Retinal Oxygen Saturation in Patients with Systemic Hypoxemia

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Purpose. To assess spectrophotometric oximetry across a broad range of arterial saturation levels and to study the effect of chronic systemic hypoxemia on retinal oxygen extraction.

Methods. The study included 16 patients with Eisenmenger syndrome, a cyanotic cardiac defect, and 17 healthy volunteers. Oxygen saturation in selected major retinal arteries and veins was assessed using noninvasive spectrophotometric oximetry. Arterial blood gases were determined within 1 day of the ophthalmic examination in blood samples from the femoral artery.

Results. The retinal arterial oxygen saturation of 81% ± 9% (mean ± SD) in patients with Eisenmenger syndrome was subnormal and demonstrated more interindividual variation than the 93% ± 3% observed in healthy subjects ($P < 0.001$). A comparable difference was found for the respective retinal venous oxygen saturations of 44% ± 12% and 59% ± 5% ($P < 0.001$). Fractional arteriovenous oxygen extraction was comparable between the two groups (37% ± 6% and 34% ± 5%, respectively; $P = 0.29$). Retinal and femoral artery oxygen saturation were correlated ($\rho = 0.82$; $P < 0.001$), the former approximating the latter at least as well as fingertip oximetry.

Conclusions. When compared to arterial blood gas analysis of blood samples drawn by arterial puncture, the gold standard in the field, fundus oximetry was found to be in good overall agreement with the arterial blood samples. Blood flow measurements will be needed to determine whether the systemic hypoxia is completely compensated, as suggested by oxygen extraction being comparable between the two groups. (*Invest Ophthalmol Vis Sci.* 2011;52:5064–5067) DOI:10.1167/iovs.11-7275

Retinal hypoxia is a characteristic of several retinal diseases and believed to be a major pathogenic factor conditions where retinal blood flow is disrupted, such as retinal artery and vein occlusion. Abnormal retinal tissue oxygenation is also believed to be involved in the pathogenesis of other retinal diseases, such as diabetic retinopathy.[1,2] A reliable method of measuring oxygen saturation in the retina is therefore of potential value for the study of the pathogenesis of retinal diseases and for their management.

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Hemoglobin and oxyhemoglobin have different absorption spectra that intersect at several isosbestic points over the visible to near-infrared range. Retinal vessel oximetry can be performed by comparing the light absorption in the blood in the retinal vessels at selected wavelengths, for instance an isosbestic wavelength and a wavelength where the two absorption spectra are distinctly different.[3] A method based on spectral snapshot imaging has previously been tested in healthy subjects and glaucoma patients.[4–7]

Retinal vessel oximetry has not previously been tested against an ulterior or previously validated method. In the present study, we examined patients suffering from varying degrees of chronic systemic hypoxia and compared retinal blood oxygen saturation assessed by spectrophotometry with conventional blood gas analysis of arterial blood samples.

Subjects and Methods

The study included 16 clinically stable adult patients with Eisenmenger syndrome and 17 healthy volunteers. Eisenmenger syndrome is a cardiac condition where a congenital left-to-right shunt produced by a congenital atrial or ventricular septum defect or a patent ductus arteriosus is reversed after the patient has developed secondary pulmonary hypertension so that a right-to-left shunt and systemic hypoxia are produced.[8–10] Patients with Eisenmenger syndrome have an abnormally low systemic arterial oxygen saturation at rest that is further aggravated by exercise.[11] In severe cases, exertion can be invoked by simple daily activities. Fifteen of the Eisenmenger patients were being treated for pulmonary hypertension with sildenafil, bosentan, or sitaxentan or a combination of these drugs. The study included one eye from each participant.

Retinal oximetry was made with the subjects seated at rest using a prototype commercial instrument (Oxymap Retinal Oximeter P3; Oxymap ehf, Reykjavik, Iceland) consisting of a fundus camera (Canon CF-60u; Canon Inc., Tokyo, Japan) that acquires images simultaneously (Alta U2 digital camera, Apogee Instruments Inc., Roseville, CA) at two different wavelengths (605 and 586 nm) selected by a beam splitter (Cairn Optosplit II; Cairn Research, Kent, UK) and a computerized fundus image storage and analysis system. Software automatically identifies retinal blood vessels and estimates retinal blood oxygen saturation by spectrophotometric point-by-point analysis of the reflectivity and optical density of the vessels at the two wavelengths. Variations in optical density with changing hemoglobin oxygen saturation occur at 605 nm but not at 586 nm.[5,12]

Transcutaneous pulse oximetry with a fingertip device was made continuously during the eye examination (MD300C2; Beijing Choice Electronic Technology Co., Beijing, China). Data reported below were read out during fundus oximetry. Participants underwent a full ophthalmologic examination by an ophthalmologist (ICM). One patient in the hypoxemic group had a history of glaucoma and was treated with prostaglandin and timolol/brinzolamide combination therapy. No other participant had history of eye diseases in the included eye. All included eyes had clear optical media.

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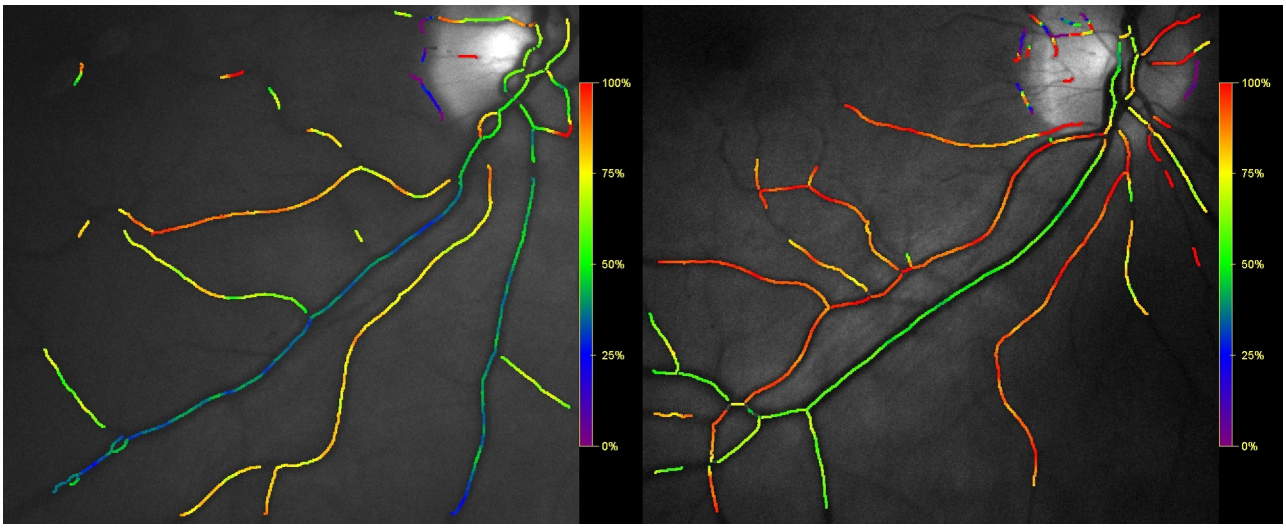

FIGURE 1. Fundus photographs overlaid with color-coded oxygen saturation values in a patient with systemic hypoxemia secondary to Eisenmenger syndrome (*left*) and a healthy volunteer (*right*).

Pupils were dilated before oximetry using topical tropicamide 0.5% (Mydriacyl; Alcon Couvreur NV, Puurs, Belgium) and phenylephrine hydrochloride 10% (Metaoxidrin; Sygehus Apotek Danmark, Copenhagen, Denmark). Retinal blood oxygen saturation was calculated for major arteries and veins of the superior and inferior temporal vascular arcades using proprietary software (Oxymap Analyzer, version 1.0t; Oxymap ehf). Results reported below represent averages of three consecutive image pairs. The arteriovenous saturation difference was calculated for each subject and then a mean value for each group was calculated. Femoral arterial blood samples were obtained from the Eisenmenger patients during routine cardiac catheterization within 24 hours of the ophthalmic examination and analyzed immediately using a conventional blood gas analyzer (Radiometer A/S, Husum, Denmark). Arterial blood samples were not obtained from the healthy subjects.

Statistical analyses were made using the R software package, version 2.12.1 (The R Foundation for Statistical Computing, www.r-project.org). Two-tailed *P* values were obtained from Mann–Whitney rank sum tests. The level of statistical significance was set at $P < 0.05$. The study was conducted according to the most recent amendments to the Declaration of Helsinki and in adherence to good clinical practice guidelines. The study was approved by the Danish National Committee on Biomedical Research Ethics (protocol number: H-A-2009–014) and written informed consent was obtained from all participants.

RESULTS

Femoral arterial blood oxygen saturation in Eisenmenger patients was consistently subnormal and broadly distributed around a mean of 81% (SD, 4%; range, 74–92%; normal range, 95–100%; Fig. 1; Table 1).

Retinal arterial oxygen saturation was correlated with femoral oxygen saturation ($\rho = 0.82$; $P < 0.001$; Spearman rank correlation test; Fig. 2). There was no detectable effect of age on any measure of oxygen saturation. The two patients with the lowest femoral artery saturations had even lower retinal artery saturations, the discrepancy between the modalities being most pronounced in these two patients (Figs. 2 and 3).

Pulse oximetry consistently showed higher oxygen saturation values than did femoral arterial blood gas analysis, and retinal artery saturation was closer to the femoral artery saturation in the majority of patients.

The SD of the saturation values between consecutive images was 1.80% (mean; range, 0.3–6.0%) in arteries and 3.1% (mean; range 0.3–12.4%) in veins in Eisenmenger syndrome patients versus 1.2% (mean; range, 0.1–4.7%) and 2.6% (mean; range, 0.0–6.5%), respectively, in healthy subjects.

The arteriovenous difference in saturation was 37% ± 6% in Eisenmenger patients and 34% ± 5% in healthy subjects ($P = 0.29$; Mann–Whitney test; Table 1).

DISCUSSION

The severely systemically hypoxic patients in this study had subnormal and highly variable blood oxygen saturation levels in their retinal veins and arteries, as determined by spectrophotometric oximetry. When compared to arterial blood gas analyses of blood samples drawn by arterial puncture, the gold standard in the field, fundus oximetry was in good overall

TABLE 1. Demographics and Oxygen Saturation Values for Patients with Eisenmenger Syndrome and for Healthy Volunteers

	Systemic Hypoxemia	Healthy Subjects	*P*
Retinal artery oximetry, % (mean ± SD)	81 ± 9	93 ± 3	<0.001*
Retinal vein oximetry, % (mean ± SD)	44 ± 12	59 ± 5	<0.001*
Retinal arteriovenous saturation difference, % (mean ± SD)	37 ± 6	34 ± 5	0.29*
Fingertip pulse oximetry, % (mean ± SD)	88 ± 5	98 ± 0.2	<0.001*
Femoral artery blood gas analysis, % (mean ± SD)	83 ± 5	—	—
Age, y (mean [total range])	50 [25–77]	38 [22–71]	0.01*
Sex distribution (female/male)	14/2	6/11	0.007†

* Mann-Whitney rank sum test.
† Chi-square test.

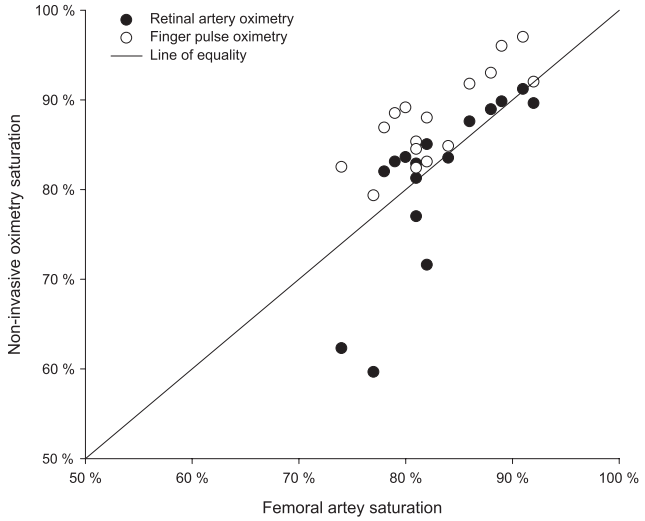

FIGURE 2. Noninvasive arterial oxygen saturation estimated by retinal oximetry (*filled circle*) and finger pulse oximetry (*empty circles*) in relation to saturation measured by blood gas analysis of a femoral artery blood sample in 16 patients with systemic hypoxemia secondary to Eisenmenger syndrome.

agreement with the arterial blood samples. Retinal oxygen saturation was diminished in both retinal arteries and veins, the latter being decreased in proportion to the decrease in femoral artery saturation found in patients with Eisenmenger syndrome. This suggests that systemic hypoxia was fully compensated, although measurements of volumetric blood flow and blood hemoglobin concentration would be needed to test this hypothesis.

A recent study using methods similar to ours found that venous oxygen saturation is higher than normal in diabetic retinopathy, whereas retinal arterial oxygen saturation was normal. This suggests that oxygen extraction from retinal vessels may be decreased in diabetic retinopathy.[13] In contrast, the arteriovenous oxygen gradient is higher than normal in central retinal vein occlusion, indicating that slow blood flow is partially compensated by increased oxygen extraction.[14]

The normal arteriovenous oxygen difference in patients with Eisenmenger syndrome indicates that retinal adaption to systemic hypoxia can occur. A previous study from our group suggests that it also happens in people living in low atmospheric oxygen concentration high above sea level.[15]

Retinal oximetry is based on using the reflection of visible light from vessels and the surrounding background to assess the light absorption of the corresponding columns of blood at two different wavelengths. Fingertip oximetry is based on using the absorption of red and infrared light to assess arterial blood oxygen saturation by diffuse transmission of light through the intact extremity, using the arterial volumetric pulsations to exclude signals from other tissue types. Blood gas analysis is based on drawing a sample of arterial blood from a major artery, usually the radial artery on the wrist, protecting the sample from exposure to the atmosphere, and injecting the sample into an instrument where oxygen saturation is measured by multispectral spectroscopy of hemolyzed blood in a controlled environment. Of these methods, the latter is best validated and is the standard for critical care. It is therefore to be considered the gold standard method in this study.

Limitations of the present study include retinal oximetry not having been performed simultaneously with arterial blood sampling. Some of the discrepancies between the methods used in this study may arise from the extremely poor condition of some of the patients. Eisenmenger patients can be exhausted for hours after a short walk. This may help explain why the two most severely affected patients had markedly lower retinal oxygen saturations when seated in front of the oximeter that when resting in the recumbent position during a cardiac catheterization procedure.

The patients with the lowest femoral artery saturation levels were found to have higher finger pulse oxygen saturations than their femoral saturations. As has been previously described, finger pulse oximeters are less accurate at low systemic oxygen saturation levels and they tend to overestimate the oxygen saturation at levels below 80%.[16–18]

Blood flow measurements will be needed to determine whether the systemic hypoxia is completely compensated, as suggested by oxygen extraction being comparable between the two groups.

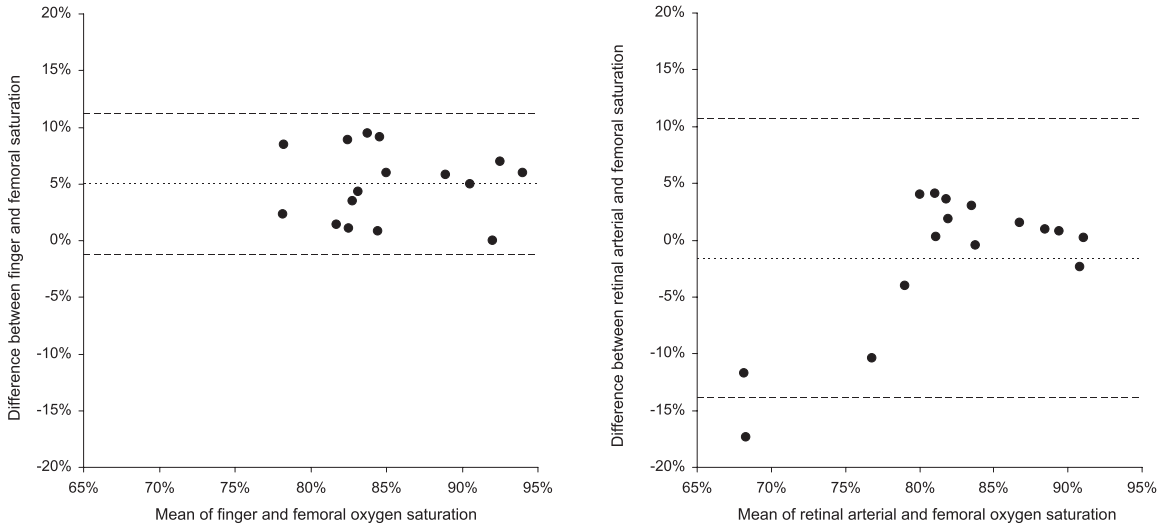

FIGURE 3. Bland–Altman plots comparing femoral artery blood gas analysis to finger pulse oximetry (*left*) and retinal artery oximetry (*right*) in 16 patients with systemic hypoxemia secondary to Eisenmenger syndrome. *Short dash lines* indicate ± 1.96 SD, and *dotted lines* indicate mean difference between measurements.

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