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OPERATION EVEREST II: COMPARISON OF FOUR INSTRUMENTS FOR MEASURING BLOOD OXYGEN SATURATION

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Running Head: Measurement Of Blood Oxygen Saturation

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ABSTRACT

The accuracy of four devices for measuring arterial and venous saturation (SO_2) was evaluated during a study of hypobaric hypoxia conducted with eight male subjects exposed progressively to simulated altitudes from sea level to 29,000 ft. Saturation was measured with the Lex-O_2-Con-K (galvanic cell; oxygen content (O_2 Con)/modified Siggard-Anderson Equation; Lex), IL-282 Co-Oximeter (spectrophotometric; Co-Ox), and the Radiometer ABL-300 (PO_2/Siggard-Anderson Equation; ABL-300). Non-invasive spectrophotometric measurements of SO_2 were made with an HP 47201A Ear-Oximeter (Ear-Ox). Saturation was calculated from O_2 Con. as: $SO_2 = (O_2\ Con/1.39 \times Hb) \times 100\%$. The Co-Ox, which correlates with the Van Slyke method over a wide physiological range (Maas, et al., Clin. Chem. Acta 29:303, 1970), was used as the reference method for measuring SO_2. The results were: Co-Ox vs ABL-300 (Y=0.97X+1.79,r=0.98,N=577), Co-Ox vs Lex (Y=0.86X+1.25,r=0.97,N=431), and Co-Ox vs Ear-Ox (Y=1.23X-18.0,r=0.90,N=203). Above 65%, the Co-Ox vs Ear-Ox was (Y=1.16X+11.8,r=0.92,N=92); below 65%, the relationship diminished significantly. With the exception of the Ear-Ox, each instrument compared favorably with the Co-Ox over a broad range (10-90%). In conclusion, the ABL-300 and the Lex are comparable in accuracy to the Co-Ox.

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Key Words: Blood Oxygen Saturation, Hypobaric Hypoxia

INTRODUCTION

Measurement of oxyhemoglobin saturation is essential to monitor oxygenation in clinical medicine and research. Arterial oxygen saturation (SaO_2) is used to assess the efficiency of the respiratory system for the uptake of alveolar oxygen. Mixed venous saturation reflects both oxygen uptake and metabolic rate at the tissue level. Since diseases of the pulmonary and cardiovascular systems can interfere with oxygen uptake and delivery, arterial and mixed venous saturation can be used to monitor the progression of those diseases. For example, oxygen saturations of 60% in arterial blood and 20% in mixed venous blood have been observed in patients with congenital heart disease or chronic lung disease. Consequently, the instruments used to measure saturation should be accurate over a wide range of saturations.

Blood oxygen saturations can be measured by either invasive or non-invasive methods. Invasive techniques require the removal of a blood sample from the body under anaerobic conditions. Oxyhemoglobin saturation is then measured in blood samples by either direct or indirect methodologies. Direct measurements are made in one of three ways: gasometric measurement, spectrophotometric measurement, or using galvanic cells. Indirect measurements first measure the partial pressure of oxygen (PO_2), then use the oxygen dissociation curve to extrapolate the oxygen saturation. These methods are subject to errors because the curve is affected by temperature, pH, PCO_2, and other parameters (15).

Non-invasive measurements are made using oximetry techniques which measure the absorption of light at the ear or finger tip through the skin. Since hemoglobin derivatives absorb light at different wavelengths, errors can

occur due to the scattering of light by cell bodies or the different absorption characteristics of various hemoglobin species (2,6,8). Several studies have shown close agreement between arterial saturation values determined by both invasive and non-invasive methods, such as ear and pulse oximetry when blood levels exceeded 70% saturation (9,10,11). Comparison of direct methods against the classical Van Slyke method, have shown a high correlation (P<0.01) in a range of saturations from 50-100% in non-smokers (8,15) whereas indirect methods did not correlate well below 70% saturation. No studies have compared saturation values determined by different methods over a wider range of saturations.

Recently, a study entitled "Operation Everest II" provided a unique opportunity to compare arterial and venous blood oxygen saturation values with ear oximetry measurements in human subjects at rest and during exercise from sea level to pre-selected altitudes up to 29,000 feet. Four different instruments were used to accurately measure oxyhemoglobin saturation in human blood over a larger physiological range than has ever been reported in the past.

MATERIALS AND METHODS

Operation Everest II was a study of acclimatization to hypoxia conducted with eight physically fit males who were gradually decompressed over 40 days in a hypobaric chamber to a barometric pressure of 240 mmHg. All subjects were non-smokers, had no cardiopulmonary abnormalities, and were medically screened prior to the start of the study.

The study began with measurement of baseline arterial and venous saturations at rest and during exercise at sea level. Additional blood samples were then obtained at altitudes of 12K, 15K, 20K, 25K, 27K and finally at 29K feet. Two anatomical sites for sampling of blood were used: 1) mixed venous blood from a pulmonary artery catheter and 2) arterial blood from a catheter placed in the radial or the brachial artery. Samples were drawn into sterile, airtight, 5-ml glass syringes (matched sets) which contained 0.2 ml of beef lung heparin (UpJohn Company, Kalamazoo, Michigan) to prevent clotting. The samples were drawn anaerobically after a volume was discarded to minimize mixing with deadspace fluids. Blood collection syringes were immediately placed into on ice to reduce metabolism within the sample and analyzed within several minutes. Prior to analysis, the samples were mixed well and divided anaerobically for analyses on each instrument. The blood samples were measured in triplicate with a variation of no more than 0.5% between repetitions of the same sample.

Oxygen saturation measurements were made with three instruments utilizing direct and invasive techniques: 1) Lex-O_2-Con-K (Lexington Instruments Co., Lexington, MA), 2) the Co-Oximeter (IL-282, Instrumentation Laboratory, Inc., Lexington, MA), and 3) ABL-300 Blood Gas System (Radiometer A/S, Copenhagen, Denmark). Saturation was measured directly with the Co-Oximeter and ABL-300, and calculated from the Lex-O_2-Con data using oxygen content and the Siggard-Anderson formula (14). The hemoglobin concentration used for the calculation of saturation was taken from measurement on a hemoglobinometer (Coulter Electronics, Inc., Hileah, Florida). This method of measuring hemoglobin was chosen over other methods after repeated measurements because it was not subject to errors due to handling or choice of anticoagulants. Saturations were

also measured non-invasively by an indirect method using an ear oximeter, (HP47201A Hewlett Packard Co., Lexington, MA) during resting and exercise protocols.

All the analyzers were maintained and operated in accordance with the standard operating procedures described in the operator's manuals. To ensure proper calibration and evaluation of oxyhemoglobin saturation measurements in blood samples, tonometered human blood at several oxygen concentrations was analyzed prior to any measurements of saturation. To achieve adequate equilibration blood was tonometered for 45 to 60 minutes using a large bubble Dynex-3M tonometer (Analytical Products, Inc., Belmont, CA). The gas mixtures used in tonometry were assayed by the Scholander technique (12) and were chosen to fit a range of saturations from 12% to 98%. All instruments were calibrated with these tonometered bloods and several measurements were made to ensure repeatability and accuracy of each value. These measurements provided useful assessment of each instrument's ability to measure saturation over a wide range of oxygen concentrations without the complicating physiological changes in the resting and exercise blood samples.

All raw blood-sample data were examined for outliers by taking the means of triplicate samples and using a margin of ± 2 standard deviations around the best fit line for each instrument's data. The best fit line was determined from all data collected with all comparisons made on each instrument used in this study. The oxygen saturations, as measured by each instrument, were compared graphically on x-y plots against Co-Oximeter. Correlation coefficients, means, slopes, and y-intercepts were calculated using BMPD software packages on a Vax 11/780 computer (Digital Equip. Co., Maynard, MA.).

The data from the ABL-300, Lex-O_2-Con, and Ear-oximeter were compared to the Co-Oximeter(Co-Ox) because the Co-Ox had the best correlation coefficient and provided the smallest standard deviation, when compared with all instruments using mean saturation values from triplicate samples. Oxygen saturations measured with ABL-300 and Lex, were compared to the Co-Ox and correlation coefficients were obtained from analysis of variance equations.

RESULTS

Several hundred measurements of oxygen saturation were made using four the instruments. Mean values for arterial and mixed venous samples measured on the Co-Oximeter and the Radiometer ABL-300 (Fig.1) yielded a correlation coefficient of R=0.98 (N=577). This was the highest correlation of all the instruments compared in this study. Values showed a linear relationship within a range of 10 to 90%, with an equation for the line depicted by this relationship as: Y=0.97X +7.19. The slope is not significantly different from the line of identity, where as the intercept is significantly elevated above this line (P<0.001).

A similar relationship was also observed for the Co-Oximeter and Lex-O_2-Con (Fig. 2) which yielded a correlation coefficient of R=0.97 (N=431). The equation for the line depicted by this relationship is: Y=0.86X +1.25. The slope in Figures 1 & 2 are similar, however, the intercepts are significantly different when compared to the line of identity (P<0.01).

The relationship between the Co-Oximeter and the Hewlett Packard ear oximeter (Fig.3) yielded a correlation of R=0.90 (N=203), which was the lowest correlation between the instruments. The equation for the line depicted by this

relationship is: Y=1.23X-18.0. The arterial saturations were linear within a range of 65 to 90%. When these values between 65% and 90% were compared the correlation coefficient improved to R=0.92 (N=92). The equation for the line depicted by this relationship is: Y=1.16X+11.80. The slopes and intercepts in figures 3 & 4 are significantly different from those obtained in the other comparisons when compared to the line of identity (P<0.001).

DISCUSSION

The purpose of this study was to examine the differences in oxygen saturation with four clinical instruments over a wide range (10-90%) and in an area of the oxyhemoglobin dissociation curve where small changes in partial pressure of oxygen (PO_2) resulted in large differences in SaO_2. We have reported only the saturation values measured in the four instruments below 90% saturation. Measurements above 90% are well-documented in the literature and all the instruments have been shown to be very accurate above this value.

The results from the Co-Oximeter and the ABL-300 were in good agreement throughout a wide range of saturations, although the ABL-300 consistently overestimated (P<0.001) saturations through this range (10-90%). While the error is slightly greater with the ABL-300 as it approaches lower arterial saturations, it is less likely to have operator-induced errors because of its automated sampling mechanism. One explanation for this consistent overestimation may be due to the fact that the ABL-300 measures the PO_2 directly instead of SaO_2. The calculation of SaO_2 from PO_2 may result in overestimation due to differences in various factors such as temperature, pH, PCO_2, red cell 2-3 di-phospho-glycerate and carboxyhemoglobin concentration, which are known to effect the oxygen dissociation curve. In addition, errors

may result from using standard variables for hemoglobin concentration or oxygen binding capacity when saturation is calculated with the Siggard-Anderson equation. In several studies (6,8,14), the calculated values of SaO_2 derived from PO_2 were shown to be in error. Possibly one of the factors above is responsible for the overestimation error in the ABL-300. We have no definitive data to identify which factor might be responsible for any error in the ABL-300. Further studies using tonometered blood over as wide a range of saturations and different correction equations would possibly identify where the error lies. We are confident that a calibration error could not have resulted in the instrument's overestimation of oxygen saturation during this study. Calibrations were performed with tonometered human blood as well as quality control standards (Radiometer Quali-check[TM] for normal, acidemia, and alkalosis ranges) prior to any blood gas measurements. Further, the calibrations were performed every 30-minutes (displayed and recorded) and were within the range of these arterial and venous blood oxygen saturations.

As mentioned previously, several factors which may be responsible for errors in instruments which measure PO_2 and calculate SO_2 have been assessed in the past for their effect on the oxygen dissociation curve. One in particular, carboxyhemoglobin (HbCO) concentration, has received considerable attention in the literature. It is unlikely that HbCO caused errors in the measurement of PO_2 in this study because all these subjects were non-smokers and had normal blood levels of HbCO during initial medical screening. However, severe exercise and hypoxia has been shown to increase the level of carboxyhemoglobin (2,3). Analyses of carboxyhemoglobin and SaO_2 values from one of these studies using the Co-Oximeter has revealed a 3 to 8 % decrease in oxygen saturation when 5% HbCO is induced. Data from these studies has also revealed a small

deviation of the normal oxygen dissociation curve with low levels of HbCO when induced into normal subjects. A correlation between the percent HbCO and the amount of the shift was also shown (9) and HbCO does in fact shift the oxygen dissociation curve to the left. This shift in the curve, caused by HbCO, can result in errors when the measurement of oxygen saturation is made during light exercise. However, during severe exercise, the HbCO can be elevated significantly and the result is an even greater overestimation of blood oxygen saturation. Furthermore, HbCO concentration was measured on each blood sample with the Co-Ox in all subjects during this study and found to be negligible.

The relationship as depicted by the equation for the lines of the Co-ox and the Lex-02-Con revealed a consistent error of underestimation of SaO_2 as the level of oxygenation increased. The regression line deviates noticeably from the line of identity above 45% saturation. This deviation may be due to an infusion of a saline solution which was tonometered with a gas mixture containing ten percent cyclopropane, 20 percent sulfur hexaflouride and 70 percent ethane and infused intravenously into these subjects. The galvanic cell of the Lex-02-Con has been shown to be inaccurate in the presence of certain anesthetic gases. We have no direct evidence to support that theory, since the Lex-O_2-Con has not been evaluated with this gas mixture. Since direct measurement devices are not affected or dependent on PO_2, and they generally provide a better assessment of SaO_2. The correlation coefficient is somewhat better with the ABL-300 than with the Lex-O_2-Con when both are compared with the IL-282 Co-Oximeter, but this difference is not statistically significant. It should be mentioned that the Lex-O_2-Con does not read SaO_2 directly. It measures oxygen content, and a conversion to SaO_2 is performed using the Siggard-Anderson equation (14). The Lex-O_2-Con should not have as

great an error as the ABL-300 when calculating SaO_2 as long as the hemoglobin is accurately measured in each sample.

To calculate the oxygen content both the IL-282 and the Lex-O_2-Con used an oxygen binding capacity of 1.39 ml/g. This is a well accepted value for the oxygen binding capacity for hemoglobin in blood in normal humans. Dijkhuizen (3) has reported a value of 1.37 ml/g for the oxygen binding capacity in blood. This change may only be necessary when using different blood species.

When the Co-Oximeter and Ear oximeter were compared, the Ear-Oximeter noticeably underestimated oxygen saturation (P<0.001). These data reveal that below 65% saturation, the ear oximeter does not accurately determine SaO_2 when compared to the three invasive clinical devices used in this study. While the results were linear for saturations greater than 65%, the greatest deviation from the best fit line was below 45% . Thus the ear oximeter is not a useful device for measuring saturations below 45% unless corrections are applied to the data. Corrections for ear oximeter values below 65% have been reported in the literature (5); however, we applied no corrections to these data.

In two previous studies (10,11), it was shown that the ear oximeter accurately measures SaO_2 under conditions of steady-state hypoxia at levels greater than 65% when compared to spectrophotometric methods. Rebuck et al.(10) also measured SaO_2 levels in arterial blood samples spectrophotochemically during hypoxic studies. They found a high correlation between oximetry and spectrophotometric measurements of oxygen saturation above 70%. The correlation coefficient for these relationships is R=0.97 and this relationship did not vary more than ±3 percent of the measured arterial saturation (10,11). Some evidence suggests that ear-oximeters are less accurate because the capillary blood supply is subject to peripheral vasoconstriction in response to hypoxia

(11). This results in greater underestimation of SaO_2 at low levels of oxygenation. Some of these problems with oximetry can be eliminated by knowing the characteristics of the instrument, insuring vasodilation of the ear lobe to provide adequate blood flow and proper placement of the probe. Despite these errors, the ear oximeter is useful as a continuous and non-invasive method to provide an estimation of SaO_2 in specific situations when oxygenation is above 65% and changing during mild hypoxic stimuli.

In comparison studies, the Co-Oximeter and the Lex-O_2-Con have been compared to the classical direct measurement method, the Van Slyke (1,13,15). The Van Slyke is the classical method by which all other instruments are judged when blood oxygen saturation was measured in the respiratory laboratories during the past 100 years. However, the instruments used in the present study revealed good performance criteria that provide the clinician or researcher with the valid values over a wide range of saturations, easier operation, and smaller sample size. Their advantage over the classical method is speed, accuracy, small sample volumes, and less skill to perform measurement of SaO_2.

ACKNOWLEDGEMENTS

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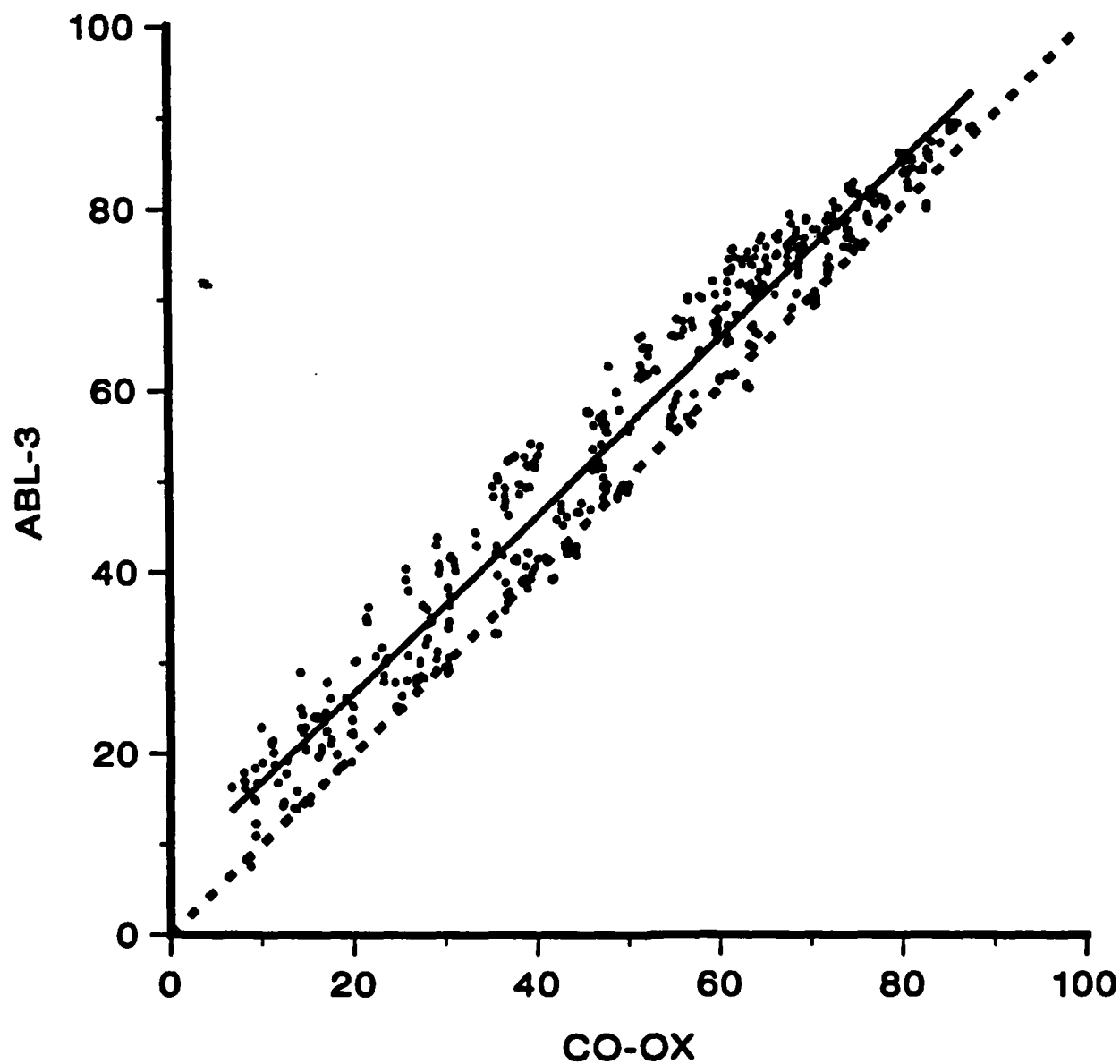
LEGEND FOR FIGURE ONE:

Fig.1 Comparisons of simultaneous arterial and venous O2 saturations (N=577) with the ABL-300 (ordinate) and the Co-oximeter (abscissa) in 9 subjects during exposure to hypobaric hypoxia at rest and during maximal exercise. Solid line is the line of regression. Dashed line is the line of identity.
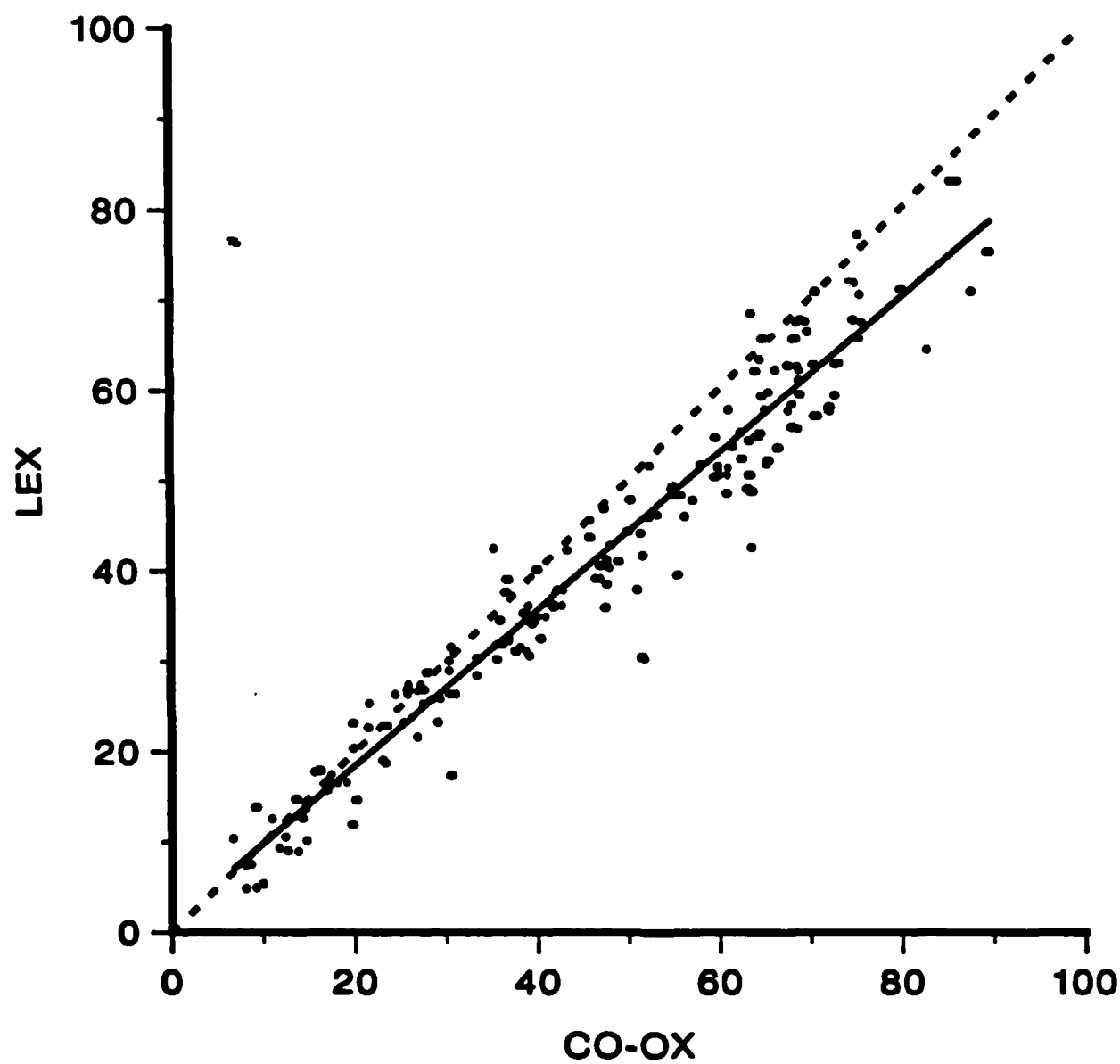
Y = .97X + 7.19

r = .98

n = 577

LEGEND FOR FIGURE TWO:

Fig.2 Comparisons of simultaneous arterial and venous O2 saturations (N=431) with the Lex-O2-con (ordinate) and the Co-oximeter (abscissa) in 9 subjects during exposure to hypobaric hypoxia at rest and during maximal exercise. Solid line is the line of regression. Dashed line is the line of identity.
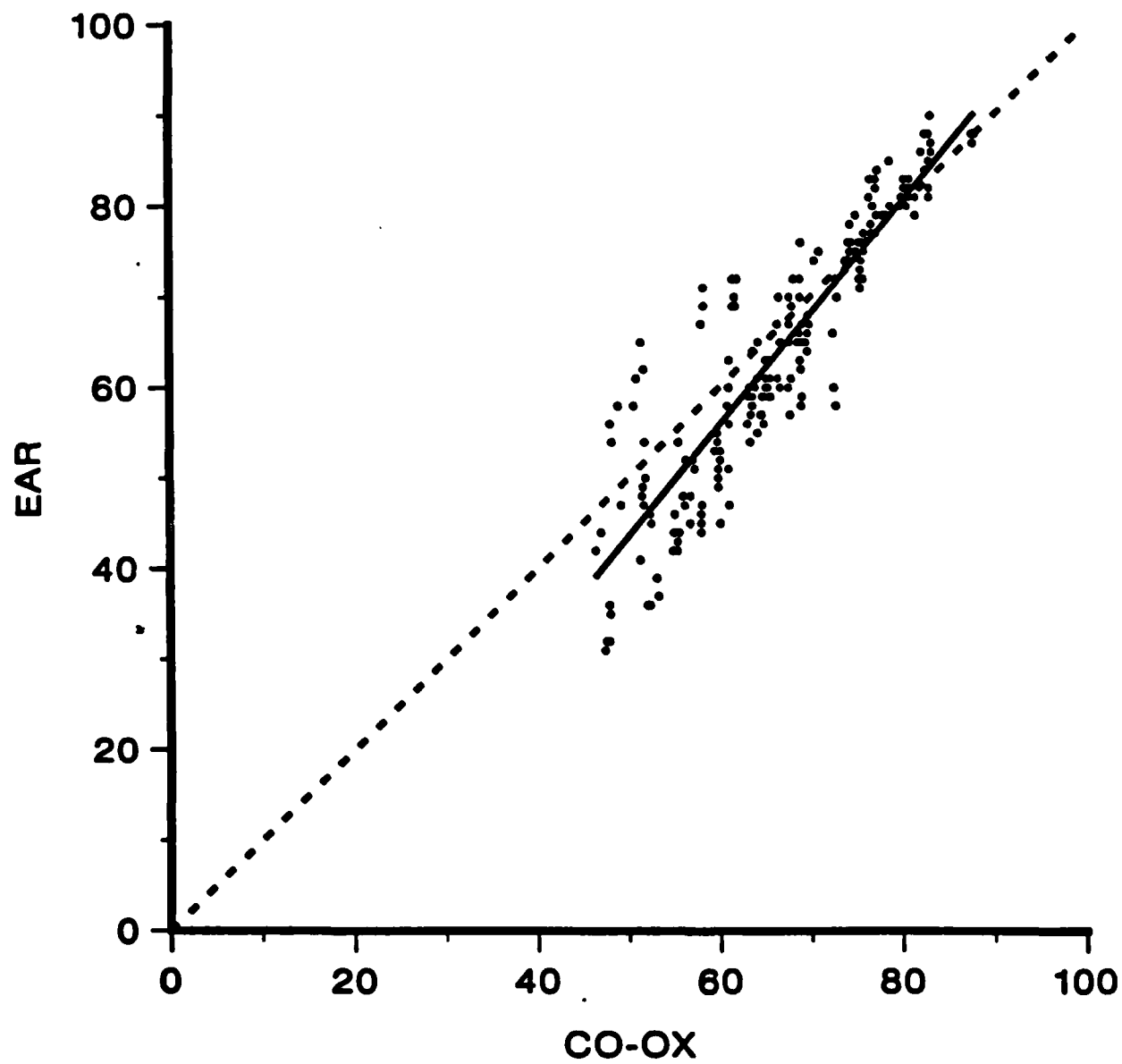
LEGEND FOR FIGURE THREE:

Fig.3 Comparisons of simultaneous arterial and venous 02 saturations
(N=203) with the ear oximeter (ordinate) and the Co-oximeter (abscissa)
in 9 subjects during exposure to hypobaric hypoxia at rest and during
maximal exercise. Solid line is the line of regression. Dashed line is the
line of identity.
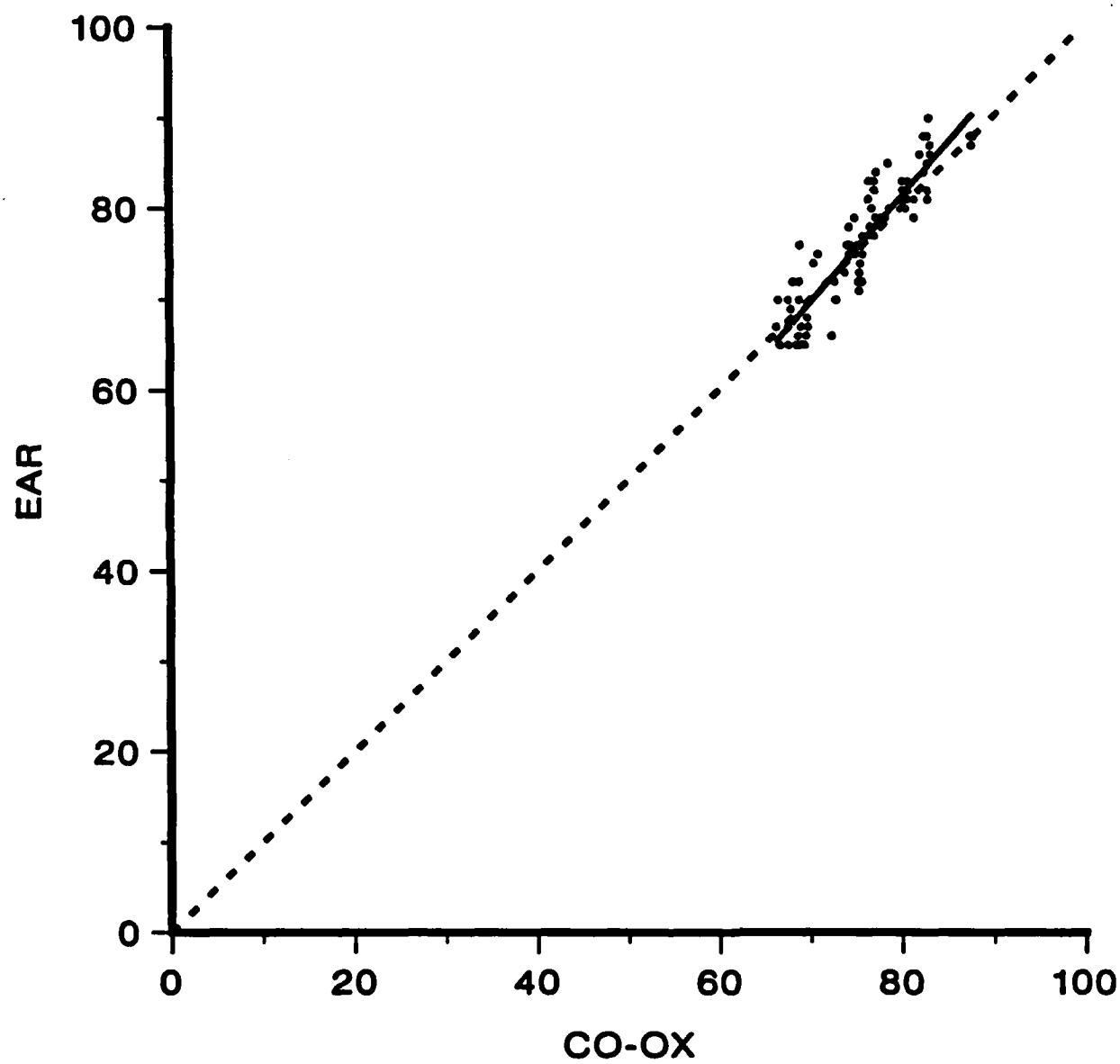
$Y = 1.23X - 17.96$

$r = .90$

$n = 203$

LEGEND FOR FIGURE FOUR:

Fig.4 Comparisons of simultaneous arterial and venous O2 saturations (N=92) with the ear oximeter (ordinate) and the Co-oximeter (abscissa) in 9 subjects during exposure to hypobaric hypoxia at rest and during maximal exercise. Abridged range of 65%-90%. Solid line is the line of regression. Dashed line is the line of identity.

$$Y = 1.16X - 11.80$$
$$r = .92$$
$$n = 92$$

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