp configuration. Saturation of the aCSF with carbogen and nitrogen mixture affected neither voltage sag (1.18 ± 0.31 relative to carbogen only; n = 5; $P > 0.05$) nor rebound delay (0.92 ± 0.20 relative to carbogen only; n = 5; $P > 0.05$). (*C*) Slices were perfused with artificial cerebrospinal fluid that was aerated with both carbogen and nitrogen mixture under control conditions, followed by the experimental condition in which nitrogen mixture was replaced by xenon mixture. Substitution of nitrogen mixture with xenon mixture significantly reduced I_h amplitude by 23.2 ± 18.2% compared to I_h amplitude (at membrane potential of −133 mV) in the presence of carbogen + nitrogen mixture (n = 5; $P < 0.05$). ns = no significant difference ($P > 0.05$).

However, this argument is not entirely reasonable: It should hardly come as a surprise as, unlike the vast majority of cellular conductances that are activated upon membrane depolarization, I_h is in fact activated by hyperpolarizing voltage steps to potentials negative to the resting potential of cells.[24] As we reported in our original publication, the voltage required for channel activation is significantly left-shifted by xenon in both thalamocortical neurons (respectively approximately −99 mV and approximately −108 mV) and HEK293 cells expressing murine HCN2 channels (approximately −94 and −99 mV); in both instances, the xenon-induced left shift was prevented by cyclic adenosine monophosphate. These results suggest that xenon stabilizes HCN channels in the closed configuration by preventing cyclic adenosine monophosphate-mediated relief of cyclic nucleotide-binding domain–dependent inhibition of channel opening.[25] That the observed effect on macroscopic currents is more pronounced at hyperpolarized membrane potentials merely reflects the fact that more channels are already open. Whether xenon inhibits cyclic adenosine monophosphate synthesis or competes for the cyclic adenosine monophosphate binding site is an open question.

Summary of Amendments and Corrections Relevant for the *In Vitro* Data of the Original Manuscript by Mattusch *et al.*

- Aeration of the aCSF with carbogen under our experimental conditions revealed an oxygen partial pressure of approximately 516 Torr ([501 + 531]/2) in the recording chamber.
- Our slices were perfused with a flow rate of 5 to 8 ml/min, and the storage chamber was not connected to a perfusion system as described in Mattusch *et al.*[1]

- All xenon concentrations (except of 100% xenon, see below) were applied within gas mixtures of 30% O_2/5% CO_2 and, dependent on the xenon concentration, topped up to 100% with nitrogen. These xenon gas mixtures were applied together with carbogen. This information was erroneously described in the original manuscript.
- The co-application of carbogen and 100% xenon (equivalent to 2.8 mM as assessed by gas chromatography) as originally described in Mattusch *et al.*[1] might indeed have resulted in insufficient partial pressure of carbon dioxide to ensure a constant pH, as well as a lowered oxygen tension. Consequently, the validity of the data point reported for 2.8 mM xenon and thereby also the validity of the calculated IC_{50} value (2.89 mM; fig. 1D in Mattusch *et al.*[1]) can be questioned; *i.e.*, this could have led to quantitative overestimation of the xenon effect against FSD amplitudes. Nevertheless, even without considering the data point for 2.8 mM xenon, we still show a dose-dependent effect of xenon against FSD amplitudes with a calculated IC_{50} of 4.52 mM.
- The simultaneous aeration of the aCSF with carbogen and the xenon gas mixtures does reduce oxygen partial pressure by ~64 Torr. The additional experiments clearly demonstrate that this degree of reduction does not affect neuronal signaling or HCN channel-mediated currents.
- The effects of xenon on HCN channels are observed only at hyperpolarizing potentials because these receptors are exclusively activated at potentials negative to the resting potentials of the neurons.

In summary, xenon inhibits HCN2 channels by shifting the voltage dependence of channel activation to more negative voltages and also reduces I_h. By using brain slices of HCN2$^{-/-}$ mice, we could show that the xenon-induced reduction of thalamocortical activity propagation was significantly attenuated, suggesting a putative role for HCN2 channels in mediating the anesthetic effects of xenon.[1]

In Vivo Results

The sedative properties of xenon were tested by measuring spontaneous locomotor activity after the application of a xenon gas mixture (70% xenon/30% oxygen) for 5 min at a flow rate of 0.5 ml/min. Since the open field chamber was not fully equilibrated within 5 min, this information was incorrectly stated, and the mice were actually never exposed to 70% xenon. We now provide an analysis of the gas fraction in the open field chamber at the same level mice normally occupy while monitoring locomotor activity. After the application of the gas mixture for 5 min, mass spectrometry (MAT271; Thermo Fisher Scientific, Germany) revealed 22 ± 1, 25 ± 2, and 53 ± 2 vol percentage for xenon, oxygen and nitrogen, respectively (n = 2).

A further criticism was the short adaptation time of 5 min between placing the mice in the open field chamber and starting monitoring locomotor activity. When placed in a new environment, explorative behavior of the animals is greatest in the first 5 min and then adapts over the course of the next 15 to 20 min. The observed reduction of locomotor activity therefore cannot be reliably attributed to an effect of xenon alone. In other words, the reduced activity could partially be due to the expected reduction in activity independent of xenon. Taken together, the study protocol did not permit an adequate test of our hypothesis. Hence, the *in vivo* data should be disregarded.

Competing Interests

The authors declare no competing interests.

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