Author’s response to reviews

Title: Photoacoustic gas monitoring for anesthetic gas pollution measurements and its cross-sensitivity to alcoholic disinfectants

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Author’s response to reviews:

Dear Prof. Cassady-Cain

On behalf of my co-authors, I am re-submitting the enclosed original contribution for possible publication in BMC Anesthesiology.

We appreciate the constructive and fair comments of the reviewers and have revised our manuscript according to their suggestions. The attached point-by-point reply to the reviewers’ individual comments contains all modifications made to the manuscript and are marked in yellow.

Basically, we restructured the Methods and the Results sections. Methods statements were transferred from the figure legends to the main manuscript and a clear hypothesis is now defined in the Introduction. Statistical tests were expanded as appropriate.
I attest to the fact that all authors listed on the title page have read the revised manuscript, attest to the validity and legitimacy of the data and its interpretation, and agree to its submission to BMC Anesthesiology.

This manuscript has not been published or presented elsewhere in part or in entirety and is not under consideration by another journal. We have read and understood your journal’s policies, and we believe that neither the manuscript nor the study violates any of these. There are no conflicts of interest to declare.

Thank you for your consideration. I look forward to hearing from you.

Sincerely,

Jennifer Herzog-Niescery, MD
(17th of June 2019)

Point-to-Point-Reply

Habib Md Reazaul Karim, M.D., D.N.B., I.D.C.C.M. (Reviewer 1):

Greetings. A well conducted study and well written manuscript. I suggest a very minor changes

In page 9, line 204, "the base line values were.... Although the data presentation appears to be as mean +/- SD... it is not clear, so, the authors can mention it for easy understanding by the readers.

Answer: Yes, you are right. We now give additional information in the Methods and changed the sentence in the Results section accordingly.
New version Methods: Continuous variables are shown as mean (standard deviation (SD)) or median (interquartile range (IQR)).

New version Results: Mean ± SD baseline values were 0.05 ± 0.01 ppm for ISO, 0.01 ± 0.01 ppm for SEVO (median: 0.01 ppm; IQR: 0.001 ppm) and 0.04 ± 0.01 for DES (n = 5 per VA).

In a few place, the SD is equal to mean or more than half of the mean. While it is not an error or wrong presentation, I believe the data here can also be presented as median (inter-quartile range) or in min-max range.

Answer: Yes, that is true. We still prefer to present data as mean ± SD, however, we now additionally mention the median and IQR when the SD is equal to the mean.

New version Results: Please compare the sentence above.

Thank you very much. Best of luck

Evan G. Pivalizza (Reviewer 2):

Thanks for the opportunity to review this manuscript which is a combination laboratory and clinical study of a relevant topic. However, several areas require attention to be able to understand the protocol and implications:

1. The study method is detailed in part but there is no information on # of measurements in lab and OR, important since there are repeated measures which will need correction

Answer: Yes, you are right. We added the necessary information throughout the manuscript.

New version Results:

Mean ± SD baseline values were 0.05 ± 0.01 ppm for ISO, 0.01 ± 0.01 ppm for SEVO (median: 0.01 ppm; IQR: 0.001 ppm) and 0.04 ± 0.01 for DES (n = 5 per VA).

The decay curves corresponded to recovery times of 52 minutes and exponential functions with $R^2 = 0.999$ for ISO, $R^2 = 0.995$ for SEVO, and $R^2 = 0.999$ for DES) (n = 5 per VA).

The gas monitor detected VA concentrations, although only alcohols and alcoholic disinfectants were used (n = 5 per interfering agent and for each VA) (Figure 3A-C).

SEVO pollution was measured in the surgeons’ breathing zones during abdominal surgeries (n = 20).
New version Table 2:

[...] N = 5 per interfering agent and for each VA.

New version Figures:

[...] N = 5 per anesthetic gas.

The gas monitor with filters for isoflurane (A), desflurane (B), or sevoflurane (C) mistakenly detects anesthetic gases, although alcohols and alcoholic disinfectants (AD) were used (n = 5 per interfering agent).

2. There is no detail of hypothesis, statistical power and repeat measurements (see above)

Answer: We now define a clear hypothesis in the Introduction and perform a power analysis to justify the sample size. The number of measurements is added throughout the manuscript (please compare our answer to your comment No. 1).

New version Introduction: We hypothesized that there is a cross-sensitivity for all three VA and that the elimination of the cross-sensitivity would reduce the average false-high VA concentration significantly by 30%.

New version Methods: The sample size required for measurements in hospital is based on a pilot study of 10 surgeons, who were exposed to a mean SEVO concentration of 0.58 ± 0.27 ppm including cross-sensitivity. For an α-risk of 0.05 with a power of 80% at least 16 measurements are needed to demonstrate a 30% reduction of the average SEVO concentration by elimination of the cross-sensitivity.

3. Requires significant editing for brevity, flow and organization - methods statements in results and figure legends explaining methods and results

Answer: We restructured the Methods and the Results sections for clarity. Figure legends were shortened significantly, and methods statements transferred to the main manuscript. However, our methodical approach to eliminate the cross-sensitivity is a result and therefore explained in the Results section. Furthermore, we think that Figure 4 is helpful for readers to understand this approach, even if we repeat parts of the procedure in the figure legend. Hopefully this is acceptable.
Additional comments below.

Thank you very much for your help to improve the linguistic quality of our manuscript. We changed all sentences as suggested by you.

Abstract:

Methods: delete 'the example of', ...... surgeons who were exposed intraoperatively ......

New version: The practical impact of the cross-sensitivity was investigated on abdominal surgeons who were exposed intraoperatively to sevoflurane.

Results: 10th percentile

New version: We replaced the cross-sensitivity peaks with the 10th percentile baseline of the anesthetic gas concentration.

Conclusion: ... but cross-sensitivity caused one ....; delete 'especially'

New version: Photoacoustic gas monitoring is useful to detect lowest anesthetic gases concentrations, but cross-sensitivity caused one third of the measured (false-high) mean gas concentration in. […]

Caution should be taken while measuring sevoflurane, since marked cross-sensitivity peaks are to be expected.

Background:

Delete already; …achievable… (sp)

New version: Although exposure levels of healthcare professionals have been minimized, it still is good clinical practice to reduce gas pollution ‘as low as reasonably achievable’ [3]

3rd paragraph: anesthesiology

New version: This sentence is no longer part of the manuscript.
Methods:

1st: which hospital?

New version: VA pollution measurements were conducted in a German University hospital (Katholisches Klinikum Bochum, St. Josef Hospital).

PA monitoring:

2nd: ... demonstrate any cross

New version: Filters for alcohols were not used in this study to demonstrate any cross-sensitivity.

.... probe, time to flush ...

New version: A measurement interval lasted 35 seconds and depended on the size of the measurement cell, the length of the sampling probe, time to flush both with fresh air (30 seconds), and on the sample integration time (5 seconds).

Volatile: Explain recovery time (related to ref 7) and regression line calculations

Answer: Yes, you are right, definitions or explanations are missing. We now define the ‘recovery time’ according to ISO 14644 part 3 in the Methods. An exemplary calculation is shown in Figure 4. The calculation of the regression line is explained.

New version Methods: The approach is based on the recovery time, which is the time needed to reduce the gas concentration in the room by two log steps (corresponds to a reduction of 99%). The recovery time was calculated according to DIN EN ISO 14644 [7] and depended primarily on the type of air-conditioning, the supply air volume, the volume of the operating room, and on the position of the exhaust air slots.

[...] Regression lines, which appear as linear curves when using a semi logarithmic diagram, were calculated after the maximum concentration was reached by the formula $c = a \cdot \exp (-b \cdot t)$ with $c$: VA concentration [ppm]; $a$: factor to calculate the regression; $b$: gradient; $t$: time.

Approach: To demonstrate practical significance and an approach to overcome cross-sensitivity, the gas monitor ....

New version: To demonstrate practical significance of this approach, the gas monitor was calibrated for SEVO and the VA exposure measured during abdominal surgery in the surgeons’ individual breathing zones (25 cm around nose and mouth).
Results:

Volatile: .... to a maximum of ...

New version: The concentrations of all three VAs increased within approximately five minutes to a maximum of 21.01-23.99 ppm.

Alcohols: .... concentrations, although only alcohols ....

New version: The gas monitor detected VA concentrations, although only alcohols and AD were used (n = 5 per interfering agent and for each VA) (Figure 3A-C).

Cross- sensitivity: 1st 2 sentences in methods. Move most of explanation from figure legend here for approach

Answer: We re-wrote the whole paragraph and now give additional information in the Methods and the Results section. The capacitation was also shortened significantly.

New version Results: SEVO pollution was measured in the surgeons’ breathing zones during abdominal surgeries (n = 20). The gas monitor, which did not differ between VA and interfering agents, reported false-high mean and maximum SEVO concentrations of 0.61 ± 0.26 ppm and 15.27 ± 14.62 ppm, respectively.

To overcome cross-sensitivity, a 10th percentile baseline is drawn after logarithmization of the data. Then, the recovery time is marked. Therefore, a straight line is drawn from the upper left corner (0/log 10; intersection X-Y-axis) to the X-axis and moved to the peak’s maximum. The intersection with the curve marks the end of the cross-sensitivity peak. This time interval is replaced by the baseline concentration (Figure 4).

This technique resulted in corrected mean and maximum SEVO concentrations of 0.38 ± 0.09 ppm and 0.91 ± 0.49 ppm, respectively, which is a significant reduction of 38% for mean (p < 0.001) and 86% for maximum (p < 0.001) SEVO concentrations.
New version: Capacitation: Figure 4: Approach to eliminate cross-sensitivity peaks. Figure 4A shows the false-high ‘sevoflurane exposure’ of a surgeon (purple line; [ppm] mean: 0.73 ± 0.70, maximum: 6.93; red triangle: use of disinfectant). After logarithmation of the data (purple line in 4B), the 10th percentile baseline is drawn (green line; here 0.29 ppm), and the recovery time is marked (red dotted line in 4C; here 39 minutes). This line is moved to the peak’s maximum (black arrow in 4C). The intersection with the curve marks the end of the cross-sensitivity peak (blue cross in 4C). This time interval is replaced by the baseline concentration (dark blue line in 4C). If interfering agents are used before the decay curve has reached the baseline concentration (back star in 4C) the cross-sensitivity interval should not be replaced by the 10th percentile, but by the measured concentration at the beginning of the cross-sensitivity peak (orange in 4C). In this example the ‘corrected’ mean and maximum sevoflurane concentrations were 0.53 ± 0.33 ppm and 1.76 ppm, which is a reduction by 28%.

Discussion:

1st: a photoacoustic

New version: This study investigated a photoacoustic gas monitor’s cross-sensitivities against alcohols and alcoholic disinfectants while measuring VA pollution.

2nd: .... allow for identification of the smallest… AND .... it may help reduce

New version: The very low detection limits allow for identification of the smallest concentrations of VAs and the immediate feedback of the VA exposure during a procedure makes the gas monitor valuable in practice, because it may draw the personnel’s attention and it may help reduce the occupational gas burden.

.... during multiple procedures including ..... - why this discussion here - no mention in results

Answer: We aimed to list different procedures which are regularly performed in the operating room and typically associated with the use of alcoholic disinfectants (or other interfering agents). However, we obviously expressed it misleadingly; we deleted most parts of the paragraph.

New version: However, its cross-sensitivity to alcohols is problematic, because interfering agents are regularly used in the perioperative setting (e.g. for skin disinfection or surgical hand disinfection).
3rd: Delete furthermore, indeed

New version: The gas monitor can simultaneously be used with filters for the VA, water vapor, and up to four alcohols.

... still may be insufficient as ...

New version: However, this still may be insufficient as other substances interferer as well (e.g. permanent marker: ethyl alcohol and 4-chloro-3-methylphenol).

Delete practically

New version: Another restriction is the high costs of the optical filters.

Delete to the anesthesiologist; AND.... measured or verified in

New version: The presented approach can be retracted quickly and performed without technical equipment; even the recovery time can be verified in the appropriate documents for every operating room (according to ISO 14644-3 for turbulent ventilation systems) [7].

Delete further

New version: Each peak is replaced by the 10th percentile baseline and not just waived, which takes the actual VA concentration into account.

noted instead of annotated

New version: However, it should be noted that the VA pollution during cross-sensitivity peaks is not measured but estimated.

... which is a limitaiton

New version: Thus, it is possible that the actual VA concentration is higher than the baseline value during a cross-sensitivity peak, which is a limitation (corrections lead to false-low VA concentrations).
Answer: We shortened the sentence and deleted the phrase you mention.

New version: Another finding was that the strength of the cross-sensitivity reaction was influenced by the measured anesthetic gas (SEVO > DES, ISO).

New version: First, we demonstrated the gas monitor’s cross-sensitivity for selected alcohols and disinfectants only, which are regularly used in hospitals.

AND

Much larger amounts would have increased the time to eliminate the alcohol out of the room, which correlates with increased false-high VA measurements.

... might be difficult for substances ....

New version: This might be difficult for substances, which contain ‘veiled ‘interfering agents (e.g. permanent markers).

Conclusions:

... often unaware of cross .....  

New version: Photoacoustic gas monitoring is an excellent method to detect trace concentrations of anesthetic gases, but clinicians are often unaware of its powerful cross-sensitivity and overestimate VA pollution levels.

Delete 'especially'

New version: Caution should be taken while measuring SEVO concentrations, since marked cross-sensitivity peaks are to be expected.

Abbreviations: Des and Iso spelling with e on the end

New version: Desflurane; Isoflurane
Shorten all legends:

Table 1 legend: Commonly sued disinfectants and alcoholic components which may be interfering

New version: Commonly used disinfectants and alcoholic components which may be interfering substances while using the gas monitor. n (right column) = number of alcoholic components.

Table 2: Are rows aligned correctly - doesn't seem to fit with statement that Sevo worse? First time see an n=5 - needs to be clarified in methods and stats

Answer: We re-checked the data and still think that everything is correct; but we agree that the presentation may be misleadingly. Therefore, we now explain every significant difference between the three anesthetic gases in the capacitation. The number of all measurements were added throughout the manuscript (please compare our answer to your main comment No. 1).

New version legend: Impact of the volatile anesthetic on the strength of the cross-sensitivity reaction for different interfering substances. * = sevoflurane caused higher false-high ‘VA’ pollution levels than desflurane or isoflurane; # = desflurane caused higher false-high ‘VA’ pollution levels than isoflurane.

shorten all figure legends

Answer: We shortened all legends significantly as requested. Please compare the figure legends at the end of the manuscript for details.

Figure 1: Old version: 105 words; New version: 64 words
Figure 2: Old version: 83 words; New version: 52 words
Figure 3: Old version: 127 words; New version: 59 words
Figure 4: Old version: 296; New version: 175 words
1: How did the fan assure uniform distribution? Could have made it worse

Answer: We utilized the fan for tests in laboratory only, since no air-conditioning or other mechanical ventilation system was used in this room. It was used to distribute the emitted anesthetic gases homogeneously and to avoid any accumulation or pooling. The fact that the curves of all three volatile anesthetics as well as the curves of all tested interfering agents demonstrated R² of > 99% (regression curves) ensures that results are reproducible.

Qing Peng (Reviewer 3):

Waste anesthetic gases may cause VA pollution, even are harmful to staffs working in the operation room. The authors used a new method to find out the interferences to ensure valid VA measurements in the anesthesiological environment. The idea of this article is good. But my question are:

1. Are the methods of measurements in the tests are suitable for different sizes of operations rooms?

Answer: The efficacy of an operating room to eliminate or dilute anesthetic gases (and particles) depends on the air-conditioning (e.g. unidirectional displacement flow or turbulent flow system), on the supply air volume, on the volume of the operating room (its size), and on the position of the exhaust air outlets. This efficacy, which is different for every operating room, is described as ‘recovery test’ and must always be tested as a basic quality characteristic for each operating room with turbulent flow (compare ISO 14644-3, reference 7). The recovery time, which is the time needed to reduce the gas concentration in the operating room by two log steps, is the result of the recovery test. Our approach to overcome the cross-sensitivity is based on the recovery time and thus already considers - amongst other things – the size of the operating room. In practice, the recovery time can easily be looked up in the appropriate documents (specific operating room characteristics).

We now mention the impact of the operating room’s size.

New version: The recovery time, which is the time needed to reduce the gas concentration in the room by two log steps (corresponds to a reduction of 99%), was calculated according to DIN EN ISO 14644 (compare Figure 4) [7]. It depends primarily on the type of air-conditioning, the supply air volume, the volume of the operating room, and on the position of the exhaust air slots.
2. Whether the different temperature and brightness in the operation room will affect the tests results?

Answer: The recovery time is essentially independent of the temperature and brightness in the operating room and the consideration of both factors is not recommended according to ISO Standard 14644 for turbulent airflow conditions. That is because the temperature in operating rooms vary between 19-26°C, which is a very small range (compare ISO 7730 - ergonomics of the thermal environment of operating rooms), and the brightness of modern operating lamps have a very small thermal effect only, since LED-technique is established.

3. If the N2O gas is used during the operation, how would the results change?

Answer: This is a very interesting question. First, it is important to know that the gas monitor must be calibrated with specific optical filters to measure anesthetic gases. These are UA 0970 for sevoflurane and desflurane with a wavelength of 8.2 \( \mu \)m; and UA 0971 for isoflurane with a wavelength of 8.5 \( \mu \)m (compare Methods - Photoacoustic gas monitoring). The absorption spectra of the interfering agents are very similar to those of the volatile anesthetics, which explains the cross-sensitivity. Furthermore, these two filters can even be used to measure the concentration of some alcohols in the air.

Nitrous oxide has a different infrared spectrum, and completely different optical filters (UA 984 and UA 985, wavelengths 4.7 and 4.5 \( \mu \)m) are used. Thus, a cross-sensitivity between alcohols and nitrous oxide is not to be expected.

Sometimes anesthesiologists might use a combination of nitrous oxide and sevoflurane or nitrous oxide and isoflurane during surgery. This would go along with reduced concentrations of sevoflurane and isoflurane, and could probably reduce the strength of the cross-sensitivity reaction. However, we did not investigate the effect of two contemporaneously used different anesthetic gases on the strength of the cross-sensitivity reaction and thus decided not to mention nitrous oxide in this manuscript.
Ankur Sharma (Reviewer 4):

I must congratulate the authors for designing of such a nice study. My specific concerns are

1. Did Authors registered this study on any clinical trial registry website? If yes please mention the number.

Answer: No, our study was not registered at clinical trial registry, because it does not involve any assignment of patients / participants to treatment groups. However, ethical approval was granted by the local research ethics committee. Written informed consent was obtained from all participants and all measurements were performed according to the Declaration of Helsinki as requested by the journal’s guidelines. Please compare the first paragraph in the Methods section and the ‘Ethics approval and consent to participate’ paragraph in the Declarations section for details.

2. In this study, Twenty patients undergoing major abdominal surgery were enrolled in this study for eliminate cross-sensitivity peaks. How authors choose the figure of 20. How did they calculate the sample size?

Answer: Yes, you are right, the sample size justification is missing. First, measurements in laboratory were performed as an observational pilot study, in which we confirmed the assumed cross-sensitivity for ISO, SEVO and DES. No sample size analysis was performed for these laboratory experiments, but R² of >99% verify the reproducibility of the tests.

The sample size calculation for measurements in hospital is based on the fact the cross-sensitivity influences the ‘VA pollution’ considerably (we assumed that measurements were overestimated by at least one third). We than had to measure the surgeons’ VA exposures in our operating room, which was 0.58 ± 0.27 ppm (sevoflurane). Power analysis revealed that at least 16 measurements for an α-risk of 0.05 with a power of 80% were needed to demonstrate this effect.

The sample size analysis is now described in the Methods (Statistical Analysis).

New version: The sample size required for measurements in hospital based on a pilot study of 10 surgeons, who were exposed to a mean SEVO concentration of 0.58 ± 0.27 ppm including cross-sensitivity. For an α-risk of 0.05 with a power of 80% at least 16 measurements are needed to demonstrate a 30% reduction of the average SEVO concentration by elimination of the cross-sensitivity.