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Accuracy of non-invasive haemoglobin (SpHb) depends on the type of infusion fluid

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Short title: Pulse oximetry Hb and infusion fluids

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Abstract

Context Measurement of blood haemoglobin (Hb) concentration by pulse oximetry (SpHb) could be of value to determine when erythrocytes should be transfused during surgery, but the effect of infusion fluids on the results is unclear.

Objective To study the effect of crystalloid and colloid fluid on the accuracy (bias) and precision of SpHb to indicate the venous Hb concentration in volunteers.

Design Open interventional crossover study.

Setting Single university hospital.

Subjects Ten male volunteers aged 18-28 (mean, 22) years.

Interventions Each volunteer underwent three infusion experiments on separate days and in random order. The infusions were Ringer's acetate (20 ml kg⁻¹), hydroxyethyl starch 130/0.4 (10 ml kg⁻¹) and a combination of both.

Results At the end of the infusions of Ringer's acetate, SpHb had decreased more than Hb (15 *versus* 8%; $P<0.005$; $n=10$) while starch solution decreased SpHb less than Hb (7 *versus* 11%; $P<0.02$; $n=20$). The same differences were seen when the fluids were infused separately and when they were combined. The overall difference between all 956 pairs of SpHb and Hb (the bias) averaged only -0.7 g l⁻¹ while the 95% prediction interval was wide, ranging from [-24.9] to 23.7 g l⁻¹. Besides the choice infusion fluid, the bias was strongly dependent on the volunteer (each factor $P<0.001$).

Conclusion The bias of measuring Hb by pulse oximetry is dependent on whether a crystalloid or a colloid fluid is infused.

Trial registration ClinicalTrials identifier: NCT01195025

Introduction

Measurement of haemoglobin concentration (Hb) is usually made in blood sampled from a cubital vein. During surgery, Hb is essential for decisions about whether to transfuse erythrocytes. Therefore, sporadic measurement of Hb is performed during major surgery as a guide to when transfusion should be initiated.

The Hb concentration can also be inferred non-invasively and continuously by multi-wavelength pulse CO-oximetry (SpHb), which might serve as an attractive alternative to invasive sampling. This recently reviewed technique¹ has been used in studies involving volunteers and surgery, with varying conclusions about accuracy and precision.²⁻¹¹ However, little is known about how SpHb reacts to specific procedures performed during surgery, such as intravenous infusion of crystalloid and colloid fluid. There is some evidence that SpHb changes more than Hb during volume loading with Ringer's acetate⁷ but no evaluation of the accuracy of SpHb during administration of colloid fluid has been performed.

In the present study, we investigate the reliability (accuracy and precision) of SpHb to measure Hb during and after infusion of Ringer's acetate and 6% hydroxyethyl starch 130/0.4 in volunteers. These fluids were given separately and in combination, as crystalloid and colloid fluids are often administered together in major surgery. The hypothesis was that both infusions would change the accuracy of SpHb as a measure of Hb. The perfusion index (PI) was also recorded, because SpHb seems to provide lower values when PI is low.²

Methods

Ten male volunteers aged between 18 to 28 (mean, 22) years and with a body weight between 65-101 (mean, 79) kg underwent three infusion experiments between August and December 2010. The protocol was part of a project evaluating the blood volume expanding effects of mixed fluid therapy (starch solution followed by crystalloid solution). The study was approved by the Regional Ethics Committee, Karolinska Institutet, 171 77 Stockholm, Sweden, on September 18, 2009 (Dnr 2009/1091-31/2; Chairperson Ulla Erlandsson) and registered at ClinicalTrials by identifier NCT01195025. Each volunteer gave his consent for participation after being informed about the study both orally and in writing.

The experiments started between 7:30 and 8:30 AM in the Department of Intensive Care at Linköping University Hospital. The volunteers had fasted since midnight but were allowed to eat one sandwich and drink one glass (200 ml) of liquid at 6 AM. When they arrived at the department, they rested on a bed below an OPN Thermal Ceiling radiant warmer (Aragon Medical, River Vale, NJ, USA) placed about 1 m above them. The heat was adjusted to achieve maximum comfort. A cannula was placed in the antecubital vein of each arm to infuse fluid and sample blood, respectively. Thirty minutes of rest to reach haemodynamic steady state was allowed before the experiments started.

Infusions

Each volunteer underwent the following three experiments in random order, separated by at least 7 days (Fig. 1):

- A. Infusion of Ringer's acetate, 20 ml kg^{-1} , over 30 minutes (2 received 25 ml kg^{-1}).
- B. Infusion of starch, 10 ml kg^{-1} , over 30 minutes.
- C. Infusion of combined starch and Ringers' acetate; 10 ml kg^{-1} of starch was infused between 0 and 30 minutes, followed by 20 ml kg^{-1} of Ringer's between 105 and 135 minutes.

The crystalloid fluid was acetated Ringer's (Baxter, Deerfield, IL; sodium 130,

chloride 110, acetate 30, potassium 4, calcium 2, and magnesium 1 mmol/l).

The colloid was hydroxyethyl starch 6% 130/0.4 (Voluven, Fresenius Kabi; Bad Homburg, Germany; sodium 154, chloride 154 mmol/l).

The volume of colloid was chosen to correspond to previous work using albumin.¹² The infused volume of Ringer's acetate has usually been 25 ml/kg in studies of plasma volume expansion in healthy volunteers¹³ but it was slightly reduced here to avoid excessive cardiovascular strain in the combined experiment.

The fluids were administered at room temperature (23°C) via infusion pumps (Volumat MC Agilia, Fresenius Kabi).

Measurements

Venous blood (3-4 ml) was withdrawn from the antecubital venous cannula, using a vacuum tube, without stasis of the upper arm. The baseline sample was drawn in duplicate, and the mean was used in further calculations. A small volume of blood was drawn before each sampling, and the volume replaced by 2 ml of 0.9% saline to prevent clotting. The venous blood Hb was measured on a Cell-Dyn Sapphire hematology cell counter (Abbot Diagnostics, Abbot Park, IL, USA). Duplicate samples drawn at baseline ensured a coefficient of variation of 1.2%.

The sampling intensity varied slightly depending on the length of the experiment. In the Ringer experiment, blood was drawn every 5th min up to 60 min, and thereafter every 10th min up to 180 min. The same protocol was followed when starch alone was infused, but the follow-up continued with blood sampling every 30th min up to 420 min. In the combined experiment, the higher sampling intensity (every 5th min) was re-instituted for 60 min when the second infusion started.

SpHb and PI were measured by the Radical 7 pulse CO-oximeter (Masimo Corp., Irvine, CA, USA) which uses light of multiple wavelengths and also advanced filtering and processing of the signals to yield these values¹. A single-use patient adhesive sensor of type R2-25a was attached to the middle finger of one hand. The venous samples were drawn from the same arm and the infusions were given in the other. The software delivered by the manufacturer was SET V7.6.0.1. The data were averaged every 8 seconds.

PI is a measure of the pulse amplitude in the finger and is obtained as the ratio

between the pulsatile and the non-pulsatile absorption of infrared light. For each invasive blood sample, we recorded the SpHb and PI displayed on the front of the Radical 7. Haemodynamic monitoring also included non-invasive blood pressure and heart rate.

Statistics

Data are given as the median and 25th-75th percentiles, except where noted. Differences between paired data were evaluated by the Wilcoxon matched-pair test, and differences between unpaired samples by the Mann-Whitney U test. Comparisons between three groups were made by applying the Kruskal-Wallis test.

The influence of several factors on a continuous variable was tested by two-way ANOVA, and the relationship between parameters by simple and multiple linear regression (where r = correlation coefficient).

The accuracy (bias) of using SpHb to indicate Hb was expressed as the absolute or relative difference between the paired measurements, the latter being:

$$\text{Relative difference (\%)} = \frac{\text{SpHb} - \text{Hb}}{(\text{Hb} + \text{SpHb})/2} \bullet 100$$

The precision of using SpHb to indicate Hb was expressed the absolute value of the relative difference between the paired measurements.

The 95% prediction interval for the absolute difference between SpHb and Hb is the range in which 95% of the SpHb-Hb differences are to be found.

The accuracy and precision of SpHb to indicate Hb is also illustrated by Bland-Altman plots. Calculations were considered statistically significant if $P < 0.05$.

Results

All 10 volunteers completed the study, which comprised 30 experiments altogether (Fig. 1). Baseline data are shown in Table 1.

Haemoglobin changes during infusion

At the end of the first infusion of Ringer's acetate, SpHb had decreased *more* than Hb (15% *versus* 8%; $P < 0.005$; $n=10$; Fig. 2 A).

At the end of the infusions of starch, SpHb had decreased *less* than Hb (7% *versus* 11%; $P < 0.02$; $n=20$; Fig. 2 B-C).

At the end of the infusion of Ringer's acetate in the combined experiment, SpHb had again decreased *more* than Hb (11% *versus* 5%; $P < 0.03$; $n=10$; Fig. 2 C).

Differences between SpHb and Hb

SpHb tended to be lower than Hb at baseline (median 136.5 g l^{-1} *versus* 144 g l^{-1} ; $P=0.07$; $n=30$) which yielded a bias of -3.8% and a precision of 6.6%.

Infusion of Ringer's acetate increased the bias by 7.0 (2.5-11.1)% ($P < 0.04$, median, 25th-75th percentile range) while starch decreased the bias by 4.3 (0.9-7.2)% ($P < 0.02$; $n=20$; Table 2).

The precision had become 4.6% ([-1.7]-6.1%) poorer at the end of the Ringer infusions ($P < 0.02$) while starch did not affect the precision, the median change being 0.8% ([-3.5]-3.7%) (not statistically significant, Table 2).

The mean difference between all 956 pairs of SpHb and Hb (the bias) was -0.7 g l^{-1} . The median (25th-75 percentiles) were -2 ([-10]-8) g l^{-1} which corresponds to an accuracy of -0.8 ([-7.5]-5.9)% and a median precision of 6.6 (3.1-10.7)% (Table 2). The 95% prediction interval for the SpHb-Hb difference ranged from -24.9 to 23.7 g l^{-1} (Figs. 3, 4).

Two-way ANOVA showed that the bias was dependent on the infusion experiment,

but also strongly dependent on the volunteer (each factor $P < 0.001$; Table 3).

The difference between SpHb and Hb became more positive (so that $\text{SpHb} > \text{Hb}$) with lower Hb concentrations ($r=0.42$, $P < 0.001$; Fig. 4).

Perfusion index

PI was 7.0 (4.3–9.2)% at baseline. The Ringer infusions decreased PI from (median) 7.0 (4.4–11.0)% to 2.5 (1.3–6.4)% and the starch infusion from 5.4 (5.0–8.1)% to 3.0 (1.9–6.1)% (repeated-measures ANOVA $P < 0.01$ and 0.02, respectively; Table 2).

The SpHb-Hb difference increased with a higher PI. Thus, a median PI above 7.0% during the experiments was associated with a positive bias whereas for $\text{PI} \leq 7.0\%$ the average bias was negative (Table 4). This was explained by that SpHb but not Hb increased with PI (Fig. 5). Multiple regression analysis showed that the effect of PI on the bias was statistically independent from the opposite effect of Hb *per se* that is illustrated in Fig. 4 (combined factors; $r=0.49$; $P < 0.001$).

Discussion

The results show that the accuracy of non-invasive SpHb is dependent on the type of infusion fluid administered. Starch caused SpHb to decrease much less than Hb, and the difference was long lasting. On the other hand, when infusing Ringer's acetate, the decrease in SpHb was greater and more transient. Both of these effects could also be discerned in the combined experiment (Fig. 2).

Other factors were also found to affect the bias of the SpHb measurement. In addition to the choice of infusion fluid, the between-subject variation was important (Table 3). A low Hb concentration *per se* promoted a more positive bias, which means that SpHb overestimated Hb when a correct indication could be clinically important. Moreover, SpHb increased slightly with PI, which confirms previous findings.² Other authors have also reported a positive SpHb-Hb difference when PI is below 2^{3,9} while our findings propose that the same relationship exists also when PI exceeds 7 (Table 4).

Starch administration, low Hb and high PI were all factors that promoted a more positive SpHb-Hb difference, thereby acting to mislead the clinician with regard to the need for erythrocyte transfusion. The reasons for inconsistency of the SpHb measurement are unclear. One hypothesis is that our fluid load might have disturbed this balance by expanding the vessels and also by diluting Hb differently in arterioles, capillaries, and veins.¹⁵ Faster disappearance of crystalloids than colloids from the bloodstream^{16,17} promotes tissue oedema, which could diminish the relative strength of the pulsatile part of the signal by affecting the background noise. The time-course of the negative SpHb-Hb difference when acetated Ringer's is infused (Fig. 2A) is consistent with findings that the net movement of fluid from plasma to the interstitium in the arm is reversed within 2.5 minutes after the end of a brisk infusion.¹⁷ In contrast, accumulation of infused fluid in peripheral tissues is more long-lasting when the whole body is studied.¹³ The opposite change of the SpH-Hb difference in response to starch might possibly be due to overlapping of physical absorbance characteristics of starch and Hb. Experimental studies investigating the microvasculature in combination with the spectrophotometry and the optical physics may give answers to the open questions in this study.

The *bias* calculated from a large number of paired measurements is usually quite small in studies using the SpHb technology. The bias when infusing crystalloid fluid was -1.6% in a previous study⁷, and in blood withdrawal followed by crystalloid fluid the figure averaged -1.5 g l⁻¹.⁹ In spine surgery, the bias was -2.6 g l⁻¹,² -3 g l⁻¹,¹⁰ and -12.7 g l⁻¹.¹¹ Other data from the perioperative setting were -0.2 g l⁻¹,⁸ -2.9 g l⁻¹,⁴ and 0.⁵ Extreme bias include -13 to -17 g l⁻¹ in cardiac intensive care³ and -18 g l⁻¹ in emergency care.⁶ In all these studies the SpHb showed a lower mean value than Hb, thereby the negative bias.

In contrast, poor *precision* is a problem. According to published graphs and charts, the 95% prediction interval for the SpHb-Hb difference has been 40 g l⁻¹,^{4,9,10} 40-50 g l⁻¹,⁸ 67-80 g l⁻¹,^{2,3,11} and 110 g l⁻¹.⁶ In the present study, the range was almost 50 g l⁻¹. Some of the wide variability in the SpHb-Hb difference in previous studies might well be caused by the fluid therapy used when data was collected.

The SpHb difference at baseline differed slightly between the three experiments (Table 2). Small variations can be due to the state of hydration of the volunteers, as the Radical 7 measures SpHb in arterial blood while the sampled blood was venous. The arteriovenous Hb difference has been reported to be -1.8 g l⁻¹ of non-fasting volunteers in the afternoon¹⁸, but amounted only to -0.3 g l⁻¹ in semi-fasting male volunteers studied in the morning.¹⁹ The gradient might even become zero or slightly positive after an overnight fast²⁰ as evidence of fluid transport away from the arm. The Radical 7 can be set to reflect SpHb in venous blood, which simply makes it to report 0.7-1.0 g l⁻¹ higher values. This possibility was not used in the present study as the arteriovenous Hb difference was likely to be close to zero at baseline. However, the true difference was probably increased to approximately -1 g l⁻¹ during the infusion of Ringer's acetate¹⁹. The arteriovenous Hb difference induced by the infusion can therefore only explain a fraction of the difference between SpHb and Hb at the end of the Ringer's infusions, which amounted to almost -11 g l⁻¹.

In a previous report PI decreased when Ringer's acetate was infused⁷, and the same change was seen in the present study. This effect is surprising, since PI is an index of blood flow that is expected to increase as the result of volume loading. As this did not occur, we have suspected that the oedema caused by the infusion had decreased the ratio between pulsatile and non-pulsatile flow. However, this cannot be correct, since the PI

also decreased when starch was infused, despite the fact that colloid fluids are not deposited extravascularly early on during an infusion.¹⁶ On the other hand, the fluids infused at room temperature cooled the body and thereby resulted in vasoconstriction and less perfusion. But since all fluids were of the same temperature, and the amount of Ringer's was twice that of starch, the cooling effect would then logically be twice as large in the Ringer's experiment. However, the fall in PI was much greater when infusing starch. Therefore, temperature offers no satisfying explanation for the change in PI.

Limitations include that the infusions were administered to normovolaemic subjects, which is often not the case in clinical practice. The difference between the SpHb and Hb might be different when a hypovolaemic patient is infused. Moreover, differences between healthy volunteers may not completely reflect the situation in anaesthetized patients. Moreover, only male volunteers were studied as females have difficulty to void in the lying position.

In conclusion, the SpHb changes in response to intravenous fluid differ depending on whether a crystalloid (Ringer's acetate) or colloid fluid (starch solution) is given. Starch administration, low blood Hb concentration and high perfusion index are all factors that promote a positive SpHb-Hb difference, which can mislead the clinician to underestimate the need for erythrocyte transfusions. On the other hand, infusion of Ringer's solution, a high blood Hb and a low perfusion index act to exaggerate the need for transfusing erythrocytes.

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Table 1

Data on volunteers, baseline values.

Parameter		Median	SD	25 – 75% percentiles
Age (years)	10	21.0	3.4	19.0 – 23.8
Weight (kg)	10	80.0	10.4	73.8 – 83.2
Length (cm)	10	183.5	5.5	180.8 – 187.0
Body mass index (kg m ⁻²)	10	23.4	3.2	21.9 – 25.1
Blood volume (litre)*	10	5.4	0.4	5.2 – 5.7
Initial Hb (g l ⁻¹)	30	142.0	5.6	138.5 – 146.0
Initial SpHb (g l ⁻¹)	30	136.5	9.9	130.0 – 146.5

* Blood volume was estimated according to Nadler¹⁴: $BV = 0.03219 \text{ weight (kg)} + 0.3669 \text{ length}^3 \text{ (m)} + 0.6041$

Table 2

The non-invasive Hb (SpHb) and invasive venous Hb concentrations and the accuracy and precision of SpHb to predict invasive Hb in the course of the three infusion experiments. The perfusion index is also shown.

Fluid	SpHb (g l ⁻¹)	Hb (g l ⁻¹)	Accuracy of SpHb (relative difference, %)	Precision of SpHb (absolute relative difference, %)	Perfusion index (PI) %
Ringer's acetate					
Start of infusion	136.1 (6.6)	141.8 (3.3)	-4.1 ([-8.2] – [-2.5])	4.8 (3.2 – 8.2)	5.4 (5.0 – 8.1)
End of infusion	119.6 (12.6)	128.6 (5.0)	-8.8 ([-14.8] – [-5.0])	8.8 (5.0 – 14.8)	3.0 (1.9 – 6.1)
End of test	130.0 (12.6)	137.5 (6.6)	-7.6 ([-15.7] – 3.1)	9.1 (6.2 – 15.7)	4.8 (3.3 – 7.1)
Entire experiment	127.5 (12.7)	134.6 (6.4)	-5.3 ([-10.4] – 1.5)	7.9 (3.2 – 11.5)	4.6 (2.5 – 7.8)
Starch					
Start of infusion	135.4 (9.0)	143.2 (8.0)	-6.1 ([-10.9] – [-3.0])	7.4 (4.4 – 11.5)	7.0 (4.4 – 11.0)
End of infusion	123.5 (5.2)	126.7 (6.3)	-0.4 ([-10.0] – 2.4)	4.8 (0.8 – 10.0)	2.5 (1.3 – 6.4)
End of test	137.7 (9.5)	140.9 (7.3)	-2.3 ([-4.9] – 3.3)	4.0 (3.3 – 7.1)	4.4 (3.1 – 5.3)
Entire experiment	131.9 (8.5)	133.0 (7.8)	0.0 ([-6.8] – 4.6)	5.5 (2.5 – 8.8)	5.1 (3.3 – 7.8)
Starch+Ringer's acetate					
Start of starch infusion	143.4 (12.1)	141.4 (4.7)	0.7 ([-6.2] – 9.6)	9.2 (1.7 – 10.3)	7.9 (4.3 – 9.5)
End of starch infusion	132.7 (11.6)	124.2 (4.2)	5.2 ([-1.6] – 14.8)	5.7 (3.9 – 14.8)	3.0 (2.0 – 6.5)
Start of Ringer infusion	137.3 (10.6)	130.3 (5.6)	5.8 ([-3.2] – 13.1)	7.5 (4.7 – 13.1)	6.0 (4.2 – 6.9)
End of Ringer infusion	120.8 (11.1)	123.2 (5.6)	-5.0 ([-8.6] – 7.6)	8.4 (6.7 – 14.4)	2.6 (1.5 – 5.3)
End of test	133.9 (9.2)	134.0 (6.0)	2.9 ([-4.5] – 7.8)	6.3 (3.6 – 8.7)	3.2 (2.3 – 4.4)
Entire experiment	131.9 (12.3)	128.1 (6.5)	1.5 ([-4.9] – 10.9)	5.7 (2.2 – 10.3)	4.8 (2.8 – 7.6)

Data are the mean (SD) or the median and 25th-75th percentiles.

$$\text{Relative difference (\%)} = \frac{\text{SpHb} - \text{Hb}}{(\text{Hb} + \text{SpHb})/2} \cdot 100$$

Table 3

The accuracy (bias) of SpHb in indicating invasive Hb concentration during infusion experiments, expressed as the mean relative difference for all data in each of 10 volunteers.

Volunteer n:o	Body weight (kg)	Accuracy (relative difference, %)			All three experiments
		Ringer's	Starch	Starch+ Ringer's	
1	86	-10.0	-0.5	13.9	3.0
2	82	-12.1	-11.5	-5.2	-9.0
3	73	-4.6	4.8	-3.7	-1.2
4	79	-22.1	-8.9	-8.4	-12.2
5	75	-7.5	-4.9	7.1	-0.7
6	101	-5.1	-0.7	-1.4	-2.1
7	83	-1.2	7.0	-4.4	0.1
8	80	0.05	6.2	16.3	8.8
9	66	12.9	-3.2	11.1	9.1
10	66	-7.6	-3.8	0.4	-3.1

Data are the mean for one experiment.

$$\text{Relative difference (\%)} = \frac{\text{SpHb} - \text{Hb}}{(\text{Hb} + \text{SpHb})/2} \cdot 100$$

Table 4

Differences in the accuracy (bias) and precision of non-invasive SpHb in indicating invasive Hb during infusion experiments in 10 volunteers, depending on the perfusion index.

Parameter	Perfusion index (% range)			Kruskal-Wallis test
	≤ 2	2-7	≥ 7	
<i>N</i>	105	535	312	
Hb (g l ⁻¹)	130 (124 – 135)	131 (126 – 137)	132 (126 – 136)	Not significant
SpHb (g l ⁻¹)	125 (120 – 131)	129 (123 – 137)	133 (125 – 144)	$P < 0.0001$
SpHb – Hb (g l ⁻¹)	-7 ([-12]–0)	-3 ([-10]–4)	3.5 ([-6]–13)	$P < 0.0001$
Relative difference (%)	-5.3 ([-9.2]–0.0)	-2.4 ([-7.8]–3.4)	2.4 ([-4.8]–9.6)	$P < 0.0001$
Absolute relative difference (%)	7.4 (4.8–10.1)	6.1 (3.0–10.4)	8.4 (3.6 – 12.4)	$P < 0.0001$

Data are the median and 25th-75th percentiles.

$$\text{Relative difference (\%)} = \frac{\text{SpHb} - \text{Hb}}{(\text{Hb} + \text{SpHb})/2} \bullet 100$$

Legends for figures

Fig. 1.

Flowchart describing the three parts of the study.

Fig. 2.

Change in Hb (red) and SpHb (blue) measurements over time during the tests.

(A) Ringer's only. (B) Voluven only. (C) Starch first, then Ringer's. Thick black lines indicate the duration of the infusions. Note that the decrease in SpHb when starting the Ringer's infusion in (C) resembles the one seen in (A).

Fig. 3.

Bland-Altman plots showing the agreement between SpHb and Hb for all data sampling points in the three series of experiments: (A) Ringer's only. (B) Voluven only. (C) Starch first, then Ringer's.

Fig. 4.

The bias of the SpHb measurement *versus* the invasive Hb concentration for all data sampling points in the three series of experiments. The shaded areas illustrate a risk of misjudging Hb levels below 120 (g l⁻¹) by relying on SpHb. The positive bias was greatest at low Hb levels.

Fig. 5.

(A) Lack of linear correlation between the perfusion index and invasive Hb.

(B) Statistically significant linear correlation between the perfusion index and SpHb.

In both plots, $N=956$.

Fig. 1.

Fig. 2.

Fig. 3.

Fig. 4.

Fig. 5.