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Coronary artery bypass surgery independently associates with retinal vascular oxygen saturation.

Running title: *Retinal non-invasive oximetry in CABG patients.*

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Abstract

Purpose

The retinal vasculature is the only part of the microcirculation that can be directly studied by non-invasive imaging. Based on the hypothesis that the systemic circulation is reflected in retinal vessels, we investigated if coronary artery bypass grafting (CABG) is related to changes in retinal vascular oxygen saturation ($rSatO_2$).

Methods

Retinal metabolism was evaluated by Oxymap T1, which simultaneously captures two retinal images at different wavelengths measuring the retinal arteriolar ($raSatO_2$) and venular ($rvSatO_2$) oxygen saturation. 3 to 4 days after surgery, we measured the median $rSatO_2$ after CABG in 38 patients and in 39 healthy controls (operated for cataract).

Results

CABG patients had higher $raSatO_2$ (median ± standard deviation 93.1 ± 6.7% vs. 90.5 ± 11.2%, p=0.001) and $rvSatO_2$ (57.4 ± 8.3% vs. 53.5 ± 15.4%, p=0.048) compared to healthy controls. In multivariable linear regression models, $raSatO_2$ independently associated with CABG (coefficient +3.6% in CABG patients, p=0.007), and $rvSatO_2$ correlated with gender (coefficient +9.4% for females, p=0.001) and CABG (coefficient +8.2% in patients with CABG, p=0.001).

Conclusions

Comparing patients with and without cardiovascular disease, $raSatO_2$ and $rvSatO_2$ positively and independently associated with CABG, suggesting their potential as non-invasive markers for coronary large artery disease.

Keywords:

Retinal microcirculation, retinal oximetry, CABG, imaging, oxygen metabolism.

Introduction

The transparent eye enables the only direct in vivo inspection of the human microcirculation. The metabolism of the retinal microcirculation can be measured non-invasively with retinal oximetry and provides information on oxygen saturation in arterioles and venules of the central nervous system (Eliasdottir 2018). In 1959, the first non-invasive measure of retinal arteriolar ($raSatO_2$) and venular ($rvSatO_2$) oxygen saturation were described by Hickam and Frayser (Hickam et al. 1959). With technological developments over the years, Beach et al. developed the dual-wavelength system, as we know it today (Beach et al. 1999; Geirsdottir et al. 2012; Hardarson 2013). Previously, several studies associated changes in retinal oxygen saturation with ocular diseases including diabetic retinopathy, glaucoma and central retinal vein occlusions (Hardarson 2013; Rilven et al. 2017; Stefánsson et al. 2017).

In recent years, attention to utilize retinal oximetry beyond ocular disorders included studies in Alzheimer's disease, chronic obstructive pulmonary disease, and Eisenmenger syndrome (Traustason et al. 2011; Einarsdottir et al. 2016; Eliasdottir et al. 2017; Van Keer et al. 2018). However, retinal oximetry has not been evaluated as a marker in ischemic cardiovascular disease. Ischemic heart disease often results from occlusion of one or more large coronary arteries, and it remains a leading cause of death worldwide (Collaborators 2017). Coronary artery bypass grafting (CABG) is a well-established method for re-vascularization with a positive outcome in general, but close monitoring of vital parameters is crucial in the aftermath. The

properties of retinal oximetry in relation to ischemic heart disease are interesting, and if CABG is reflected in the retinal circulation the method might be used to non-invasively assess and monitor the risk of developing ischemic heart disease.

The retinal blood circulation is characterized by a slow blood flow ensuring optimal conditions for a high oxygen extraction (Eliasdottir 2018). The auto-regulatory properties of retinal arterioles ensure this by keeping a relatively constant blood flow. Retinal tissue is highly metabolically active represented by a higher arteriovenous difference (AV-difference) in oxygen concentration than in other organs (Eliasdottir 2018).

In severe illness and injury, central and vital organs are perfused at the expense of peripheral tissues due to hemodynamic stress (Denninghoff et al. 1998). Since the retinal circulation is part of the central nervous system circulation (Eliasdottir 2018), we hypothesize that there will be an increase in retinal perfusion related to major vascular surgery with the assumption that CABG is a considerable traumatic intervention.

We therefore investigated whether CABG is associated with alterations in retinal arteriolar and venular oxygen saturation.

Method and Materials

The study was performed at Odense University Hospital, Odense, Denmark, from March 2018 to December 2018.

We included 85 Caucasian participants who were either operated for CABG (cases, n=43) or cataract (cardiovascular healthy controls, n=42).

Patients were recruited at the Department of Cardiac, Thoracic and Vascular Surgery, Odense University Hospital, around day 4 after surgery.

Examinations were performed when pace-wires and monitoring scope had been discontinued, which in general was 4 to 6 days after surgery.

Recruitment of controls took place at the Department of Ophthalmology, Odense University Hospital on the day of cataract surgery, and examinations were performed on the following day.

In both groups, we excluded patients with age <18 years, mental inability, retinal disease and need for re-surgery. Cases were CABG patients who had

coronary surgical intervention alone, and were excluded if they had combined CABG and valve replacement surgery. Furthermore, controls were excluded if they had any history of heart disease. Demographic and other characteristics of case and control individuals are summarized in Table 1.

Ocular mydriasis was achieved with tropicamide 1% and phenylephrine 10%. While waiting for adequate pupil dilation, the patients provided a full medical interview including history of smoking, disease, height and weight as well as medicine consumption. In addition, information from the patient records was added.

Further examinations included blood pressure as a mean of 3 sphygmomanometric measurements on the right upper arm (Omron M6 AC, Kyoto, Japan), and blood samples for the determination of haemoglobin 1Ac (HbA1c), cholesterol profile and triglycerides (Table 1).

Retinal oximetry imaging (Oxymap model T1, Oxymap, software V.2.4.2, Reykjavik, Iceland) was captured after two minutes in dimmed light. We selected the eye estimated to have the best potential for high quality imaging. Disc centred images were obtained with an external dim fixation light. Images with overall quality above six (scale: 0-10) were included.

The retinal oximeter is based on a conventional fundus camera. Attachment of an image splitter, containing two narrow band-pass light filters, allows the acquisition of two fundus images taken simultaneously, at two different wavelengths. One wavelength is sensitive to changes in oxygen bound to haemoglobin (non-isobestic 600nm) and the other is insensitive (isobestic 570nm). The oximeter utilizes the fact that a vessel with oxygenated blood and a vessel with deoxygenated blood have different optical densities and, thus, different light absorbance. The Oxymap analyser software automatically generates an optic density-ratio linearly related to differences in haemoglobin oxygen saturation.

The principles of the retinal oximeter are described in more detail elsewhere (Geirsdottir et al. 2012; Hardarson 2013), and, the reproducibility in healthy and diseased retinas has been tested by others (Hardarson et al. 2006; Palsson et al. 2012; Türksever et al. 2015).

The grading analysis was done in accordance with a pre-specified protocol by a trained grader (SD). Two rings were semi-automatically placed around the optic disc. The inner ring was manually placed 30 pixels from the edge to avoid confounding reflection from the optic disc. The outer ring, with 3 times the diameter of the inner ring, was placed automatically. All calculations were performed in the area in between the two rings (Figure 1A and 1B). The largest arteriole and venule for each quadrant were identified and traced starting most proximally from the inner ring. The vessels were traced at an interval between 50-200 pixels until the first branching point. Second-order branches were measured when the vessel length of the proximal part was less than 50 pixels. From each patient, the $raSatO_2$ and $rvSatO_2$ was calculated as a mean of all 4 quadrants.

Previous studies found an association between increased vessel diameter and artefactual low measurement of vessel saturation (Beach et al. 1999; Hammer et al. 2008). The Oxymap analyser software has a built in correction tool to compensate for vessel diameter that lowers the risk of artifactual decreased vessel saturation, however, it has not been sufficiently documented that the software is fully independent from vessel diameter.

Based on a pre-specified protocol, the semi-automatic software VAMPIRE (Vessel Assessment and Measurement Platform for Images of the REtina, The Vampire Group, Edinburgh, United Kingdom) was used to calculate retinal arteriolar and venular vessel diameters. The method is explained to detail elsewhere (Perez-Rovira et al. 2011; Emanuele Trucco & MacGillivray 2015) and will only be briefly outlined here.

Initially retinal landmarks were automatically located, including the centre and outer diameter of the optic disk and the macula centre. This enabled the establishment of a coordinate system with circular zones A (0-0.5 disc diameters from the optic disc centre), B (between 0.5-1.0) and C (between 0.5-2.0) around the optic disc. Vessels were automatically traced as arterioles or venules, ranging from zone A and peripheral to zone C creating a skeletonized pattern. Manual correction was made when the automatic localization of the optic disc and macula as well as the vessel tracing was not on point. In some cases traced vessels were erased, when it was unclear

which vessel type was represented, and when VAMPIRE misinterpreted an artefact or the underlying choroid layer as a retinal vessel.
Finally, the software automatically calculate the central retinal arteriolar and venular equivalents (vessel diameter) as a mean of the biggest six retinal arterioles and venules coursing through zone B.

The study was approved by the regional ethical committee (project-ID: S-20170205) and The Danish Data Agency (journal no.: 18/29227) and was performed in accordance to the Declaration of Helsinki and good clinical practice. All patients participated voluntarily and gave written consent on an informed basis.

Continuous variables are presented as medians and categorical variables are presented as percentages. Differences between cases and controls were tested by Mann-Whitney U test and Chi-square test used for continuous and categorical data, respectively.
Uni- and multivariable linear regression model adjusted for age and gender was used to test the association between independent variables and $raSatO_2$ and $rvSatO_2$. In the univariable linear regression model independent variables included gender, age, BMI, systolic and diastolic blood pressure, smoking history, diabetes, CABG, total-cholesterol, HDL-cholesterol, LDL-cholesterol, triglycerides and HbA1c. The multivariable linear regression model included age, gender and the statistically significant variables from the univariable analysis. The regression coefficients and 95%-confidence intervals from the analyses are presented in Table 2 and 3, respectively.
A p-value < 0.05, calculated using Stata Intercooled 15 (StataCorp, College Station, Texas, USA), was considered to denote statistical significance.

Results

Of the 85 Caucasian participants, eight were excluded due to poor image quality (six patients), central retinal vein occlusion (one patient in the control group) and previous percutaneous coronary intervention (one patient). The remaining patients were 38 cases and 39 controls.

As shown in Table 1, there was a higher number of men among cases (79% vs. 49%, p=0.006), and cases had a higher BMI (28 vs. 25, p=0.005) but lower systolic (132.0mmHg vs. 143.0mmHg, p=0.001) and diastolic blood pressure (68.5mmHg vs. 90.0mmHg, p=0.001). Cases were more likely to have diabetes (32% vs. 8%, p=0.008) and to be treated with anti-hypertensive (87% vs. 49%, p<0.001), and cholesterol lowering drugs (95% vs. 28%, p<0.001). Also, cases had lower plasma concentrations of total-cholesterol (3.6mmol/L vs. 5.7mmol/L, p=0.01) and LDL-cholesterol (1.4mmol/L vs. 3.4mmol/L, p=0.01).
Finally, cases had higher retinal arteriolar (median ± standard deviation (sd) 93.1 ± 6.7% vs. 90.5 ± 11.2%, p=0.001) and venular oxygen saturation (57.4 ± 8.3% vs. 53.5 ± 15.4%, p=0.048) illustrated in Figure 2.
There were no differences between cases and controls in age, smoking history, HDL-cholesterol, triglycerides, HbA1c, arteriolar-venular saturation difference (AV-difference), vessel diameters or image quality.

In a univariable linear regression model (Table 2), $raSatO_2$ was associated with BMI (coefficient +0.2% per 1%-point increase in BMI, p=0.04) and CABG (coefficient +4.1% increase in CABG vs. no CABG, p=0.001).
In a multivariable linear regression model (Table 2), $raSatO_2$ was associated with CABG (coefficient +3.6% increase with CABG vs. no CABG, p=0.007) but not with BMI.
No association was found between $raSatO_2$ and gender, age, systolic and diastolic blood pressure, smoking history, diabetes, and the plasma levels of total-cholesterol, HDL-cholesterol, LDL-cholesterol, triglycerides and HbA1c.

In a univariable linear regression model (Table 3), $rvSatO_2$ was associated with female gender (coefficient +6.7% increase in females vs. males, p=0.01) and CABG (coefficient +5.4% increase in CABG vs. no CABG, p=0.03).
Table 3 also shows a multivariable linear regression model adjusted for age and gender, in which $rvSatO_2$ was associated to female gender (coefficient +9.4% increase in female vs. male, p=0.001) and CABG (coefficient +8.2% increase in CABG vs. no CABG, p=0.001).

There was no relation between $rvSatO_2$ and age, BMI, systolic and diastolic blood pressure, smoking history, diabetes, total-cholesterol, HDL-cholesterol, LDL-cholesterol, triglycerides and HbA1c.

Discussion

With this case-control study, we report that retinal arteriolar and venular oxygen saturation were independently elevated in patients who had CABG surgery as compared to cardiovascular healthy controls.

Early identification of cardiovascular disease is important. Since the retinal microcirculation shares structural and functional properties with those of the heart, it potentially provides a non-invasive window to evaluation of the systemic circulation (Wong et al. 2001). The concept of using the eye to assess and to make early risk stratification of cardiovascular disease was a driving force behind this study.

In a previous small short-term prospective study (Dinesen et al. 2019) in which we performed retinal oximetry before and after cardiovascular surgery in 8 patients, we found that $raSatO_2$ and $rvSatO_2$ were significantly elevated after surgery. Based on this finding, we cannot exclude that the surgery itself can cause changes in retinal oxygen saturation. Hemodynamic stress induced by surgery may initiate physiological peripheral vasoconstriction, increasing blood flow to neurological cells that require a sufficient oxygen delivery under all circumstances (Eliasdottir 2018). However, we found no difference in retinal vessel diameters between the two groups investigated in the present study.

Van Keer et al. (Van Keer et al. 2018) reported a correlation between retinal arteriovenular oxygen saturation difference (rAVD) and cardiac output. In our previous study (Dinesen et al. 2019) we found a similar tendency with the rAVD changing from 40.0% before surgery to 25.2% after cardiac surgery supporting the results from Van Keer et al. This indicates that cardiovascular disease and its manifestations in general are reflected in the retinal microcirculation, and that the surgery itself cannot be unambiguously the only plausible explanation.

The possibility of improved cardiac function as a result of CABG could explain

the elevated oxygen saturation measured in retinal vessels as previously seen (Dinesen et al. 2019). The increased blood flow resulting from increased perfusion pressure, due to a higher cardiac output, may result in a reduced extraction of oxygen. To confirm this theory, retinal blood flow should be measured before and after surgery, and one can speculate why the retinal vessels do not adapt to the increased blood flow ensuring optimal conditions for oxygen extraction to the retinal cells. Chronic vasoconstriction may have compromised the auto-regulatory properties leaving the arterioles structurally rigid and less contractile, and it might be the lacking retinal vascular adaptation due to chronic remodelling, rather than improved cardiac output that defines our findings. (Wong et al. 2001; Rizzoni & Agabiti-Rosei 2012).

Endothelial dysfunction is widely recognized as an initial step in atherogenesis finally leading to cardiovascular disease. Smoking, age, diabetes, hypercholesterolemia and hypertension, all dispose to the development of endothelial dysfunction (Farah et al. 2018). The pathophysiology is rather complex. A simplified version is that imbalance between endothelium-derived vasoconstrictors and vasodilators results in an overall vasoconstriction by means of a down regulation of nitric oxide and up regulation of endothelin-1 (Pournaras et al. 2008; Farah et al. 2018). This results in elevated blood pressure that has been shown to increase the arteriolar tone by auto-regulation, and it may in time lead to rigid and structurally narrowed retinal resistance arterioles. (Wong et al. 2001; Rizzoni & Agabiti-Rosei 2012; Rizzoni et al. 2012; Flammer et al. 2013).
Nonetheless, as mentioned, the groups showed no difference in retinal vessel diameters, but a higher use of anti-hypertensive and cholesterol-lowering drugs in CABG patients suggests that risk factors may have been present. Secondly, it may be presumed that some of the patients' blood pressure was not well regulated before in contrast to during their hospitalization. Wong et al. reported that not only current, but also past hypertension are associated with microvascular structural abnormalities (Wong et al. 2001). On the other hand, Rizzoni et al. (Rizzoni & Agabiti-Rosei 2012) reported that arteriolar remodelling in hypertension can be reversed by long-term treatment with ACE-inhibitors, angiotensin II receptor blockers and calcium antagonists.

Retinal arteriolar auto-regulatory mechanisms are not sufficiently understood, especially regarding the relation between the systemic circulation and its potential consequences to retinal circulation. Especially the auto-regulatory nature of the retinal circulation must be taken into account when interpreting the results.

Retinal oximetry and its relation to CABG have, to our knowledge, not been studied before. However, other extra ocular diseases with reduced systemic oxygen content have been associated with alterations in retinal oxygen metabolism, such as Eisenmenger syndrome (Traustason et al. 2011). Traustason et al. found lower mean $raSatO_2$ (81 ± 9% vs. 93 ± 3%, p=<0.001) and $rvSatO_2$ (44 ± 12% vs. 59 ± 5%, p=<0.001) in Eisenmenger syndrome compared to healthy controls.
Chronic obstructive pulmonary disease was associated with lower $raSatO_2$ (87.2 ± 4.9% vs. 93.4 ± 4.3%, p=0.02) and $rvSatO_2$ (45.0 ± 10.3% vs. 55.2 ± 5.5%, p=0.01) compared with healthy controls in a study by Eliasdottir et al. (Eliasdottir et al. 2017).
These studies support the findings of the present study and the theory that the retinal vasculature has potential to measure conditions beyond the limits of the eye.

Interestingly, we noticed that women had a higher $rvSatO_2$ compared to men. In the case group 5 out of 8 (62.5%) women had diabetes compared to 10 out of 30 (33.3%) men. This difference in diabetes prevalence might be part of the explanation, because diabetic retinopathy associates with higher levels of $raSatO_2$ and $rvSatO_2$ compared to persons without diabetes (Hammer et al. 2009; Hardarson & Stefansson 2012). Since the groups were not matched for diabetes, an impact on our overall findings cannot be excluded. Another possible explanation is that the difference between sexes reflects the relatively small study population.

Our results showed no difference in image quality, which is considered a strength, because poor image quality tends to lower the oxygen saturation in

especially retinal venules (Hardarson 2014). The fact that controls had a higher median image quality further strengthens the findings.
Our study has several limitations. We did not manage to match the two groups on cardiovascular parameters. We would have benefitted from a group of patients with ischemic heart disease who did not undergo surgery or and from measurements prior to surgery. Furthermore, the control group had cataract surgery the day before the study examinations took place, and the ocular surgery itself cannot be excluded as a potential source of error, given that local microvascular changes related to the surgery may occur in the eye. The retinal circulation has a lot of potential because of its unique accessibility. More research is needed to fully establish proof-of-concept for non-invasive retinal imaging as a tool to assess systemic vascular dysfunction. The next step is to test if retinal oximetry can predict clinical outcomes from CABG such as mortality, graft-closure and stroke.

In conclusion, there were large differences in retinal oxygen saturation between patients with and without CABG. The explanation could relate to differences between the extents of cardiac or large vessel disease or other clinical parameters, but could also be related to our previous observation, that there is a difference in retinal oxygen saturation before and after cardiovascular surgery, since observations were done after. More research is needed, and future studies should include retinal blood flow measurements to clarify the underlying mechanisms.

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Fig. 1A and 1B:

Case (top picture) and control (bottom picture) fundus oximetry images with overlaying colormap. On the right site is a colour scale with the red colour indicating 100% oxygen and the blue colour 25% oxygen.

The difference between the case and control subject can visually be seen with a mean venular oxygenation of 68% (yellow to green colours) in the top image (case) and a mean venular oxygenation of 38% (green to blue colours) in the lower image (control). The mean arteriolar saturation in the case example is 96% (red to orange colours) and 81% (orange to yellow colours) in the control example.

An arteriole and a venule were traced in one quadrant of each picture to highlight the method of the analysis.

Fig. 2:

Box plot of median retinal arteriolar and venular oxygen saturation (%) in CABG- and control patients. Edges of the box represent the 25th and 75th percentiles. Whiskers: minimum to maximum values.

Table 1: Demographic and clinical properties of CABG patients (cases) and cardiovascular healthy controls (controls). All participants are Caucasian.

	Cases (n = 38)	Controls (n = 39)	P-value
Gender, men (%)	79	49	0.006
Age (years)	70.5	72.0	0.29
Body mass index (kg/m^2)	28.0	25.3	0.005
Systolic blood pressure, mmHg	132.0	143.0	0.001
Diastolic blood pressure, mmHg	68.5	90.0	<0.001
History of smoking (%)	74	74	0.94
Co-morbidities			
Diabetes Mellitus (%)	31.6	7.7	0.008
Type I (n)	2	1	
Type II (n)	13	4	
Prevalence, men (%)	33	11	
Prevalence, women (%)	63	15	
Medication			
Anti-hypertensive (%)	87	49	<0.001
Cholesterol-lowering (%)	95	28	<0.001
Plasma levels			
Total-cholesterol, mmol/L	3.6	5.7	0.01
HDL-cholesterol, mmol/L	1.3	1.5	0.24
LDL-cholesterol, mmol/L	1.4	3.4	0.01
Triglycerides, mmol/L	1.5	1.5	0.39
HbA1c, mmol/mol	37.0	37.0	0.91
Vessel O_2 saturation (Median ± SD)			
Arteriolar saturation (%)	93.1 ± 6.7	90.5 ± 11.2	0.001
Venule saturation (%)	57.4 ± 8.3	53.5 ± 15.4	0.048
Arteriolar-venular ratio (%)	36.6 ± 7.4	37.8 ± 10.3	0.60
Retinal vessel diameter (µm ± SD)			
Central retinal arteriolar equivalents	37.6 ± 7.4	39.0 ± 6.9	0.47
Central retinal venular equivalents	58.8 ± 9.7	58.3 ± 8.5	0.80
Image Quality (Median)			
Quality of imaging	7.4	7.6	0.054

Data presented as medians. Tested for differences between cases and controls. P-values <0.05 is statistically significant. History of smoking = former or current, anti-hypertensive medication = all kinds of anti-hypertensive drugs,

HDL-cholesterol = high density lipoproteins-cholesterol, LDL-cholesterol = low density lipoproteins-cholesterol, HbA1c= glycosylated haemoglobin, O_2 = oxygen, SD = standard deviation.

Table 2: Uni- and multivariable linear regression model with regression estimates for factors with an influence on retinal arteriolar oxygen saturation. Data from 77 participants (38 cases and 39 controls) are included in the uni- and multivariable regression model.

Characteristic	Increment	Univariable linear regression β coefficients (95% - Confidence Interval)	p-value	Multivariable linear regression β coefficients (95%-Confidence Interval)	p-value
Gender	Female versus male	-0.3 (-3.0 to 2.4)	0.81	+1.2 (-1.6 to 3.9)	0.39
Age	1 year	-0.03 (-0.2 to 0.1)	0.71	+0.03 (-0.1 to 0.2)	0.72
BMI	1%-point	+0.2 (0.01 to 0.5)	0.04	+0.2 (-0.1 to 0.4)	0.18
Systolic blood pressure	1 mmHg	+0.01 (-0.1 to 0.1)	0.79		
Diastolic blood pressure	1 mmHg	-0.03 (-0.1 to 0.1)	0.44		
History of smoking	Yes versus no	-1.5 (-4.5 to 1.6)	0.34		
Diabetes Mellitus	Yes versus no	+1.1 (-2.2 to 4.3)	0.52		
CABG	Yes versus no	+4.1 (1.7 to 6.5)	0.001	+3.6 (1.0 to 6.1)	0.007
Total-cholesterol	1 mmol/L	-0.7 (-2.7 to 1.4)	0.51		
HDL-cholesterol	1 mmol/L	-4.7 (-11.1 to 1.7)	0.14		
LDL-cholesterol	1 mmol/L	-0.1 (-2.5 to 2.2)	0.90		
Triglycerides	1 mmol/L	-0.01 (-2.8 to 2.8)	0.99		
HbA1c	1 mmol/mol	-0.04 (-0.3 to 0.2)	0.79		

β coefficients (95%-confidence intervals) in a uni- and multivariable regression model including independent variables tested for association to retinal arteriolar oxygen saturation. P-values <0.05 was considered statistically significant. BMI = body mass index, CABG = coronary artery bypass grafting, HbA1C = glycosylated haemoglobin.

Table 3: Uni- and multivariable linear regression model with regression estimates for factors with an influence on retinal venular oxygen saturation. Data from 77 participants (38 cases and 39 controls) are included in the uni- and multivariable regression model.

Characteristic	Increment	Univariable linear regression β coefficients (95% - Confidence Interval)	p-value	Multivariable linear regression β coefficients (95%-Confidence Interval)	p-value
Gender	Female versus male	+6.7 (1.5 to 11.8)	0.01	+9.4 (4.2 to 14.5)	0.001
Age	1 year	+0.1 (-0.3 to 0.4)	0.64	+0.1 (-0.2 to 0.4)	0.65
BMI	1%-point	+0.02 (-0.4 to 0.5)	0.93		
Systolic blood pressure	1 mmHg	+0.1 (-0.1 to 0.2)	0.40		
Diastolic blood pressure	1 mmHg	-0.1 (-0.2 to 0.1)	0.51		
History of smoking	Yes versus no	-0.8 (-6.9 to 5.2)	0.79		
Diabetes Mellitus	Yes versus no	+0.7 (-5.9 to 7.2)	0.84		
CABG	Yes versus no	+5.4 (0.3 to 10.4)	0.03	+8.2 (3.3 to 13.2)	0.001
Total-cholesterol	1 mmol/L	+0.2 (-4.0 to 4.4)	0.92		
HDL-cholesterol	1 mmol/L	-1.4 (-15.0 to 12.3)	0.84		
LDL-cholesterol	1 mmol/L	+0.7 (-4.1 to 5.4)	0.78		
Triglycerides	1 mmol/L	-1.2 (-6.7 to 4.4)	0.67		
HbA1c	1 mmol/mol	-0.07 (-0.5 to 0.4)	0.75		

β coefficients (95%-confidence intervals) in a uni- and multivariable regression model including independent variables tested for association to retinal venular oxygen saturation. P-values <0.05 was considered statistically significant. BMI = body mass index, CABG = coronary artery bypass grafting, HbA1C = glycosylated haemoglobin.

Fig. 1A

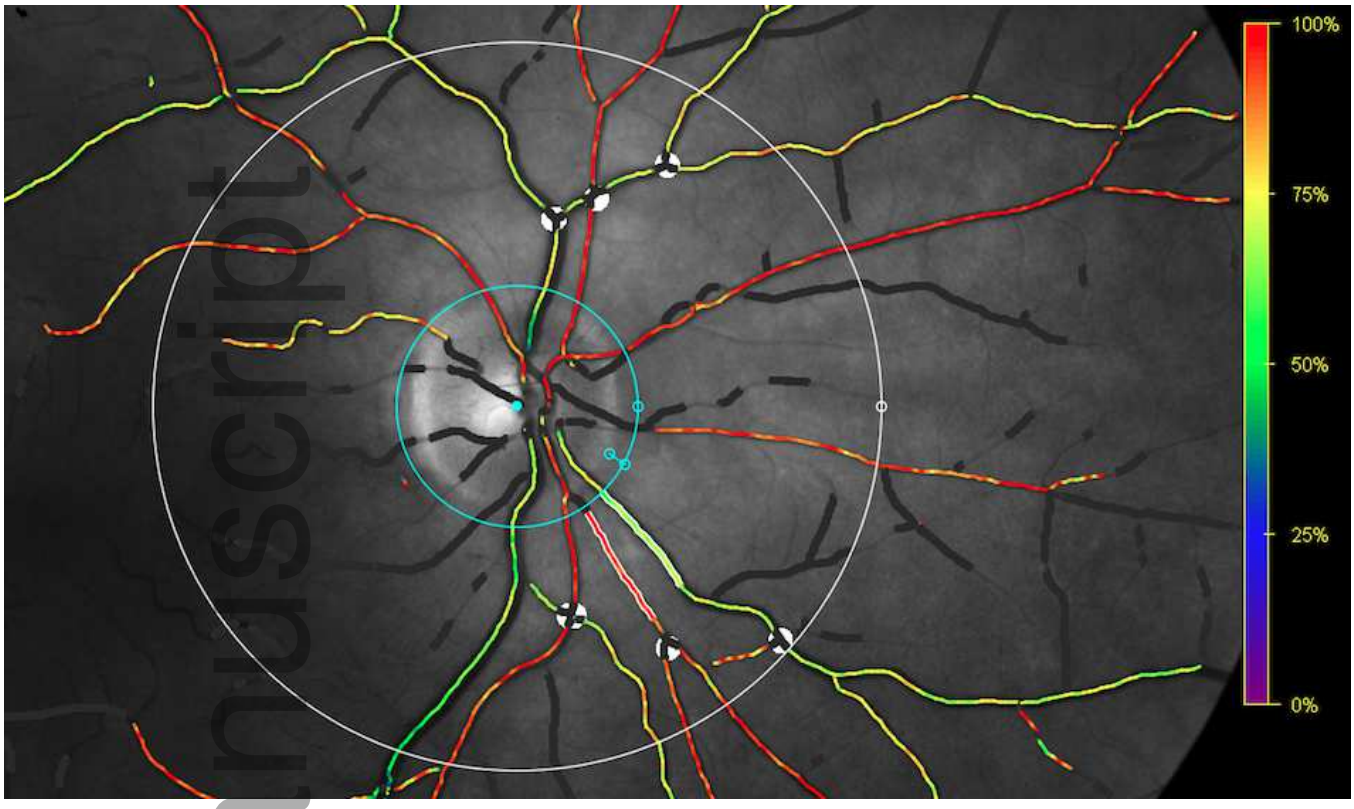


Fig. 1B

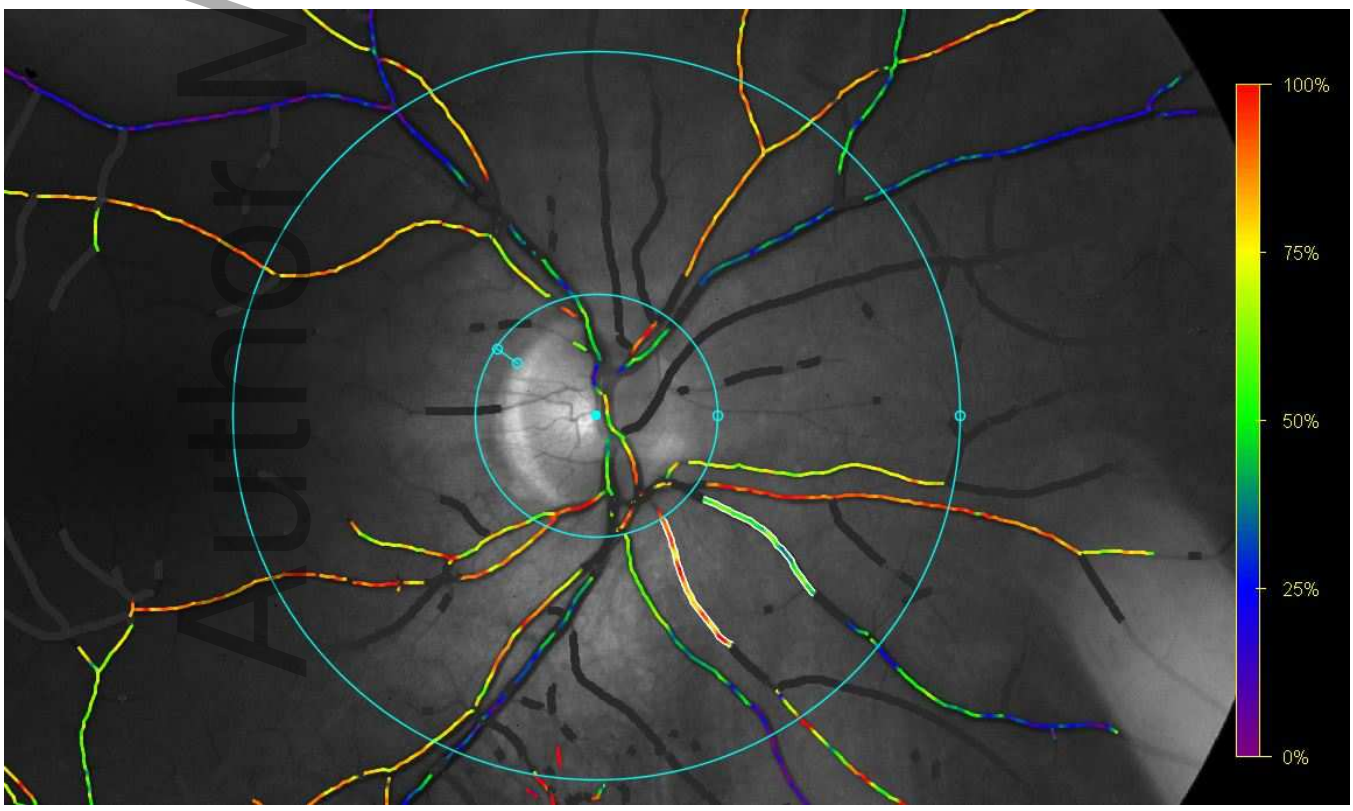
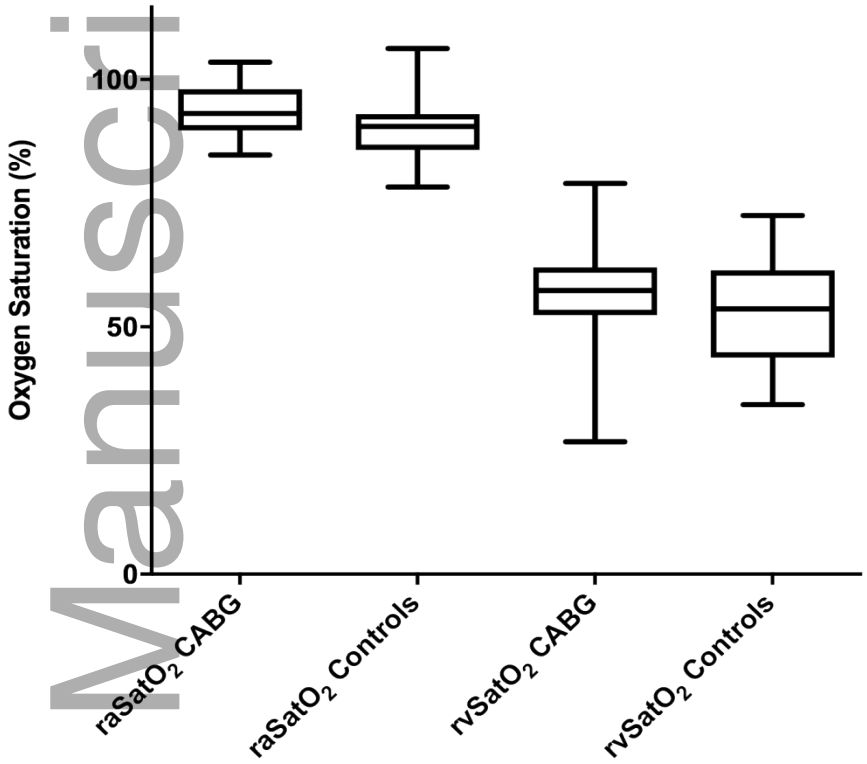
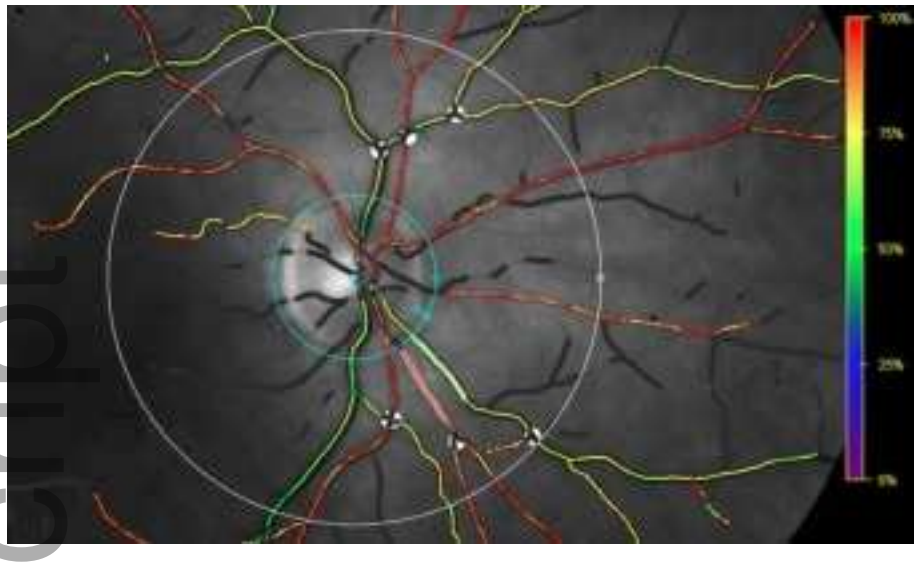


Fig. 2





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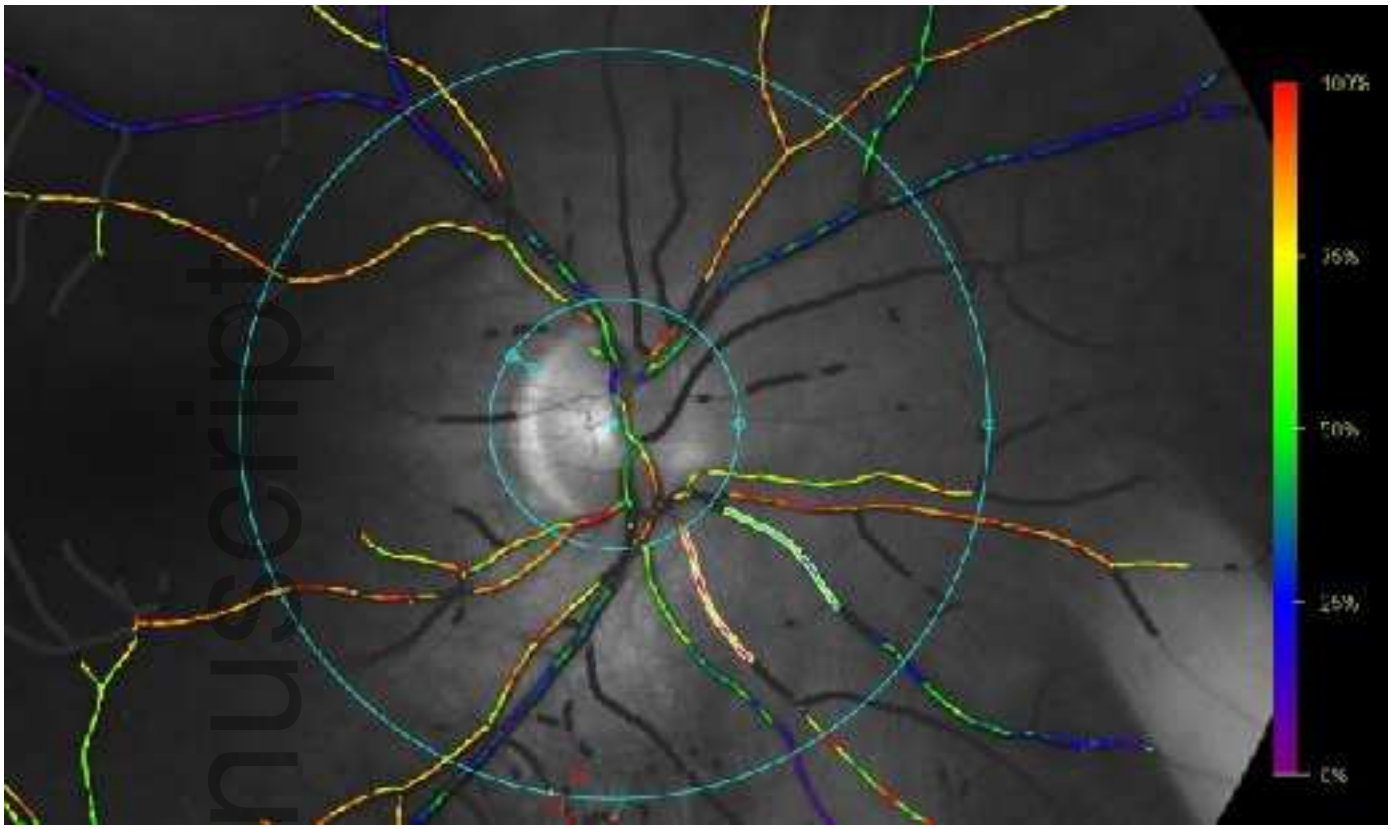

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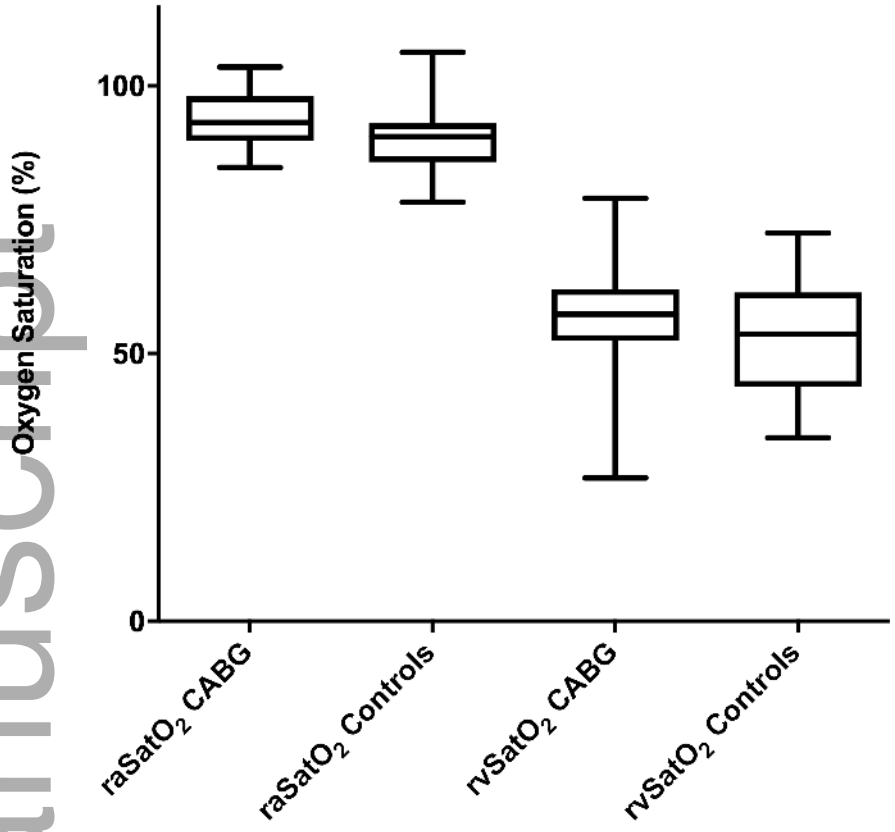

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