Original Article

Clinical evaluation of a novel technology for non-invasive and continuous measurement of plasma haemoglobin concentration

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Summary

We undertook the first clinical evaluation of a novel, non-invasive device for the continuous measurement of plasma haemoglobin concentration in 25 patients undergoing elective cardiac surgery. At four pre-determined intervals, samples of blood were taken for plasma haemoglobin estimation on a blood gas analyser and a laboratory device and were compared with the plasma haemoglobin estimation on the novel device using the Bland–Altman method. The 95% limits of agreement for estimation of plasma haemoglobin concentration for the device vs. laboratory, the device vs. the blood gas analyser and the blood gas analyser vs. the laboratory were 101.3 $g.l^{-1}$, 103.1 $g.l^{-1}$ and 14.5 $g.l^{-1}$, respectively. The bias (mean difference) in each case was 27.4 $g.l^{-1}$, 25.1 $g.l^{-1}$ and 2.4 $g.l^{-1}$, respectively. We conclude that the novel device in its current form is not a suitable replacement for more invasive methods of determining plasma haemoglobin concentration in patients in the setting of cardiac surgery; however, lessons learnt from the study will help to improve the device's future performance.

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Introduction

In many clinical situations (such as during cardiac or vascular surgery or following trauma), plasma haemoglobin concentration is measured frequently and/or urgently. Currently, this requires sampling and processing of blood, either with a formal laboratory full blood count, with a blood gas analyser, or with a point-of-care device. A continuous, non-invasive and accurate method would allow for more rapid decision making in such situations.

The Optical Fibre Sensor Research Centre at the University of Limerick, together with the Institute of General Electrical Engineering at the University of Rostock, Germany, have co-developed a novel device for the non-invasive, optical, real-time measurement of haemoglobin concentration that calculates a ratio of the absorbance of different wavelengths of light passed through a finger tip in a similar manner to a standard pulse oximeter [1]. Masimo Corporation has previously gained FDA approval for a non-invasive pulse haemoglobinometer (the Radical-7 pulse CO-oximeter; Masimo Corporation, Irvine, CA, USA) and several studies have evaluated its accuracy [2–6]. This device uses multiple wavelengths of light to determine haemoglobin concentration (although the wavelengths employed have not been published). The device that is the subject of this investigation utilises just two wavelengths of light and much of the signal processing

takes place within the finger probe itself to minimise interference.

During cardiopulmonary bypass, patients can undergo large and rapid changes in haemoglobin concentration secondary to blood loss, fluid administration, or transfusion of blood products. In addition, the institution of cardiopulmonary bypass results in haemodilution, and accordingly these cases present an ideal opportunity to study a wider range of haemoglobin within the population group. The primary objective of this study was to compare the novel device with a standard laboratory device (XE-2100; Sysmex Corporation, Kobe, Japan) for estimation of haemoglobin concentration. The secondary objectives were to compare the novel device with a blood gas analyser (GEM Premier 4000; Instrumentation Laboratory, Bedford, MA, USA) and finally to compare results from the standard laboratory device with those from the blood gas analyser.

Methods

With institutional ethical committee approval and having obtained written informed consent from each, 25 patients of ASA physical status 3, scheduled for elective cardiac surgery requiring cardiopulmonary bypass, were studied. Exclusion criteria were the presence of any known haemoglobinopathy, recent dye or contrast studies, or the intra-operative use of an intra-aortic balloon pump.

Each patient's age, sex, height, weight, body mass index, baseline haemoglobin concentration and temperature (via a nasal temperature probe) were recorded. In addition, each patient's smoking history was noted. Following induction of anaesthesia, the study device was fitted on the index finger of each patient's right hand (unless the right radial artery was to be used for grafting, in which case the left index finger was used). Blood was drawn from the arterial catheter via the port closest to the patient at four standard time points using the following technique. Initially, 10 ml blood/heparinised saline was drawn from the arterial catheter. Subsequently, 6 ml arterial blood was drawn (in a second syringe) and 4.1 ml of this blood was transferred to a standard lithium-heparin blood sample bottle and sent to the haematology laboratory for haemoglobin estimation using the hospital's standard CO-oximeter (XE-2100; Sysmex Corporation, Kobe, Japan) for analysis. The remaining blood from this syringe was then transferred to an arterial blood gas syringe, and processed using the GEM Premier 4000 blood gas analyser. The original 10 ml blood/heparinised saline was then returned to the patient to minimise unnecessary blood loss. To determine haemoglobin concentration, the device first calculated a coefficient from the measured absorbances of two wavelengths of light through the varying part of the pulse signal, similar to the method used in standard clinical pulse oximeters. The device then referred this coefficient to a reference table and displayed the result on-screen as haemoglobin concentration. This initial determination served as an additional calibration for further measurements within the same patient. At each time point, the patient's haemoglobin concentration as displayed by the novel device was recorded, and an on-screen button was pressed that recorded the 50-point moving average of the haemoglobin coefficient at that time (i.e. the average of the most recently acquired 50 haemoglobin coefficients).

The four time points selected were: (i) skin incision; (ii) two minutes after completion of administration of the first dose of heparin (pre-bypass); (iii) two minutes after completion of the first dose of protamine (post-bypass); and (iv) at completion of the final skin suture at the end of surgery.

We chose a study sample size (25 subjects) arbitrarily to generate 100 paired samples across the four time points for each comparison. Scatter plots were constructed and a line of equality was included for each of the following comparisons: (i) device haemoglobin concentration vs. full blood count haemoglobin concentration (the primary outcome); (ii) device haemoglobin concentration vs. blood gas analyser haemoglobin concentration; and (iii) blood gas analyser haemoglobin concentration vs. full blood count haemoglobin concentration. Stata Statistical Software: Release 13 (StataCorp LP, College Station, TX, USA) was used for these, and also to construct Bland–Altman [7] plots for each comparison. The method proposed by Bland and Altman [8] for the calculation of bias and limits of agreement was applied using MedCalc (MedCalc Software, Ostend, Belgium), as this study required repeated measurements of haemoglobin

within the same subjects in a situation where the true value of haemoglobin concentration was varying. Statistical analysis included descriptive statistics and tests of equality of variances across the range of patient means (Spearman's ρ), an assumption required for Bland–Altman analyses.

Results

Twenty-five patients were enrolled in the study. Patient characteristics, baseline haemoglobin concentration and the planned surgical procedure are summarised in Table 1. On two occasions during the study, no samples were recorded across all three modalities owing to observer omission. Of the remaining 98 sets, one sample processed with the blood gas analyser was not recorded, again owing to observer omission. Two further laboratory full blood count samples were not recorded owing to breaches of protocol (one was not taken, the other not processed), leaving 95 complete sets of paired data for analysis.

Table 1 Patients' characteristics and type of surgery. Values are number, median (IQR [range]) or number (proportion).

Number of subjects	25
Age; years	67 (57–74 [34–80])
M:F	9:16
Height; cm	165 (160–172 [152–184])
Weight; kg	80 (68–90 [51–147])
Body mass index; $kg.m^{-2}$	27.9 (24.1–31.3 [20.6–56.9])
Baseline [Hb]; $g.l^{-1}$	133 (124–146 [110–163])
Baseline temperature; °C	36.2 (36–36.5 [36–37])
CABG	12 (48%)
Valvular surgery	9 (36%)
Combined (CABG and valvular) surgery	3 (12%)
Atrial myxoma	1 (4%)

[Hb], plasma haemoglobin concentration; CABG, coronary artery bypass graft.

Fifteen patients had never smoked and one patient was an active smoker of 84 pack-years. Nine patients were former smokers whose cessation dates ranged from 6 weeks to 61 years before surgery. The active and former smokers had a mean of 28.3 pack-years.

In the early part of the study period, we encountered six instances (in the first seven participants) of 'freezing' of the on-screen display of haemoglobin concentration, requiring a system reboot between sample points. The problem was found to be due to a software bug, which was corrected by the developers before enrolment of the eighth participant; the problem recurred on only one further occasion (the last participant).

The assumption that the within-subject variance was the same for all subjects was reasonable, as low values of Spearman's ρ showed that there was no evidence of a relationship between variability in the differences and the average of the two measurements. The results of the Bland–Altman analysis including the mean differences, 95% limits of agreement and Spearman's rank order correlation values for each comparison are summarised in Table 2. Bland–Altman plots and scatter plots are shown in Fig. 1.

Discussion

Our results show that, in its current form, the novel device studied is not a suitable replacement for invasive methods of determining haemoglobin concentration in patients undergoing cardiac surgery. The 95% limits of agreement in the cases of the device versus the laboratory full blood count and the device versus the blood gas analyser demonstrated a very broad range in the reference interval (101.3 $g.l^{-1}$ and 103 $g.l^{-1}$, respectively), which would be clinically unacceptable. The 95% limits of agreement for the blood gas analyser versus full blood count show a much closer agreement (a range of 14.5 $g.l^{-1}$) and a

Table 2 Comparison between the three study methods of estimating plasma haemoglobin concentration. Values are mean (upper, lower 95% limits of agreement) and number (significance level).

Method comparison	Device vs. FBC	Device vs. BGA	BGA vs. FBC
[Hb] mean difference (bias); $g.l^{-1}$	27.4 (−23.2, 78.1)	25.1(−26.5, 76.6)	2.4 (−4.8, 9.7)
Spearman's ρ*	−0.01 (0.97)	0.02 (0.92)	−0.05 (0.81)

[Hb], plasma haemoglobin concentration; FBC, full blood count; BGA, blood gas analyser.
*Calculation based on standard deviation of differences between two methods vs. average of two methods per subject.

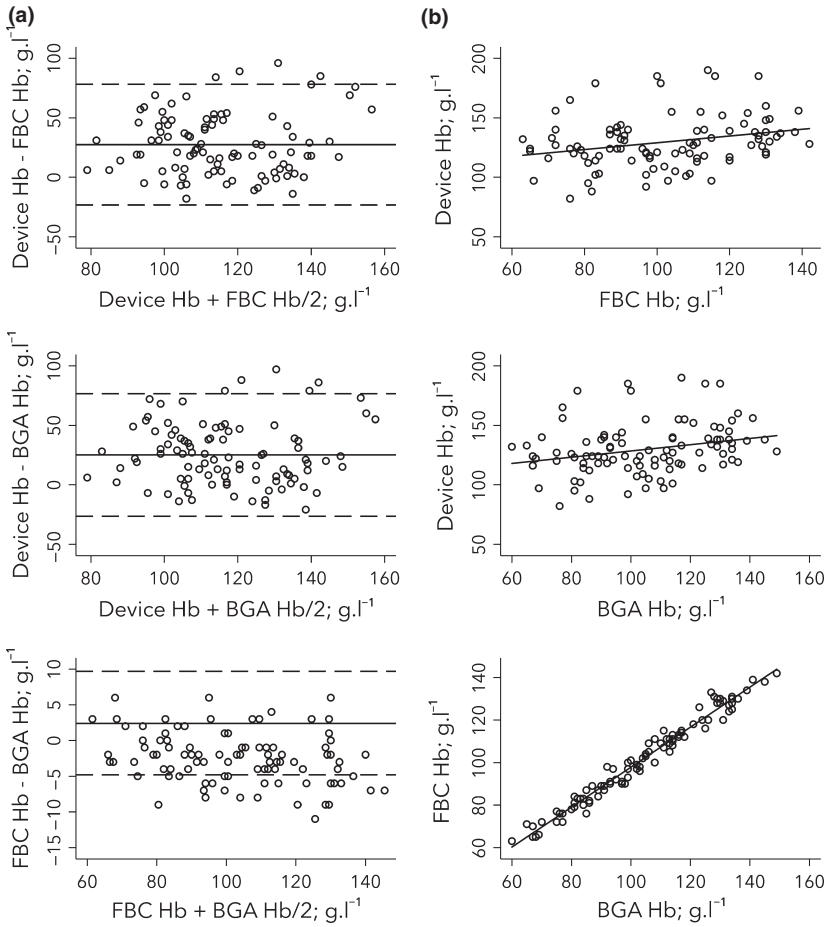

Figure 1 (a) Bland–Altman plots and (b) scatter plots for the comparisons between each method of estimating plasma haemoglobin (Hb) concentration: the novel device; laboratory full blood count (FBC); and the blood gas analyser (BGA). The solid horizontal line in each Bland–Altman plot indicates the mean difference (bias) between methods; the broken lines indicate the 95% limits of agreement.

far lesser mean difference, indicating that these two methods are likely to be interchangeable. Graphs of haemoglobin concentration measured by the study device versus those measured by the laboratory full blood count and the blood gas analyser show a large scatter about the line of equality in comparison with the blood gas analyser versus full blood count (Fig. 1).

Previous studies of non-invasive haemoglobin monitors have reported varying degrees of agreement with traditional methods. In their study analysing 335 paired measurements from 20 healthy volunteers who underwent haemodilution (i.e. where the true haemoglobin value varied), Macknet et al. [2] found a non-invasive pulse haemoglobinometer (Masimo Radical-7) and their reference method to have a mean difference of -1.5 g.l^{-1} and that the difference between methods was < 20 g.l^{-1} for 97% of the measurements. Dewhirst et al. [3] using the Radical-7 and a point-of-care analyser in children found the mean difference to be 1 g.l^{-1}, with 80% of sample sets within 20 g.l^{-1}. They concluded that the non-invasive device was valuable as a continuous trend monitor, but unacceptable as a basis for transfusion decisions. This was a similar conclusion to that of Park et al. [4] in their study of the Radical-7 in children undergoing neurosurgery. However, Nguyen et al. [5] noted a poor correlation between the Radical-7 and laboratory full blood count in 41 patients following cardiac surgery and, in particular, noted that the difference between sampling methods varied considerably in repeated samples from the

same patient at the same time (between −63 and +12 $g.l^{-1}$ for one patient). Together, these findings show that this method of non-invasive measurement of haemoglobin concentration has some promise but is, as yet, unsuitable for use in the clinical setting of cardiac surgery.

The close level of agreement between the GEM Premier 4000 blood gas analyser and the laboratory full blood count has not been shown before and is clinically relevant, as many cardiac surgical centres now rely on similar analysers for the rapid assessment of haemoglobin concentration. An alternative point-of-care device has previously been shown to be a valid method in the setting of critical care [9].

There are several potential sources of error with this device that might explain the poor level of agreement with more established methods for measuring haemoglobin concentration. First, the data used to calibrate the device were obtained from a relatively small ($n < 40$) sample of healthy volunteers, which could have led to inaccuracies in estimating haemoglobin concentration from any calculated haemoglobin coefficient. Second, as subsequent within-patient estimations of haemoglobin concentration relied in part on the initial reading, drift is likely to have occurred, leading to increasingly inaccurate estimations. During bypass (between time points (ii) and (iii) in each case), the device would have lost all data acquisition owing to the lack of a pulsatile signal, which may have exaggerated any drift present. Third, the patient group studied presented specific challenges that potentially lead to problems with signal acquisition. First, patients undergoing cardiac surgery are more likely to have lower perfusion states than healthier patients. Second, patients with moderate and severe congestive heart failure have increased stiffness and decreased compliance of the brachial arteries [10]. Third, hypothermia alters vasomotor tone, which is of particular concern in patients following cessation of cardiopulmonary bypass. Fourth, cardiopulmonary bypass itself elicits an inflammatory response, which can lead to alterations in vasomotor tone. A further analysis of our data showed that the mean difference of the device haemoglobin concentration and the full blood count haemoglobin concentration before cardiopulmonary bypass was 17.4 $g.l^{-1}$, while the mean difference was 37.4 $g.l^{-1}$ following cardiopulmonary bypass. This is likely to be due to a combination of drift as described, inflammatory effects of cardiopulmonary bypass, hypothermia following bypass and the use of vasoactive agents (which were not recorded as part of this study). In addition, the presence of carboxyhaemoglobin and methaemoglobin may lead to inaccuracies in the estimation of haemoglobin concentration. This is a potential confounder with any estimation of haemoglobin concentration where carboxyhaemoglobin and methaemoglobin concentrations are not measured and then subtracted from the estimated haemoglobin concentration. Our study was not designed to take this into account. Furthermore, following completion of the study, the continuously recorded data from the novel device were analysed to retrieve the haemoglobin coefficient at each sample point. It was discovered that for 52 of the 100 data points, the signal detected by the study device was of such a poor quality that measurements could not be obtained, and therefore the haemoglobin coefficient could not be determined. This led us to conclude that the haemoglobin concentration calculated by the device for each of these time points is likely to be inaccurate. Despite this, when these data points were excluded, the mean difference of the device haemoglobin concentration and the full blood count haemoglobin concentration was actually worse at 29.2 $g.l^{-1}$. Finally, the software issues that lead to the device's freezing in the earlier part of the study, as previously mentioned, may have further contributed to the loss of calibration in the subsequent samples in the affected patients.

Improvements could be made to the signal processing algorithms within the device, which might lead to less error in lower perfusion states or with changes in vasomotor tone. Calibrating the device empirically using a far larger group of volunteers, such as the thousands of volunteers used to calibrate standard commercial pulse oximeters, would be likely to increase the accuracy of this device. Revision of the software to ensure that further freezing during operation of the device could also prevent intra-patient calibration problems. Results could also be improved using the simple method proposed by Miyashita et al., whereby the difference between the haemoglobin reading from the device and a laboratory

or point-of-care value is used to adjust subsequent readings on the device (within the same patient) [11]. This method improved the accuracy of non-invasive haemoglobin measurement in 17 patients (with 71 measurements), but only included those undergoing abdominal surgery.

There are limitations to our study. First, the precision of our gold standard was not established at each sample point. This would have required as much as three times the volume of blood to be withdrawn from each patient at each time point, which we deemed unacceptable. Second, the acceptable 95% limits of agreement were not stated a priori, although the calculated limits of agreement were so wide as to make clear that the device would not be clinically useful at this point. Finally, the investigators were not blinded to the output from the device or the results from the blood gas analyser.

Our results indicate that, in its current form, the novel device studied is not suitable for clinical use; several technical challenges (outlined above) will need to be addressed before it could be recommended for clinical use.

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Competing interests

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References

1. Timm U, Leen G, Lewis E, McGrath D, Kraitl J, Ewald H. Non-invasive optical real-time measurement of total hemoglobin content. *Procedia Engineering* 2010; **5**: 488–91.
2. Macknet MR, Allard M, Applegate RL, Rook J. The accuracy of noninvasive and continuous total hemoglobin measurement by pulse CO-Oximetry in human subjects undergoing hemodilution. *Anesthesia and Analgesia* 2010; **111**: 1424–6.
3. Dewhirst E, Naguib A, Winch P, et al. Accuracy of noninvasive and continuous hemoglobin measurement by pulse co-oximetry during preoperative phlebotomy. *Journal of Intensive Care Medicine* 2014; **29**: 238–42.
4. Park Y-H, Lee J-H, Song H-G, Byon H-J, Kim H-S, Kim J-T. The accuracy of noninvasive hemoglobin monitoring using the radical-7 pulse co-oximeter in children undergoing neurosurgery. *Anesthesia and Analgesia* 2012; **115**: 1302–7.
5. Nguyen B-V, Vincent J-L, Nowak E, et al. The accuracy of non-invasive hemoglobin measurement by multiwavelength pulse oximetry after cardiac surgery. *Anesthesia and Analgesia* 2011; **113**: 1052–7.
6. Lamhaut L, Apriotesei R, Combes X, Lejay M, Carli P, Vivien B. Comparison of the accuracy of noninvasive hemoglobin monitoring by spectrophotometry (SpHb) and HemoCue. *Anesthesiology* 2011; **115**: 548–54.
7. Bland JM, Altman DG. Statistical methods for assessing agreement between two methods of clinical measurement. *Lancet* 1986; **1**: 307–10.
8. Bland JM, Altman DG. Agreement between methods of measurement with multiple observations per individual. *Journal of Biopharmaceutical Statistics* 2007; **17**: 571–82.
9. Ray JG, Post JR, Hamielec C. Use of a rapid arterial blood gas analyzer to estimate blood hemoglobin concentration among critically ill adults. *Critical Care* 2001; **6**: 72–5.
10. Arnold JM, Marchiori GE, Imrie JR, Burton GL, Pflugfelder PW, Kostuk WJ. Large artery function in patients with chronic heart failure. Studies of brachial artery diameter and hemodynamics. *Circulation* 1991; **84**: 2418–25.
11. Miyashita R, Hirata N, Sugino S, Mimura M, Yamakage M. Improved non-invasive total haemoglobin measurements after in-vivo adjustment. *Anaesthesia* 2014; **69**: 752–6.

