Mismatch of arterial and central venous blood gas analysis during haemorrhage

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Assessing acid-base status by venous blood gas analysis, is it possible?

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Financial support: Supported by departmental funds, and B. Braun Medical S.A., Crissier, Switzerland

Key words: lactate, hemorrhagic shock, severe acidosis, blood gas analysis
Abstract

**Background:** Arterial base excess (BE) and lactate levels are key parameters in the assessment of critically ill patients. The use of venous blood gas analysis may be of clinical interest when no arterial blood is available initially.

**Methods:** 24 pigs underwent progressive normovolemic haemodilution and subsequent progressive haemorrhage until the death of the animal. BE and lactate levels were determined from arterial and central venous blood after each step. In addition, BE was calculated by the Van Slyke equation modified by Zander (BEz). Continuous variables were summarized as mean ± SD and represent all measurements (n=195).

**Results:** BE by National Committee for Clinical Laboratory Standards (NCCLS) for arterial blood was 2.27 ± 4.12 mmol/l versus 2.48 ± 4.33 mmol/l for central venous blood (p=0.099) with a strong correlation (r²=0.960, p<0.001). Standard deviation of the differences between these parameters (SD-DIFBE) did not increase (p=0.355) during haemorrhage as compared with haemodilution. Arterial lactate was 2.66 ± 3.23 mmol/l versus 2.71 ± 2.80 mmol/l in central venous blood (p=0.330) with a strong correlation (r²=0.983, p<0.001). SD-DIFLAC increased (p<0.001) during haemorrhage. BEz for central venous blood was 2.22 ± 4.62 mmol/l (p=0.006 vs BE arterial NCCLS) with strong correlation (r²=0.942, p<0.001). SD-DIFBEz/BE increased (p<0.024) during haemorrhage.

**Conclusions:** Central venous blood gas analysis is a good predictor for BE and lactate in arterial blood in steady state conditions. However, the variation between arterial and central venous lactate increases during haemorrhage. The modification of the Van Slyke equation by Zander did not improve the agreement between central venous and arterial BE.
**Introduction**

Acid-base disturbances, in particular metabolic acidosis, are frequently encountered in severely injured and critically ill patients.\(^1\) Several previous studies have shown admission base excess (BE) and lactate levels to be reliable variables in the triage of patients requiring intensive care units (ICU) resources.\(^2\)\(^-\)\(^7\)

BE has first been introduced in 1960 by Siggard-Andersen to qualify the non-respiratory component in acid-base imbalance.\(^8\) BE is defined as the amount (mmol/l) of strong acid or strong base needed to restore arterial whole blood to a pH of 7.4, with the sample fully saturated with oxygen at 37°C and a partial pressure of carbon dioxide (pCO\(_2\)) of 40 mmHg.\(^9\),\(^10\) This approach was later modified by introducing extracellular BE or standard BE (SBE), which proved to be independent of the respiratory pCO\(_2\).\(^11\)\(^-\)\(^14\) By the availability of blood gas analyzers for easy and rapid determination of BE and lactate levels, routine determination of both has been incorporated in the clinical evaluation of critically ill patients.\(^2\),\(^3\),\(^6\),\(^7\)

Several previous investigations have established BE as well as lactate levels as valuable indicators of shock and the efficacy of resuscitation in trauma patients.\(^15\)\(^-\)\(^21\) Furthermore, both, BE and lactate levels, have been shown to be predictive of transfusion requirements,\(^22\)\(^-\)\(^24\), oxygen debt,\(^4\),\(^14\),\(^19\),\(^21\),\(^23\),\(^25\)\(^-\)\(^27\), the increased risk of shock-related complications (i.e. multiple organ failure, ARDS, renal failure, coagulopathy),\(^14\),\(^18\),\(^21\),\(^27\)\(^-\)\(^29\), the outcome of patients,\(^6\),\(^14\),\(^19\),\(^23\), survival after haemorrhage,\(^4\),\(^5\), as well as mortality after trauma.\(^4\),\(^6\),\(^14\),\(^18\),\(^21\),\(^25\),\(^27\),\(^30\),\(^31\) Thus, BE and lactate levels, respectively, are recognized as important variables to evaluate the clinical condition of critically ill patients and serve as reliable indicators for prognosis.\(^6\),\(^32\),\(^33\)

In addition, clinical decisions are often based on changes of both, BE and lactate levels, over time.\(^2\),\(^25\),\(^27\),\(^28\)

The determinations of BE and lactate levels are usually performed by standard blood gas analyzers. Most algorithms used today for calculating the BE use measured pH, pCO\(_2\) and haemoglobin (Hb) values, and are based on the fundamental Van Slyke equation modified by
Siggard-Andersen in 1977. However, arterial blood samples may be difficult to obtain due to patient size, lack of patient cooperation and required technical skills. Furthermore, arterial puncture may cause complications, including pain, arterial damage, haemorrhage, aneurysm formation, thrombosis of the artery and infection. Therefore, the possibility of using venous blood for blood gas analysis and the calculation of BE is being discussed and may be of clinical interest.

A modification of the Van Slyke equation for calculation of the whole blood BE (BE<sub>z</sub>) has been proposed by Zander et al. This approach takes the known effect of oxygen saturation of haemoglobin into account by including a correction term for oxygen saturation in the fundamental Van Slyke equation. Therefore, calculation of BE from any blood sample (venous or arterial blood) based on measured pH, pCO<sub>2</sub>, haemoglobin concentration (cHb) and O<sub>2</sub> saturation (SO<sub>2</sub>) may be possible. At present time, the accuracy of the Van Slyke equation modified according to Zander has been shown in vitro by using a wide-ranged triple-set of reference values for pH, pCO<sub>2</sub> and BE in normal oxygenated human blood. Over a wide range (-30 to +30 mmol/l) of varying BE, mean inaccuracy was less than 1 mmol/l. In a further ex vivo study, using venous blood of 50 healthy volunteers, the calculated BE from venous blood according to Zander perfectly agreed with the normal BE from arterial blood even though pH, pCO<sub>2</sub> and SO<sub>2</sub> varied widely. The aim of the present study was to investigate in vivo whether both the BE as well as the lactate level can be reliably determined in central venous blood under steady state conditions and in haemorrhagic shock. In addition, we assessed the applicability of the Van Slyke equation modified according to Zander by comparing the calculated whole blood BE according to Zander (BE<sub>z</sub>) with whole blood BE values obtained from standard blood gas analysis according to NCCLS (National Committee for Clinical Laboratory Standards) for all conditions.
Material and Methods

In the framework of another study investigating anaemia tolerance, animals were randomized into two groups of 12 pigs each, receiving HES 130 (136 kD) or HES 650 (647 kD) (blinded to the experimental investigators). Both HES solutions have identical molar substitution (0.42), C2/C6 ratio (5:1) as well as concentration (6%). The study group consisted of 24 pigs with a mean body weight of 43 ± 4 kg. The pigs were fasted overnight but allowed free access to water. The study protocol was authorized by the Veterinary office of the Canton de Vaud (Service Vétérinaire, Lausanne, Canton de Vaud, Switzerland). All experiments were performed according to the guidelines of the Swiss Federal Veterinary Office.

Premedication and Anaesthesia

Animals were premedicated with an intramuscular injection of 0.5 mg/kg xylazine (Rompun 2%, Bayer AG, Leverkusen, Germany), 20 mg/kg ketamin (Veterinaria AG, Zurich, Switzerland) and 1 mg atropine (Sintetica S.A., Mendrisio, Switzerland). After the animals were sedated, anaesthesia was induced by administration of 3 % halothane (Dräger, Lübeck, Germany) by mask, followed by tracheal intubation. Volume controlled ventilation was performed using tidal volumes of 10 ml/kg with a ventilatory rate of 13-18/min to maintain alveolar carbon dioxide pressure (pCO2) at 35-40 mmHg (Ventilator Dräger Sulla 900 V, Dräger, Lübeck, Germany). The inspired oxygen fraction (FiO2) was maintained at 1.0 during surgical instrumentation and then reduced to FiO2 of 0.4 (air-oxygen mixture). Analgesia was assured by continuous intra-venous infusion of fentanyl (Sintetica S.A., Mendrisio, Switzerland) in a dosage of 4 µg/kg/h during the entire period of surgical instrumentation. Halothane was used to anaesthetize the animals at a mean of 0.8-2.0 % according to heart rate and blood pressure response to surgical stimulation of each individual animal and left unchanged during the entire study. The ear vein was cannulated (18-gauge cannula).
**Monitoring**

The right internal jugular vein was catheterized for normovolemic haemodilution, measurement of central venous pressure, venous blood withdrawal for laboratory measurements and venous blood gas analyzes. The catheter tip was inserted into the vena cava superior. The right carotid artery was also catheterized allowing continuous measurement of mean arterial blood pressure and blood withdrawal for arterial blood gas analyzes. Via the contralateral carotid artery an arterial cannula (AAS10V, Jostra AG, Hirrlingen, Germany) was inserted and connected to a cardioplegia pump (SIII Double Head Pump; Stöckert, Munich, Germany) for controlled withdrawal of blood for normovolemic haemodilution. Vital monitoring of the pigs included continuous three-lead electrocardiogram, heart rate and temperature. Furthermore, a direct bladder catheterization was performed for urine sampling.

**Experimental protocol**

After all surgical preparations were completed; the animals were allowed to recover for 45 minutes before the investigational protocol was started and the first measurement was made. Progressive acute normovolemic haemodilution was induced by steps of 10 ml/kg body weight (BW) with a 1:1 exchange of blood with either HES 130 or HES 650 until a total exchange of 50 ml/kg BW was reached. The HES solution was infused into the right internal jugular vein at the same time and the same rate that blood was removed from the left carotid artery. Subsequently, uncompensated progressive blood withdrawal including haemorrhagic shock was performed by withdrawing blood from the left carotid artery in steps of 10 ml/kg BW until the death of the animal. Every period of haemodilution and blood withdrawal, respectively, was conducted over exactly 30 minutes followed by a stabilization period of 15 minutes. At baseline and after each step of 10 ml/kg BW blood exchange and blood withdrawal, respectively, serial blood gas analysis from arterial blood and central venous blood were obtained simultaneously.
Blood gas analysis

Arterial and central venous blood samples were collected using heparinized syringes (BD Present™, BD Vacutainer Systems, Plymouth, UK). Blood gas analyses as well as determination of lactate levels were performed immediately after collection using the Rapidlab 865 (Bayer Vital GmbH, Fernwald, Germany). One major calibration of the Rapidlab 865 (Bayer Vital GmbH, Fernwald, Germany) was made before starting the first measurement in every pig. Afterwards the blood gaze analyser made automatic calibrations as programmed by the manufacturer. Whole blood base excess was calculated automatically by the blood gas analyzer using the following standard (NCCLS) algorithm:

\[
BE = (1 - 0.014 \times cHb) \times [(cHCO_3^- - 24.8) + (1.43 \times cHb + 7.7) \times (pH - 7.40)]
\]

(Where BE denotes base excess, cHCO3 denotes bicarbonate, cHb denotes haemoglobin concentration and pH denotes potential of hydrogen)

In addition, whole blood base excess from arterial and central venous blood samples was calculated using the Van Slyke equation modified according to Zander 37:

\[
BE = (1 - 0.0143 \times cHb) \times [(0.0304 \times pCO_2 \times 10^{pH-6.1} - 24.26) + (9.5 + 1.63 \times cHb) \times (pH - 7.4)] - 0.2 \times cHb \times (1 - SO_2).
\]

(Where BE denotes base excess, cHb denotes haemoglobin concentration, pCO2 denotes partial pressure of carbon dioxide and pH denotes potential of hydrogen)

Statistical analysis

A trial database within Excel (Microsoft Office 2003, Microsoft Corporation Redmond, WA, US) was used to store study data. The statistical analyses were performed using SPSS® (version 13, SPSS Inc., Chicago, Illinois, USA).
The whole blood BE calculated by the Van Slyke equation modified by Zander for venous blood, as well as the whole blood BE obtained from standard blood gas analysis (RapidLab 865, Bayer Vital GmbH, Fernwald, Germany) of venous and arterial blood according to NCCLS were compared with each other. In addition, the central venous lactate levels were compared with the arterial lactate levels, both obtained by means of the RapidLab 865 (Bayer Vital GmbH, Fernwald, Germany). Continuous variables were summarized as mean ± standard deviation (SD). Differences between measurements were analyzed using an ANOVA for repeated measures with the animal as observational unit, period of time as within factor and HES group as between factor. The standard deviation of the difference between parameters within animals in the 2 periods of time (haemodilution versus haemorrhage) is presented as median (range) and was compared using the Wilcoxon’s signed rank test. Parameters are the difference between NCCLS BE arterial versus central venous, arterial versus central venous lactate and NCCLS BE arterial versus BE calculated by the Van Slyke equation modified by Zander for central venous blood. Linear regressions were performed and the coefficients R-square of determination are reported, in all regressions the equality line is also added. Corresponding p-values were obtained in an ANOVA for repeated measures with covariates (ANCOVA). P-values of 0.05 or less were considered significant.
Results

24 pigs were analyzed generating 195 values for each parameter over a time period of 390 minutes. The first 210 minutes were the period of haemodilution (6 points of time, generating 144 values for each parameter), the next 180 minutes the period of haemorrhagic shock (4 points of time, generating 51 values for each parameter). Haemodynamic parameters at the beginning were: heart rate was 95 ± 11 bpm, systolic arterial pressure 85 ± 9 mm Hg, diastolic arterial pressure 55 ± 8 mm Hg and mean arterial pressure 65 ± 9 mm Hg. Shortly before the death of the animals haemodynamic parameter were: heart rate was 152 ± 39 bpm, systolic arterial pressure 42 ± 15 mm Hg, diastolic arterial pressure 16 ± 7 mm Hg and mean arterial pressure 24 ± 11 mm Hg.

Whole blood base excess according to NCCLS: simultaneous measurements of central venous and arterial blood:

BE in arterial blood measured according to NCCLS was 2.27 ± 4.12 mmol/l, versus 2.48 ± 4.33 mmol/l (p=0.099) for BE in central venous blood measured according to NCCLS. During haemodilution (first 210 minutes) the difference between central venous and arterial base excess was 0.33 ± 0.80 mmol/l and -0.13 ± 0.97 mmol/l during haemorrhage (for the last 180 minutes) (p=0.002). The median standard deviations within animals were 0.56 (0.22 – 1.79) mmol/l during haemodilution and 0.76 (0.06 – 1.88) mmol/l during haemorrhage (p=0.355). The regression analysis showed a strong correlation between arterial and central venous BE according to NCCLS (r²=0.960, p<0.001) (figure 1) and a significant effect (r²=0.083; p=0.003) of time was found indicating, that there is some difference at late periods of haemodilution / severe acidosis (figure 2).

Figure 1
**Arterial and central venous NCCLS lactate levels:**

Lactate measured according to NCCLS in arterial blood was 2.66 ± 3.23 mmol/l versus 2.71 ± 2.80 mmol/l in central venous blood (p=0.330). During haemodilution (first 210 minutes) the difference between central venous and arterial lactate was 0.19 ± 0.29 mmol/l and -0.38 ± 0.91 mmol/l during haemorrhage (for the last 180 minutes) (p<0.001). The median standard deviations within animals were 0.11 (0.04 – 0.67) mmol/l during haemodilution and 0.67 (0.13 – 1.91) mmol/l during haemorrhage (p<0.001). There was a strong correlation between central venous and arterial lactate (r^2=0.983, p<0.001) (figure 3) and a significant effect (r^2=0.193; p=0.003) of time was found indicating, that there is some difference at late periods of haemodilution / severe acidosis (figure 4).

**NCCLS base excess versus base excess calculated by the Van Slyke equation modified by Zander:**

The calculated BE by the Van Slyke equation modified by Zander for central venous blood of 2.22 ± 4.62 mmol/l was significantly different (p<0.001) from the measured arterial BE according to NCCLS (2.27 ± 4.12 mmol/l). During haemodilution (first 210 minutes) the difference between arterial BE according to NCCLS and central venous BE calculated by the Van Slyke equation modified by Zander was 0.20 ± 0.79 mmol/l and -0.76 ± 1.22 mmol/l during haemorrhage (for the last 180 minutes) (p<0.001). The median standard deviations within animals were 0.48 (0.12 – 1.88) mmol/l during haemodilution and 1.15 (0.12 – 2.32)
mmol/l during haemorrhage (p=0.024). The regression analysis of the arterial BE according to NCCLS and central venous BE calculated by the Van Slyke equation modified by Zander shows a strong correlation ($r^2=0.942$, $p<0.001$) (figure 5).

**Figure 5**

**Discussion**

Central venous and arterial BE determined according to NCCLS showed an excellent correlation without a statistically significant difference between arterial and central venous measurements. The variation between values did not even increase during haemorrhage. Also central venous BE determined by the Van Slyke equation modified by Zander overall correlated well with arterial BE determined according to NCCLS. However, during haemorrhage, the variation between these values increased significantly. Finally, also arterial and central venous lactate levels overall correlated well, but again, during haemorrhage, the variation between values increased significantly.

At present time, arterial blood gas analysis is the gold standard for assessing the acid-base status, although there are reports on the agreement of base excess and lactate levels determined in arterial and venous blood. However, the popularity of venous blood gas analysis is low and some studies have expressed reservations regarding the accuracy of venous blood gas analysis. The most obvious advantage to obtaining a venous blood gas analysis instead of an arterial blood gas analysis is that a venous blood sample can be drawn using the same intravenous (IV) line that is used to draw blood for other lab tests, thus necessitating only one puncture. This translates into decreased costs, labour, and risk of needlestick injury to the health care provider. Furthermore, complications such as arterial laceration, haematoma, and thrombosis are all but negated with venous blood sampling.
Central venous and arterial BE determined according to NCCLS showed an excellent correlation without a statistically significant difference between arterial and central venous measurements (figure 1). Interestingly, the variation between arterial and central venous BE during haemodilution and haemorrhage was similar, and the difference between BE determined in arterial blood vs. central venous blood during haemodilution and haemorrhage, although statistically significant, was clinically irrelevant (0.33 ± 0.80 vs. -0.13 ± 0.97 mmol/l). Therefore, central venous blood can be used exchangeably with arterial blood to determine BE.

In our study we assessed the accuracy of the BE calculation by the Van Slyke equation modified by Zander. Thereby, the most important comparison is the comparison between arterial BE determined according to NCCLS vs. central venous BE determined by the Van Slyke equation modified by Zander (figure 5) since the correction introduced by Zander et al. aimed at correcting for the difference between the different oxygenation in arterial vs. venous blood in order to allow venous blood to be used for the determination of the BE.37 Overall, we found a close correlation between arterial BE determined according to NCCLS vs. central venous BE determined by the Van Slyke equation modified by Zander (figure 5). However, during haemorrhage the difference between the two BE measures (-0.76 ± 1.22 mmol/l) was greater than during haemodilution (0.20 ± 0.79 mmol/l) and, even more importantly, the variation during haemorrhage was significantly higher than in the more steady state condition during haemodilution. This is in contrast to the comparison between BE determination according to NCCLS where during haemorrhage the variation between arterial and central venous BE did not increase in comparison with haemodilution. The modification of the Van Slyke equation proposed by Zander et al. thus did not improve the correlation between the determination of BE in arterial and central venous blood according to NCCLS, on the contrary it even reduced it.
The good correlation between the arterial and central venous lactate levels we have found (figure 3) is in line with previous studies.\textsuperscript{39, 43-46} During haemorrhage, the difference between arterial and central venous lactate (-0.38 ± 0.91 mmol/l) was statistically greater than during haemodilution (0.19 ± 0.29 mmol/l) although the magnitude is of potential clinical relevance. However the variation between arterial and central venous lactate determination was significantly higher during haemorrhage than during haemodilution (figure 4). Central venous lactate levels thus can be used to assess the acid-base status, however, during haemorrhage and in unsteady states central venous lactate should be confirmed as soon as possible with an arterial lactate determination.

The limitation of this study is that we used a central venous line, with the tip of the catheter being placed in the vena cava superior. Therefore central venous blood is a rather accurate substitute of arterial BE and lactate in steady state conditions, but remains to be compared with mixed venous blood and evaluated when a global information about the behaviour of peripheral tissue is researched. Since we do not have any information about peripheral venous blood no recommendation for emergency situation in the clinical setting to use peripheral venous blood can be made. Furthermore we can only suppose that the animals even when being premedicated had a certain stress which induced these higher levels of lactate and BE, this was shown in a paper by Darrah \textsuperscript{47} where pigs had also elevated lactate levels.

**Conclusion**

Central venous blood gas analysis according to NCCLS is a good predictor for BE and lactate in arterial blood in steady state conditions. However, the variation between arterial and central venous lactate increases significantly during haemorrhage. Central venous lactate levels thus can be used to assess the acid-base status, however, during haemorrhage and in unsteady
states central venous lactate should be confirmed as soon as possible with an arterial lactate determination. The modification of the Van Slyke equation by Zander did not improve the agreement between venous and arterial BE and is therefore not physiologically nor clinically useful.

**Abbreviations**

- **BE**: base excess  
- **BEZ**: BE calculation using the approach of Zander  
- **cHb**: haemoglobin concentration  
- **FiO2**: inspired oxygen fraction  
- **Hb**: haemoglobin  
- **HCO3**: bicarbonate  
- **HES**: hydroxyethyl starch  
- **NCCLS**: National Committee for Clinical Laboratory Standards  
- **pCO2**: partial pressure of carbon dioxide  
- **SD-DIFBE**: Standard deviation of difference for BE  
- **SD-DIFLAC**: Standard deviation of difference for lactate  
- **SD-DIFBEz/BE**: Standard deviation of difference for BEz and BE
Figure legends:

**Figure 1:** Correlation between arterial and venous base excess, according to NCCLS indicating the equality line, the continuous line being the regression line. $(r^2=0.960, p<0.001)$. Boxplot for haemodilution (HD) and haemorrhage (HEM) showing the increase of imprecision (outliers not shown). *$p=0.002$ for the mean values of HD versus HEM

**Figure 2:** Evolution of the difference between venous and arterial base excess over time. $(r^2=0.083, p<0.001)$

**Figure 3:** Correlation between arterial and venous lactate, indicating the equality line, the continuous line being the regression line. $(r^2=0.983, p<0.001)$. Boxplot for haemodilution (HD) and haemorrhage (HEM) showing the increase of imprecision between arterial lactate and venous lactate (outliers not shown). *$p<0.001$ for the mean values of HD versus HEM, ° $p<0.001$ for the median standard deviations within animals between HD and HEM

**Figure 4:** Evolution of the difference between venous and arterial lactate over time. $(r^2=0.193, p<0.001)$

**Figure 5:** Correlation between arterial BE by NCCLS and venous BE calculated by Zander, indicating the equality line, the continuous line being the regression line. $(r^2=0.942, p<0.001)$. Boxplot for haemodilution (HD) and haemorrhage (HEM) showing the increase of imprecision between venous BE by Zander and NCCLS BE arterial (outliers not shown). *$p<0.001$ for the mean values of HD versus HEM, ° $p=0.024$ for the median standard deviations within animals between HD and HEM
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Acknowledgment

1. Assistance with the study: none

2. Financial support and sponsorship: Supported by departmental funds and B. Braun Medical S.A., Crissier, Switzerland

3. Conflict of interest: none
**Figure legends:**

**Figure 1:** Correlation between arterial and venous base excess, according to NCCLS - - - indicating the equality line, the continuous line being the regression line. ($r^2=0.960$, $p<0.001$). Boxplot for hemodilution (HD) and hemorrhage (HEM) showing the increase of imprecision (outliers not shown). *$p=0.002$ for the mean values of HD versus HEM

**Figure 2:** Correlation between arterial and venous lactate, - - - indicating the equality line, the continuous line being the regression line. ($r^2=0.983$, $p<0.001$). Boxplot for hemodilution (HD) and hemorrhage (HEM) showing the increase of imprecision between arterial lactate and venous lactate (outliers not shown). *$p<0.001$ for the mean values of HD versus HEM, ° $p<0.001$ for the median standard deviations within animals between HD and HEM

**Figure 3:** Correlation between arterial BE by NCCLS and venous BE calculated by Zander, - - - indicating the equality line, the continuous line being the regression line. ($r^2=0.931$, $p<0.001$). Boxplot for hemodilution (HD) and hemorrhage (HEM) showing the increase of imprecision between venous BE by Zander and NCCLS BE arterial (outliers not shown). *$p<0.001$ for the mean values of HD versus HEM, ° $p=0.024$ for the median standard deviations within animals between HD and HEM
$R^2 = 0.960$; $p < 0.001$
$R^2 = 0.983; p < 0.001$
$R^2 = 0.931; p < 0.001$