**Voltage changes in the lithium dilution cardiac output sensor after exposure to blood from horses given xylazine**

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**Editor’s key points**

- Some drugs may affect the lithium dilution cardiac output (LiDCO) sensor.
- Drugs may have different properties in blood rather than saline.
- The effect of xylazine on the LiDCO sensor exposed to blood from horses given xylazine was determined.
- An increase in voltage was seen in LiDCO sensors upon exposure to blood containing xylazine.

**Background.** In a previous in vitro study using saline medium, the authors showed that certain drugs changed the voltages of lithium dilution cardiac output (LiDCO) sensors and also influenced their accuracy in measuring lithium concentrations. These two parameters correlated and so we examined whether such drug–sensor interaction exists when LiDCO sensor was exposed to xylazine in blood.

**Methods.** Five healthy adult warm-blood horses were injected with 0.5 mg kg\(^{-1}\) xylazine i.v. Physiological saline solution and venous blood were consecutively sampled through the same LiDCO sensor at 60, 45, 30, 15, and 0 min before and then 5, 15, 30, 45, and 60 min after xylazine injection. Sensor voltages were recorded and the differences between saline- and blood-exposed sensor voltages were compared at each time point.

**Results.** Saline-exposed sensor voltages continuously increased in a non-linear pattern during the experiment. Blood-exposed sensor voltages also increased in a similar pattern, but it was interrupted by an abrupt increase in voltage after xylazine injection. The differences between saline- and blood-exposed sensor voltages were 7 (6.1–8) mV [median (range)] before xylazine but decreased significantly at 5 and 15 min after xylazine treatment. The highest drug-induced voltage change was 3.4 (1.6–7) mV.

**Conclusions.** This study showed that exposure of a LiDCO sensor to blood after a single clinically relevant dose of xylazine in horses changed the voltages of the sensors for 15 min. Comparison of saline- and blood-exposed sensor voltages could become a tool to detect drug–sensor interactions.

**Keywords:** anaesthesia, veterinary; analgesic techniques, infusion; horses; measurement techniques, cardiac output

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The lithium dilution cardiac output (LiDCO) measurement technique has proved to be an accurate method in many species,\(^1\) \(^3\) and it is increasingly being used as a reference method.\(^6\) \(^5\) However, in a recent study, a large positive bias was found when comparing LiDCO with bolus thermodilution in anaesthetized ponies receiving xylazine, ketamine, and midazolam infusions.\(^6\) The authors hypothesized that some of these drugs may interact with the LiDCO sensor and potentially influence its accuracy. A follow-up in vitro study found that a number of drugs (including xylazine and ketamine) influenced the accuracy of this sensor in a way which may lead to positive bias in LiDCO measurements.\(^7\) In that study, a strong correlation \((r^2=0.91)\) was found between drug-induced changes in sensor voltage and sensor accuracy (determined by calculating lithium-induced voltage changes). The weak point of that in vitro study was that 0.9% saline was used as medium (pH≈6.6). Consequently, the concentrations of presumably active (not protein-bound and ionized) fractions of basic drugs may be different in blood and in saline assuming the same total concentrations. Therefore, the findings of that study need to be confirmed in sensors exposed to blood after xylazine administration. Direct comparison of LiDCO with bolus thermodilution (or another reference method) in subjects receiving drug or saline treatments should be an ultimate proof of drug–sensor interaction, but it is relatively invasive and expensive. A reasonable intermediate step would be to consider the strong correlation found in the previous in vitro study\(^7\) and to test for drug-induced changes in sensor voltage as an indicator of drug–sensor interaction. However, the measurement of drug-induced changes in sensor voltage...
is not as straightforward in vivo as it was in vitro because the voltage of LiDCO sensors continuously drifts over time. In this regard, clear evidence would be needed to prove that a sudden voltage change was associated with a drug treatment. Such a clinically applicable method has not yet been published. Such a method would be less invasive than thermodilution cardiac output measurements (i.e. no need for the pulmonary artery catheter) and therefore preferable because it is in accordance with the 3Rs principles of replacement, refinement, and reduction. Demonstrating that a certain drug treatment at a certain dose-induced voltage changes in LiDCO sensors raises suspicion for drug–sensor interaction. This should be followed by a direct comparison of LiDCO with a reference cardiac output measurement method later on.

So far, the only publication suggesting drug-induced bias in LiDCO measurements in vivo reported data from ponies receiving xylazine, ketamine, and midazolam infusions, and according to the follow-up in vitro study, xylazine was suspected to have the major influence on the LiDCO sensor. Therefore, the aim of the present study was to demonstrate the effect of the voltages of LiDCO sensors after exposure to blood directly sampled from conscious horses after a clinically relevant dose of xylazine. It was important to use horses for this experiment since the pharmacokinetics of xylazine may be species-specific.

Methods

Animals

Five warm-blood horses (two mares and three geldings) with a mean (range) age of 16 (11–25) yr and a body weight of 544 (488–654) kg were used. The horses were considered healthy based on physical examination and routine haematological and biochemical testing. Animals were fasted overnight before the experiment, but water was not withheld. The study protocol was approved by the institutional ethics committee and the national authority according to § 8ff of Law for Animal Experiments (GZ 68.205/0253-II/3b/2011).

Experimental protocol

The horses were restrained in stocks. An 18 G indwelling catheter was inserted upstream into the left jugular vein and sutured to the skin. Although local anaesthetics would normally be used when inserting i.v. catheters to conscious horses, lidocaine could not be used because it strongly interacts with the LiDCO sensor. As the same catheter was used for sampling blood through the sensor, the possibility of even minor drug contamination of the blood samples would jeopardize the study. In order to refine the experiment, a smaller (18 G) catheter was used than would normally be used during clinical anaesthesia (12–14 G) and atraumatic needles were used to suture the catheter. A new LiDCO sensor (LiDCO, London, UK) and a bag of 0.9% saline (Fresenius Kabi, Bad Homburg, Germany) were attached to the catheter using three-way stopcocks and an infusion set. A LiDCO flow pump was also attached to the stopcocks via rigid tubing, and it was used to sample either saline or blood through the sensor. The sensor was attached to a LiDCO monitor and voltages were recorded from the screen of the monitor. At least 1 min was allowed for stabilization of the signal after exposing the sensor to a new sample. Pairs of voltage measurements (saline followed by blood samples) were performed at 60, 45, 30, 15, and 0 min before and then 5, 15, 30, 45, and 60 min after the injection of 0.5 mg kg$^{-1}$ xylazine (Eurovet Animal Health, Bladel, The Netherlands) into the opposite jugular vein. Xylazine is commonly used in horses for anaesthetic premedication at similar doses. Both the sensor and the catheter were flushed with heparinized saline (5 units ml$^{-1}$) after each pair of measurements.

Fig 1 Median (range) of LiDCO sensor voltages exposed to 0.9% saline or blood sampled directly from five conscious horses receiving 0.5 mg kg$^{-1}$ i.v. xylazine injection at 0 min (A). Median (range) of saline exposed minus blood-exposed sensor voltages (B). An increase in blood-exposed sensor voltages and a decrease in the difference between saline- and blood-exposed sensor voltages are shown at 5 and 15 min after xylazine treatment. *Significant difference from the value at 0 min. Solid green line indicates the least square regression line on blood-exposed sensor voltage data excluding 5 and 15 min time points (baseline tendency). Vertical dashed lines indicate the time of xylazine injection.
Influence of xylazine on the LiDCO sensor

Statistical analysis
Data distribution was confirmed using the Kolmogorov–Smirnov test. Differences between saline- and blood-exposed sensor voltages were compared over time with one-way analysis of variance for repeated measurements that was followed by a Bonferroni post hoc test to compare values after xylazine injection with baseline at 0 min (SPSS Statistics 20.0, SPSS, Inc., IL, USA). P-values of <0.05 were considered statistically significant.

Drug-induced voltage change was defined as the vertical difference between the median voltage of blood-exposed sensors 5 min after xylazine injection and the least square regression line on the blood-exposed sensor voltages (excluding the 5 and 15 min samples; Fig. 1a). This regression line will hereafter be referred to as baseline tendency. Data are expressed as median (range).

Results
Normal distribution of data was confirmed. The median sensor voltage was –113.4 (–114.5 to 113) mV after first exposure to saline and that is similar to what has been found previously.7 Saline- and blood-exposed sensor voltages continuously increased over time, parallel with each other, before xylazine treatment. Blood-exposed sensor voltages abruptly increased after the injection of xylazine then returned to the baseline tendency 30 min after the injection (Fig. 1a). The differences between saline- and blood-exposed sensor voltages were 7 (6.1–8) mV before the injection but decreased significantly at 5 and 15 min after (Fig. 1a). The highest drug-induced voltage change was 3.4 (1.6–7) mV.

Discussion
This study showed that a clinically relevant dose of xylazine changed the voltages of LiDCO sensors when exposed to blood after a clinically relevant dose of xylazine in horses. The effect was relatively short and blood-exposed sensor voltages returned to baseline 30 min after xylazine injection. Physiological saline solution and blood induce different voltages in the sensor because of differences in their cation (mainly sodium and potassium) concentrations and the presence of proteins, etc. in the blood. The present study showed that the differences between saline- and blood-exposed sensor voltages were stable before xylazine treatment but abruptly decreased after xylazine injection as a result of a sudden increase in sensor voltages when exposed to blood. Therefore, such drug-induced voltage differences may be useful to predict possible drug–sensor interactions during cardiac output measurements. The stability of these voltage differences should be established over a longer time period than that used in this study because other factors (e.g. changes in plasma ion concentrations) may also influence the sensor voltages.

The weak point of the study is that it did not directly prove that xylazine caused inaccuracies in LiDCO measurements. However, the results of a pilot in vitro study conducted by the current authors using horse plasma indicated that a clinically relevant concentration of xylazine (500 ng ml\(^{-1}\)) negatively affected the accuracy of LiDCO sensors (determined by calculating lithium-induced voltage changes; unpublished data).

Nevertheless, the final proof of drug–sensor interaction should result from a direct comparison of LiDCO with a reference cardiac output measurement method in subjects receiving drug or saline treatments.

In conclusion, this study showed that a sedative dose of xylazine changed the voltages of LiDCO sensors in vivo. It is reasonable to assume that such voltage changes are associated with inaccuracies in LiDCO measurements, but this assumption should be proved or disproved by follow-up studies.

Authors’ contributions
T.D.A.: study design, data collection, analysis and interpretation of data, and writing up of the first draft of the manuscript.
Y.M.: study design and critical revision of the manuscript.

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Declaration of interest
None declared.

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References