veins directly into the IJV. Stated differently, the cavernous sinus receives only a portion of xenon-enriched blood from the nasal space, but the IJV collects almost all the blood from it. Therefore, a steady concentration of xenon in the IJV 10 min after intranasal application in volunteers is more a reflection of saturation of the nasal mucosa and nasal (not cranial) venous vascular beds with xenon. The actual concentration of xenon in the cavernous sinus is probably less than 500 nl/ml because the latter collects only a portion of nasal venous blood. Furthermore, although the cavernous sinus does communicate with basilar and superficial cortical veins, it is a "blood collector" that is ultimately drained into the IJV, and retrograde flow of xenon-containing blood toward cortical matter is very unlikely. Diffusion from the sinus itself to surrounding brain tissue and then to the rest of the brain is also unlikely.

Therefore, a likely explanation of how xenon was delivered to the brain, and possibly the spinal cord, to mediate its analgesic effects would be transport with arterial blood from the left heart.

Blood collected from the IJV in the right heart passes through the lungs, so the larger part of xenon will be rapidly exchanged with alveolar air and eventually lost with exhaled gas in spontaneously breathing volunteers or in study subjects mechanically ventilated with relatively high minute volumes. Indeed, as evidenced by a pharmacokinetic study undertaken by the same research team in anesthetized pigs (minute volume, about 5 l/min), arterial blood levels of xenon were $\leq$20 nl/ml in this setting.[3] Clearly, and considering that clinically relevant anesthetic concentrations of xenon are in the micromolar range, the likelihood of such concentrations of xenon exerting clinically significant effects is very unlikely. Hence, the next question would be how intranasally delivered xenon could have reached target tissues at concentrations capable of improving (though only minimally) intraoperative analgesia and reduced postoperative pain reported in their article? Here, in our view, is one feasible explanation.

Given the usage of endotracheal tubes with inflatable cuffs impermeable to xenon, the authors allege that direct pulmonary contamination with xenon was avoided. However, did they consider that xenon-containing central venous blood would be diverted to the lungs? Here, xenon would readily escape into the alveolar space by diffusion because of its very low blood-gas partition coefficient[4] and would accumulate in the anesthetic circuit operated in the minimal-flow ventilation (oxygen flow, 300 ml/min) mode that the authors used. In our view, what the authors intended to present as solely intranasal delivery of anesthetic gas turned into inhalational anesthesia with rebreathed low-dose xenon. We think that the authors should not have limited the pharmacokinetic study to volunteers only; xenon concentrations in the anesthetic gas mixture and in the arterial blood of study subjects should also have been determined.

Finally, if the beneficial effects of low-dose xenon described in their article are indeed clinically significant and if our assumption is correct, then there is probably no need to complicate the anesthetic procedure and administer xenon intranasally. A conventional inhalational route of low-dose xenon (*e.g.*, 15–20 ml/min) implemented as a part of low- or minimal-flow, closed-circuit anesthesia should be more than sufficient to benefit from xenon as an addition to the anesthetic protocol.

Xenon is a valuable anesthetic and we appreciate the authors' efforts to overcome the limitation of its high cost by administering it at low-dose to use it more widely in clinical practice. However, would low-dose xenon result in better analgesia compared with inhalational anesthetics applied at conventional doses (not at 0.5 minimal alveolar concentration desflurane, as tested in their article) or in combination with nitrous oxide; or would the difference be insignificant if xenon is applied at a low dose? These are the questions that have to be answered in the future.

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In Reply:

In our recently published article, "Intranasal application of xenon reduces opioid requirement and postoperative pain in patients undergoing major abdominal surgery: A randomized controlled trial,"[1] we have reported data showing beneficial effects of intranasally applied xenon on intraoperative opioid requirement and postoperative analgesia in patients undergoing abdominal hysterectomy. Beside these main results we have also described the pharmacokinetic of intranasally applied xenon using blood gas analyses. We would like to thank Petrenko and Baba for their interest in our work. We are very pleased to provide additional information regarding our study results and are thankful for the opportu-

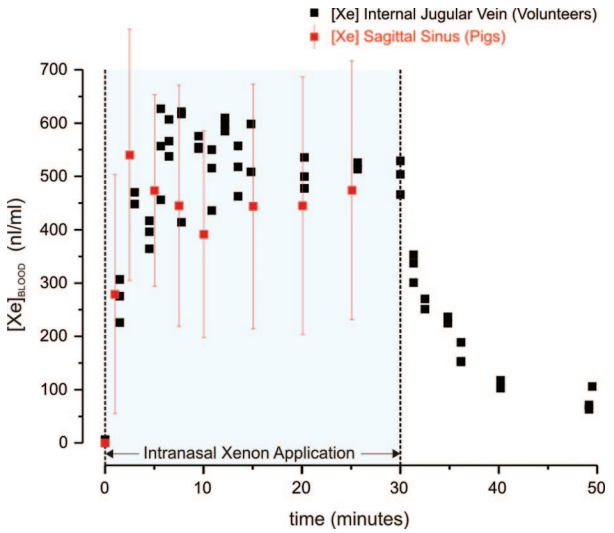

Fig. 1. Comparison of blood gas data. Human data: Concentrations of xenon measured in the blood of the internal jugular vein of two volunteers. Xenon was applied intranasally for 30 min at a rate of 1.0 l/h followed by 20 min of washout. Animal data: Concentrations of xenon measured in the venous blood of the sagittal sinus of seven pigs reflect xenon concentrations in the cerebral compartment. Xenon was delivered for 25 min into the application devices at a rate of 1.0 l/h.

nity to extend the discussion about the pharmacokinetic of intranasally applied xenon.

In their letter to the editor, Petrenko and Baba question to what extent the xenon concentrations measured in the internal jugular vein of volunteers really reflect the xenon content in cranial blood and target brain tissue under clinical conditions. In addition, they raise the important question whether and in which way lipophilic drugs can reach the brain using a nose-to-brain bypass. Moreover, they discuss the probability that an accumulation of xenon in the anesthesia circuit might be essential for the analgesic effect described in our study.

Concentrations of xenon measured in the venous blood of the sagittal sinus of seven anesthetized pigs[2] or the internal jugular vein (IJV) of two volunteers[1] reached a steady state of approximately 500 nl/ml after 10 min of intranasal application. There were no reliable differences between xenon concentrations in the venous blood comparing the intracranial sagittal sinus and the brain-draining IJV (fig. 1).

A wealth of proof-of-principle studies have already reported nose-to-brain delivery of a range of different drugs in animal models and volunteers. Thus the various pathways that a drug can follow from the nasal cavity to reach the cerebrospinal fluid or the brain tissue have been discussed thoroughly.[3,4] It is suggested in the literature that a drug administered nasally is able to reach the central nervous system by neural (olfactory, trigeminal) pathways or the bloodstream. Nevertheless, the mechanisms of transport of drugs from the nose to the brain are not yet completely understood. Considering the monoatomic and highly lipophilic nature of xenon as well as the fast wash-in kinetic of nasally applied xenon, we favored a blood-based route of action. However, a neural-related pathway or a combination of different routes cannot be excluded.

As stated in our article, the blood gas analyses in both species (pigs, volunteers) were accomplished under comparable conditions.[1] Blood gas analyses in volunteers served as a preparation of the clinical trial investigating patients undergoing abdominal surgery. To mimic the clinical conditions in the operation theater as closely as possible, the two volunteers were also anesthetized and mechanically ventilated during the blood gas assessment. Two different anesthesia workstations (Draeger Primus [Drägerwerk AG, Lübeck, Germany] for volunteers *vs.* Draeger Cicero [Drägerwerk AG] for pigs) and different ventilator settings (oxygen flow 300 ml/min for volunteers *vs.* 1,000 ml/min for pigs) were used in these studies. The concentrations of xenon measured in the blood of mechanically ventilated volunteers and pigs reached a plateau after a few minutes (IJV and sagittal sinus). In addition, under conditions that resemble the clinical setting, peripheral venous (volunteers) and arterial (pigs) xenon concentrations never exceeded 20 nl/ml.[2,1] Since the measured concentrations of xenon in the blood (IJV and sagittal sinus) of mechanically ventilated study subjects are obviously independent of the ventilator settings, and peripheral xenon concentrations barely reached the quantification limit, we conclude that a relevant accumulation of xenon in the anesthetic circuit is rather unlikely.

Given that a relevant portion of xenon was rebreathed, as discussed by Petrenko and Baba, we would expect a continuous increase of xenon concentrations over time and a time-dependent increase of peripheral xenon concentrations. However, this was not the case. We also must consider that because of their defect in xenon tightness (*e.g.*, caused by silicon tubes), the employed anesthesia workstations are inappropriate for the inhalative application of xenon using an indirect xenon supply at a rate of only 1 l/h.

Aside from the discussion about the pharmacokinetics, we would also like to emphasize that there is no evidence for the assumption that clinically relevant effects of xenon are generally limited to blood concentrations in the micromolar range. Note that even approximately 150 nl xenon/ml blood in the IJV are sufficient to suppress pain-related processes of central sensitization.[5]

As mentioned by Petrenko and Baba, every additional application device will complicate the daily anesthetic procedure. Moreover, we have to keep in mind that the maximum amount of xenon uptake using this novel route of application is limited by the available surface of intranasal structures. Therefore we agree with the excellent suggestion that further studies are needed to evaluate the breakeven point between analgesic benefit and economic reality using inhalatively applied xenon in several subanesthetic concentrations.

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Why the Gray Zone May Shift within the Fog

To the Editor:

We read the article by Cannesson[1] *et al.* and the accompanying editorial[2] with great interest, and praise the effort to better define the clinical utility and applicability of pulse pressure variation (PPV), not only as a tool to predict volume responsiveness but also to move away from a single-threshold value for conducting intraoperative volume optimization and perioperative goal-directed fluid therapy. We would like to make three points.

First, the most commonly used index to assess volume responsiveness, by far in the United States, appears to be stroke volume variation (SVV). Although the area under the receiver-operating curve, in systematic reviews,[3] shows that both PPV and SVV have excellent sensitivity and specificity in patients who are mechanically ventilated with normal tidal volumes and in a regular sinus rhythm, the threshold values discriminating between fluid responders and nonresponders are not the same for these two parameters.[3,4] Thus, although strategies using the "gray zone approach" applied to PPV identify a range of values where volume responsiveness cannot reliably be predicted, this range may not be applicable when SVV is used for determining volume responsiveness. Although it is clear from the work of Joseph Erlanger, the father of the pulse pressure concept,[5] that pulse pressure in man is proportional to left ventricular stroke volume (depending both on arterial tone and cardiac contractility) it is plausible that variations in pulse pressure may also be proportional to variations in stroke volume. To the extent that PPV and SVV are affected differently by changes in arterial tone, given the same degree of volume responsiveness,[4] these values may lose their direct proportionality as vascular tone changes. Pinsky described the potential utility of a SVV-to-PPV ratio to reflect ventricular-arterial coupling that might be helpful when extrapolating PPV threshold data to SVV.[6] Overall, applying PPV's "gray zone" to SVV seems clinically appealing but may be misleading. The "gray zone" defined for PPV should not *simply* be applied to patients who are being optimized using stroke volume variation. The "gray zone" for SVV requires its own definition.

Second, the paper does not address the issue of volume responsiveness *versus* needing to give volume or using a dynamic index to actively restrict fluids or to administer diuretics to patients under certain clinical circumstances. That is, not all patients who are volume responsive require volume therapy. Conversely, there may be untapped utility for SVV- and/or PPV-guided fluid restriction and diuretic use (consider patients with acute lung injury or acute respiratory distress syndrome).[7] The goal would be to identify patients with a PPV that is "too low" who, consequently, should receive restrictive fluid therapy or diuretics.

Third, what is, perhaps, not considered by the author[2] is the fact that PPV goals may vary within individual patients across changing clinical settings in relatively short intervals of time, such as during single lung ventilation for thoracic surgery, laparoscopic pneumoperitoneum, and conditions of pathologic intraabdominal hypertension. For example, the goals for intraoperative PPV during esophagectomy vary during the case, such that the goal during the abdominal part of the procedure is fluid liberal and during the thoracic part of the procedure is fluid restrictive.[8]

In summary, we praise Cannesson *et al.*[1] for their work and we agree that there is a "gray zone" well represented by the picture in the editorial[2] (*i.e.*, the Golden Gate Bridge with fog going across the middle represents "a static view of dynamic indices"). We contend that PPV and SVV "gray zones" are probably better described as the view one gets of the Golden Gate Bridge, with fog going across the middle as one is driving along winding hilly roads. This is a "dynamic view of dynamic indices," such that the gray zone changes at different times depending on one's changing vantage point, an analogy closer to clinical reality.

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This letter and the related letters below were sent to the author of the above-mentioned editorial. The author declined to respond.—James C. Eisenach, M.D., Editor-in-Chief

Drs. Bloomstone and McGee are on the Speakers Bureau of Edwards LifeSciences, Irvine, California. This company manufactures the FloTrac-Vigileo/EV1000 pulse contour analysis system. In addition, the company manufactures the Swan-Ganz Catheter with CCO and the Vigilance monitor.

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