

# Methaemoglobinemia after Liposuction under Tumescant Local Anaesthesia – Diagnostic Value of Pulse Oximetry

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## ABSTRACT

### Background:

Tumescant local anaesthesia with prilocain can lead to clinically significant methemoglobin levels. New generation multiple wavelength pulse oximeters (e. g. Masimo Radical 7<sup>®</sup>) can measure methemoglobin levels.

### Methods:

In this prospective observational study we compared the venous methemoglobin levels and the corresponding pulse oximetric values of the Radical 7<sup>®</sup> in patients undergoing tumescant local anaesthesia for liposuction procedures. The measurements were performed in HanseKlinik, Luebeck, Germany between 2008 and 2011.

### Results:

In 133 patients, we measured a maximum methemoglobin level of 18 per cent. In a Bland-Altman analysis we found a mean bias of +2.2 % (-4.1 to 8.4 limits of agreement) for pulse oximetric values compared to hemoximetry.

### Conclusion:

Pulse oximetric measurement of methemoglobin is an early-warning tool for the detection of clinically significant methaemoglobinemia in patients with tumescant local anaesthesia.

## KEYWORDS

Tumescant anaesthesia, Methaemoglobinemia, Pulse oximetry, Liposuction

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## INTRODUCTION

Tumescant anaesthesia is a local anaesthesia procedure, which is performed when plastic cosmetic surgical procedures such as liposuction are carried out. The subcutaneous adipose tissue is infiltrated with large volumes of a solution, which also contain local anaesthetics. Because of its low systemic toxicity, the local anaesthetic prilocaine is used in Europe amongst other agents. However, the use of prilocaine, like other local anaesthetics, can also lead to a marked production of methemoglobin <sup>1,2</sup>. Methemoglobin (MetHb) is produced as a result of the oxidation of divalent iron to its trivalent form within haemoglobin ( $Fe^{2+} \rightarrow Fe^{3+}$ ).

MetHb cannot bind or transport oxygen and is reduced by the enzyme MetHb reductase back to haemoglobin. A certain concentration of MetHb (0 to 1.5%) is also present under physiological conditions as a result of the auto-oxidation that naturally occurs within erythrocytes.

While healthy people can tolerate higher concentrations of MetHb (up to about 30%) relatively well, patients with pre-existing anaemia and cardiopulmonary disease are subject to a higher risk. During a Medline search for preparing a review, Guay found 68 published case reports on prilocaine-induced methaemoglobinemia. The maximum published MetHb concentration in the blood was 42%<sup>3</sup>.

The reference method for diagnosing methaemoglobinemia has been and remains direct measurement of MetHb in the blood using a hemoximeter, usually as a component of a blood gas analyser<sup>2</sup>. A useful addition to this invasive and discontinuous measurement procedure would be a simple, non-invasive method for continuous MetHb monitoring. Conventional 2-wavelength pulse oximeters are not, however, able to diagnose methaemoglobinemia<sup>4-6</sup>. Pulse oximeters, which measure the absorption in several wavelength ranges simultaneously, are able to determine pulse oximetrically the concentration of dyshaemoglobins such as MetHb<sup>7,8</sup>.

The aim of this method-comparison study was to investigate multi-wavelength pulse oximetry as a monitoring method for patients at increased risk for

methemoglobinemia.

## MATERIALS AND METHODS

After approval by the Ethics Committee of the University of Luebeck, Luebeck, Germany and after patient information and acquisition of written informed consent, 133 patients scheduled for liposuction employing tumescent anaesthesia were included in the study. The study was conducted in 2008 up to 2011 as collaboration between the University Hospital Schleswig-Holstein and the Hanse Clinic in Luebeck. The study was registered on [www.clinicaltrials.gov](http://www.clinicaltrials.gov) under NCT01766999.

Before surgery, all patients were subjected both to a venous blood gas analysis (GEM 4000, Instrumentation Laboratory, Bedford, MA, USA) and a pulse oximetry measurement using a multi-wavelength pulse oximeter (Radical-7<sup>®</sup>; Masimo Corp., Irvine, CA, USA). During surgery, all patients were monitored continuously using a multi-wavelength pulse oximeter, which is able to measure MetHb (%SpMet<sup>®</sup>). If there was an intra-operative increase in %SpMet<sup>®</sup> to readings  $\geq 8$ , further pulse oximetric and hemoximetric measurements were introduced after surgery and/or in the evening and the next morning. In such a case the pulse oximeter data was analysed continuously using a data acquisition program (Trendcom, Masimo Corp., Irvine, CA, USA). For detailed description see the flowchart (Figure 1).

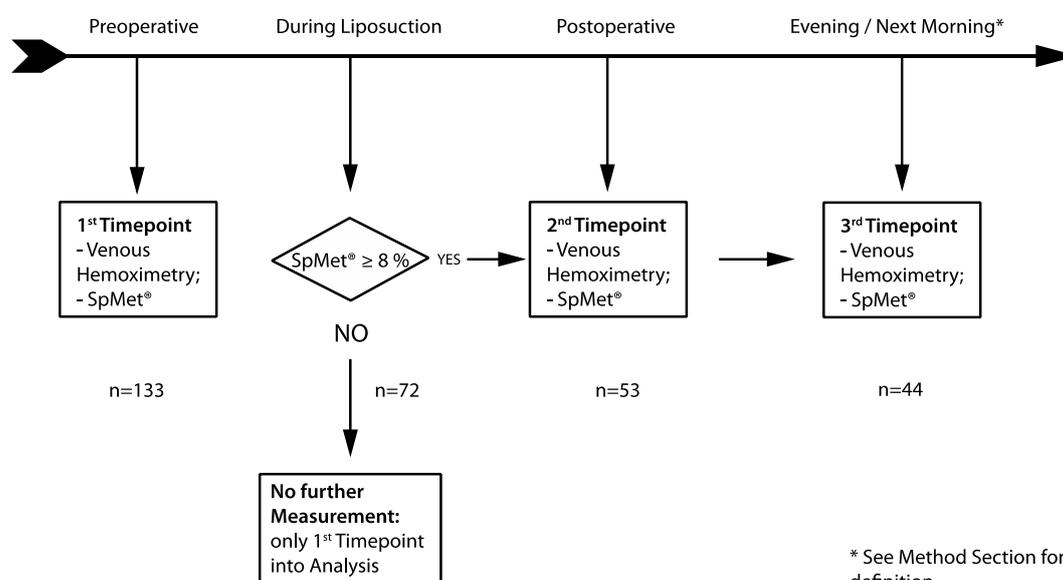


Fig. 1: Experimental Protocol

The tumescent anaesthesia was introduced using a modified solution according to Schneider-Affeld and Friedrich, containing 30 ml prilocaine 2%, 30 ml lidocaine 2%, 2 ml epinephrine 1:1,000, 20 ml sodium bicarbonate 8.4%, triamcinolone 20 mg, and sodium chloride 0.9% made up to 3000 ml<sup>9</sup>.

### Statistical analysis

The pulse oximetrically and haemoximetrically obtained values for oxygen saturation (SpO<sub>2</sub> or SaO<sub>2</sub>) and MetHb (%SpMet<sup>+</sup> or MetHb%) were evaluated using Bland-Altman for repeated measurements analysis<sup>10,11</sup>.

All analyses were performed using the software programs "R" and Prism 5.0 for Mac OS X<sup>®</sup> (GraphPad Software, Inc., La Jolla, CA, USA)<sup>12</sup>.

### Error grid analysis

In addition, we also prepared a so-called Error Grid in order to assess the clinical relevance of the deviations and to prepare graphs to illustrate them<sup>13</sup>. Clarke et al. originally developed this method to test the reliability of blood glucose meters. Morey et al. proposed this method for globin measurement<sup>14,15</sup>. The error grid shows the absolute values of the new and the reference tests, as well as the clinical relevance of the deviation. For this purpose specific zones were initially defined by experienced clinicians. Clarke et al. defined 5 different zones<sup>13</sup>. Since for MetHb there is no equivalent for hypoglycaemia, we restricted ourselves to the definition of 3 zones (A, B, C).

### Zone A (green)

In zone A all measurement pairs are located for which:

1. The difference between the reference method (MetHb haemoximetrically in %) and the test procedure (% SpMet<sup>+</sup>) is no more than  $\pm 10\%$ . In this case the accuracy of the new device can be considered as sufficient.
2. Both the reference and the test methods show values within the non-hazardous range of  $\leq 10\%$  MetHb. In this case, no further diagnostic or therapeutic decisions are affected.
3. Both the reference and the test methods show values within the hazardous range of  $\geq 15\%$ . In this case, further diagnostics will always be applied (reference procedure!) and a therapeutic decision will have to be made that will be tailored

for the individual case.

### Zone B (yellow)

Zone B contains values where the test procedure reveals a significant error compared to the reference method, but the deviation is not as severe as it is with zone C.

### Zone C (red)

Zone C includes pairs of measured values for which the error of the test method could lead to potentially dangerous erroneous decisions for the patients. Zone C is divided into two, with the lower right area containing measurements where the test procedure revealed non-hazardous %SpMet<sup>+</sup> values of  $\leq 10\%$ , and the reference procedure revealed hazardous values of  $\geq 15\%$ . The upper right area of zone C contains measurement pairs where the test procedure revealed dangerously high %SpMet<sup>+</sup> values of  $\geq 15\%$ , but the reference procedure reported levels of  $\leq 10\%$  in the safe range.

After the zones were defined, we modified a freely available script [16] from the internet for the software package MATLAB<sup>®</sup> Version 7.6.0 (The MathWorks<sup>®</sup> Inc., Natick, MA, USA) and adapted it to our needs.

## RESULTS

### Methemoglobin values

A total of 133 female patients were included in the study. Details of the patients and the surgery performed can be found in Table 1. We found no correlation between maximum MetHb value and infiltrated TLA solution volume. No serious methaemoglobinemia-related complications occurred in the study population. No patient received any antidote.

The highest MetHb value measured by hemoximetry was 18.0% (corresponding %SpMet<sup>+</sup> 28.2%), the highest measured %SpMet<sup>+</sup> value was 36.6% (corresponding MetHb 14.1%) (Table 2).

Table 1: Demographic Values

Variable	Mean $\pm$ SD
Body weight	85 $\pm$ 19 kg
Infiltrated fluids	7919 $\pm$ 2062 mL
Infiltrated prilocaine	30.8 $\pm$ 8 mg
Aspirated fluids	1292 $\pm$ 866 ml
Aspirated lipids	3169 $\pm$ 2531 mL
Liposuction time	82 $\pm$ 18 min

Table 2: Venous Blood Gas Parameters

Time point	pH	BE (mmol·l <sup>-1</sup> )	Lactate (mmol·l <sup>-1</sup> )	MetHb (%)	tHb (g·dl <sup>-1</sup> )
Preoperative n = 133	7.35 ± 0.05	-1.2 ± 1.8	1.8 ± 0.6	0.4 ± 0.3	14.1 ± 1.0
Postoperative n = 41	7.31 ± 0.05	-8.5 ± 9.4	3.0 ± 1.0	8.5 ± 2.7	12.7 ± 1.0
Evening n = 50	7.35 ± 0.04	-5.9 ± 2.5	2.5 ± 0.8	8.2 ± 3.4	12.1 ± 0.9
Next morning n = 57	7.39 ± 0.03	-3.2 ± 1.8	1.6 ± 0.8	5.5 ± 3.0	11.7 ± 0.9

### %SpMet<sup>+</sup> for the diagnosis of methaemoglobinemia

In 61 patients, pulse oximetry revealed a %SpMet<sup>+</sup> of  $\geq 8\%$  postoperatively, which according to the study protocol triggered further measurements. Between haemoximetrically measured MetHb concentrations and %SpMet<sup>+</sup> we observed a mean bias of +2.2% (-4.1 to 8.4, 95% limits of agreement; n=286) using the Bland-Altman analysis for repeated measurements (Figure 2). Lin's Concordance Correlation Coefficient between MetHb and %SpMet<sup>+</sup> was 0.79 (0.73 to 0.84 confidence level).

Furthermore, we also calculated the sensitivity and specificity for the pulse oximetric determination of %SpMet<sup>+</sup>. For the cut-off value a MetHb level of  $\geq 8\%$  was selected, which we considered to be the threshold for a clinically relevant methaemoglobinemia. For %SpMet<sup>+</sup> a sensitivity of 1.0 and a specificity of 0.45 was calculated (MetHb  $\geq 8\%$ , for details see Table 3). As demonstrated in Figure 3 the error-grid analysis yields to the following distribution of measurement pairs: Zone "A" 61 % (n=175); Zone "B" 39 % (n=110) and in Zone "C" 0.3 % (n=1).

### DISCUSSION

Using a prilocaine containing tumescence anaesthetic solution for liposuction a clinically relevant methaemoglobinemia of  $> 8\%$  was induced in 23% of our study patients. The development of methaemoglobinemia in an individual patient with tumescent anaesthesia cannot be predicted. In our patient population we found no correlation between infiltrated TLA solution and maximum MetHb. Responsible for this variability could be the existence of genetic variants for methemoglobin reductase<sup>17</sup>. In addition, a glucose-6-phosphate dehydrogenase deficiency in the patient might also have been responsible for a delayed MetHb reduction. Mang et al. reported maximum MetHb levels 12 hours post infiltration and a correlation with the TLA solution amount<sup>18</sup>. This phenomenon of "late onset" methaemoglobinemia in some patients is already known. It should always be considered when tumescence anesthetics are being carried out. Although methemoglobin levels of up to 15% are

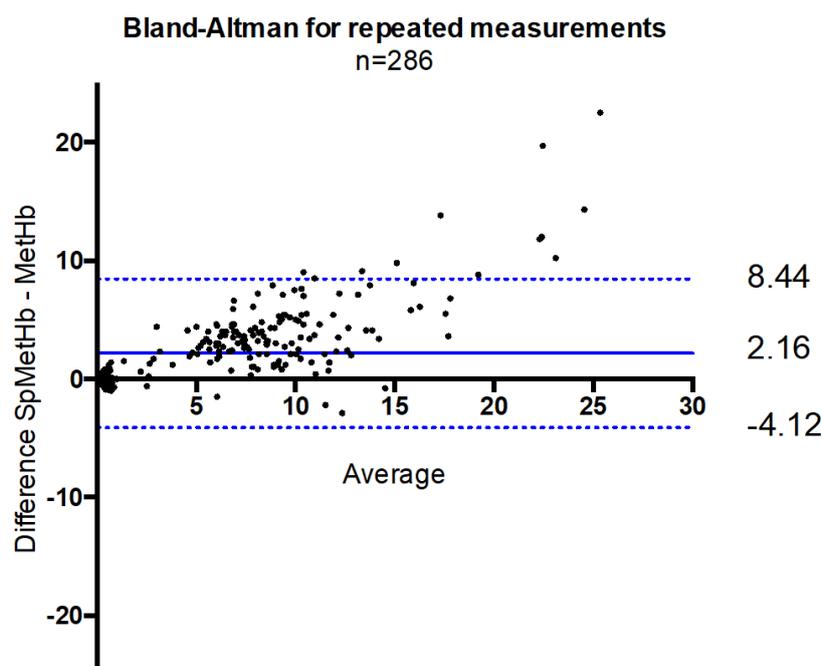
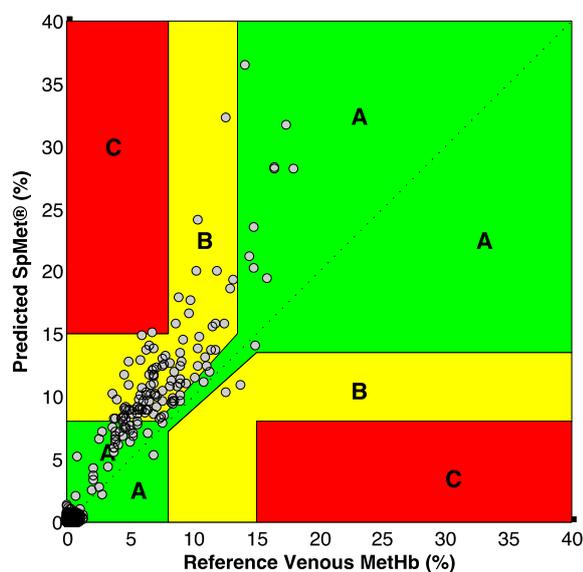


Fig. 2: Bland-Altman plot

**Table 3:** Sensitivity and specificity of %SpMet<sup>®</sup> for the detection of methaemoglobinemia  $\geq 8\%$ .

Variable	Parameter	95% confidence interval
Sensitivity	1.00	0.93 to 1.00
Specificity	0.72	0.65 to 0.77
Positive Predictive Value	0.45	0.36 to 0.54
Negative Predictive Value	1.00	0.98 to 1.00

**Fig. 3:** Error Grid Analysis

generally well tolerated in healthy individuals, risk patients (e.g. patients with anaemia or pre-existing cardiopulmonary conditions) can show clinical symptoms already from a level of 8% MetHb<sup>19</sup>.

For such patients in particular an early diagnosis is necessary to avoid complications due to the reduced oxygen-carrying capacity of the blood arising from the elevated methemoglobin. For this purpose pulse oximetric measurement of %SpMet<sup>®</sup> appears to be an appropriate monitoring procedure from our perspective. Although a clinically relevant methaemoglobinemia ( $\geq 8\%$ ) is detected with a sensitivity of 100%, the specificity of pulse oximetry at 45% is markedly inferior. The manufacturer states that the accuracy of SpMet%<sup>®</sup> in subjects with a MetHb range of 1-15%  $\pm 1\%$  is comparable to that of a hemoximeter. Feiner et al. showed that the Masimo Rainbow SET Radical 7 pulse CO-oximeter reports falsely high %SpMet<sup>®</sup> values in hypoxemic subjects<sup>20</sup>. After introducing an improved firmware version, the same group reported an acceptable accuracy in the SaO<sub>2</sub> range of 74% -100% and with MetHb levels of 0% -14%. However both studies were performed under controlled experimental conditions in volunteers.

Our results indicate firstly that the tested multi-wavelength pulse oximeter systematically overestimates the MetHb possibly in order to avoid the reporting of false-negative results. For a monitoring procedure this is certainly quite reasonable. In clinical practice this would mean that after measurement of a clinically relevant high %SpMet<sup>®</sup> value a blood sampling would have to follow to confirm the diagnosis of a methaemoglobinemia. If the %SpMet<sup>®</sup> shows no high values, a methaemoglobinemia can be excluded for that time-point.

One limitation of our study is that we measured methemoglobin haemoximetrically in venous blood, while for pulse oximetry arterial blood was used. This could theoretically be responsible for a portion of the bias observed. In an earlier study, our group showed in 276 blood samples that the difference between with arterial ( $2.16 \pm 1.48\%$ ; mean  $\pm$  SD) and venous MetHb ( $2.00 \pm 1.34\%$ ) is small<sup>21</sup>. The fitting of an arterial catheter for a period of up to 24 hours could not be ethically justified for a liposuction intervention.

Another limitation is that it is possible that the measurement accuracy of the Radical7<sup>®</sup> changed as a result of the introduction of newer firmware versions since we carried out our study. The results of the work of Feiner et al. might also indicate that the measurement accuracy has been improved somewhat<sup>20</sup>.

## CONCLUSION

The use of a multi-wavelength pulse oximeter for patients undergoing surgical procedures in TLA can be justified not only in the low MetHb range up until 6.7% MetHb, but also at higher, clinically relevant MetHb levels<sup>8</sup>. However in the tested configuration it should be used as a methemoglobin early-warning system rather than as a measurement device.

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meeting, October 2010, San Diego, CA, USA. Dr. Brandt has received funding from the European Community's Seventh Framework Programme (FP7/2007-2013) under grant agreement n° 238802 (IIIOS project). The blood gas analyser and the multi wavelength pulse oximeter were items on loan of the manufacturers.

## CONFLICT OF INTEREST

Non- declared.

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