The Oxygen Saturation in Vascular Abnormalities Depends on the Extent of Arteriovenous Shunting in Diabetic Retinopathy

Line Petersen and Toke Bek

Department of Ophthalmology, Aarhus University Hospital, Aarhus, Denmark

Correspondence: Line Petersen, Department of Ophthalmology, Aarhus University Hospital, Norrebrogade 44, Aarhus 8000, Denmark; linperse@rm.dk.

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Purpose. Diabetic retinopathy is characterized by disturbances in retinal blood flow mediated by capillary occlusion, intraretinal microvascular abnormalities (IRMAs), neovascularizations, and omega loops and reduplications. It is likely that the study of oxygen saturation in these abnormalities can provide knowledge about their role in the development of diabetic retinopathy.

Methods. The oxygen saturation in IRMA vessels and venous loops and reduplications were studied in 40 diabetic patients with severe nonproliferative or proliferative diabetic retinopathy. The saturation values in the studied vascular abnormalities were compared to those of the larger retinal arterioles and venules.

Results. There was a similar oxygen saturation (mean ± SD) in IRMAs observed to connect arterioles with venules (78.6% ± 11.8%, $n = 22$) and IRMAs connecting venules with venules (79.2% ± 9.0%, $n = 12$; $P > 0.999$). The saturation in IRMAs was significantly lower ($P < 0.0002$) than in arterioles (97.4% ± 5.2%, $n = 40$) and significantly higher ($P < 0.0001$) than the saturation in omega loops and reduplications (54.2% ± 19.3%, $n = 6$), which in turn showed no significant difference from the saturation in the venules (61.8% ± 6.8%, $n = 40$, $P = 0.4$).

Conclusions. The findings suggest that the oxygen saturation in vascular abnormalities in diabetic retinopathy depends on the extent of arteriovenous (A-V) shunting, with venous saturation due to no A-V shunting in venous loops and reduplications, and intermediate oxygen saturation due to moderate shunting in IRMAs. This may precede the development of neovascularizations with arterial oxygen saturation due to high A-V shunting.

Keywords: diabetic retinopathy, vascular shunts, intra-retinal microvascular abnormalities, loops and reduplications, neovascularizations, oximetry

Diabetic retinopathy is characterized by disturbances in retinal blood flow that are mediated by capillary occlusion,[1] intraretinal microvascular abnormalities (IRMAs),[2] omega loops and reduplications,[3,4] and neovascularizations.[5] However, the role and interrelationship of these vascular abnormalities in the development of diabetic retinopathy have not been elucidated in detail. The vascular abnormalities can be caused by and affect blood flow and oxygen supply to the retinal tissue, and therefore, it can be expected that studies of oxygen saturation in the vascular abnormalities can contribute to understanding diabetic retinopathy.

The oxygen saturation in retinal vessels can be studied by dual wavelength oximetry, which is based on the analysis of fundus photographs obtained at two different wavelengths.[6] In a recent study using this technique, it was shown that the oxygen saturation in preretinal neovascularizations is arterial,[7] which suggests that these new vessels are shunts that allow the blood to bypass an occluded vascular bed peripheral from the neovascularizations.[8] Therefore, there is a need to investigate how preretinal neovascularizations differ from vascular abnormalities with an established role as vascular shunts in the diabetic retina, such as IRMAs developing from the capillary bed, and omega loops and reduplications developing from larger venules. It is likely that an evaluation of metabolic markers, such as the oxygen saturation in the blood perfusing these vascular abnormalities, may contribute to a deeper understanding of their role in the pathophysiology of diabetic retinopathy.

Consequently, the oxygen saturation in IRMA vessels and venous loops and reduplications were studied in 40 diabetic patients with severe nonproliferative or proliferative diabetic retinopathy. The saturation values were compared to those of the larger retinal arterioles and venules.

Materials and Methods

Patients

Fundus photographs of all 285 patients referred for evaluation of severe nonproliferative or proliferative diabetic retinopathy (Early Treatment of Diabetic Retinopathy Study [ETDRS] 1991) from August 1, 2009 to December 30, 2016, at the Department of Ophthalmology Aarhus University Hospital, were studied. At referral the patients had undergone a routine ophthalmologic examination,[9] including measurement of best corrected visual acuity (BCVA) using ETDRS charts, slit-lamp examination, and

dilatation of the pupils using phenylephrine 10% (SAD, Copenhagen, Denmark) and tropicamide 1% (Alcon, Copenhagen, Denmark) eye drops, followed by 90 diopter (D) lens biomicroscopy, fundus photography, and optical coherence tomography scanning. The height, body weight, and systemic blood pressure were measured and the nearest hemoglobin A1c (HbA1c) value measured within three months from the eye examination was collected. In each patient, five retinal oximetry photographs (Oxymap model T1; Oxymap, Reykjavik, Iceland) had been obtained from both eyes with, respectively, the optic disk and upper and lower temporal vascular arcades in the center of the image as described previously.[10]

The patients were defined as having type 1 diabetes (T1D) if the onset of the disease was before the age of 30 years or between 30 and 40 years of age, and if insulin treatment had been initiated within the first year of the disease and the body mass index (BMI) was below 25. All other patients were defined as having type 2 diabetes (T2D).

The study was approved by the regional ethics committee and followed the tenets of the Declaration of Helsinki.

Identification of Vascular Abnormalities

The fundus photographs obtained by the oximeter were analyzed for the presence of omega loops and reduplications on the larger retinal venules or IRMAs, defined as connections between larger retinal vessels that could be followed across the normally invisible capillary bed and had no preretinal elements that crossed their feeder vessel. To obtain the best image quality, the photographs were analyzed successively according to age starting with the youngest person until 40 eyes from 40 patients had been included. This required evaluation of images from 83 patients where 43 patients had been excluded because of lack of visible vascular abnormalities or due to media opacities. If more than one abnormal vessel were present in the photograph of the same eye, the shortest of these was included in the analysis. When vascular abnormalities were visible on photographs from both eyes or the right eye only, the abnormal vessel on the right eye was used and otherwise the vessel on the left eye was used. This resulted in the inclusion of 24 abnormal vessels from right eyes and 16 from left eyes. Among the studied eyes, 36 also had neovascularizations defined as new vessels growing preretinally from the larger vascular arcades or the optic nerve to cross their feeder vessel. Apart from the neovascularizations, the appearance of vascular abnormalities in patients with severe nonproliferative retinopathy was similar to that of patients with proliferative retinopathy. The clinical data of the studied persons are shown in the Table.

Data Analysis

The oxygen saturations in the larger arterioles and venules were obtained as described previously.[11,12] On the image centered at the optic disk, a circle with the best fit to the disk margin was defined, followed by the definition of two larger concentric circles. The largest of these circles was set to a diameter of three disks and the smallest to a diameter 30 pixels larger than the disk. The two circles delimited a belt concentric with the disk within which the saturations, diameters, and vessel lengths were collected from the longest unbranched segment of the major arterioles and venules to each of the four retinal quadrants.[10] In each patient the saturation and diameter values from the four arterioles and venules were averaged.

The identified vascular abnormalities were divided into three categories: (1) IRMA vessels that could be followed to connect an arteriole with a venule (arteriovenous [A-V] connections, $n = 22$), (2) IRMA vessels that could be seen to emerge from a venule and be followed to connect to a more proximal location on the same venule (venovenous [V-V] connections, $n = 12$), and (3) omega loops and reduplications on larger venules not associated with any other visible vascular abnormalities (L/R, $n = 6$).

In four cases venous loops and reduplications were observed that were connected to neovascularizations. In these vascular abnormalities, the oxygen saturation was arterial, but since this could not be ascribed to one specific category of vascular abnormality, these vessels were not considered in the analysis.

Each selected IRMA vessel was marked using the vessel tracing tool in the oximeter software. If the tracing of the abnormal vessel was interrupted due to a localized narrowing or loss of contrast, a new marking was positioned next to the interruption to identify the following traceable segment, and this procedure was repeated until the tracing had reached the end of the vessel abnormality. The software traced on average 53.3% ± 16.7% (mean ± SD) of the lengths of the IRMA vessels and the skipped segments were located randomly along the courses of these vessels.

The software calculated the oxygen saturation and vessel diameter for each pixel (corresponding to approximately 9 μm) along the detected vessel segments in each IRMA vessel, which were saved in Excel (Microsoft Corp., Redmond, WA, USA) format. The values were collected in the direction from the arterial to the venous connection (A-V connections) or from the peripheral to the proximal connection on the same venule (V-V connections). The saturation values were displayed on the vessels in the fundus photograph in a color code ranging from red (100% saturation) to blue (0% saturation). Using this procedure the saturation values in the studied vessels were calculated from (mean ± SD, range) 153.2 ± 103.5, 30 to 498 individual saturation measurements.

The oxygen saturations in omega loops and reduplications were obtained similarly to the procedure followed in IRMA vessels.

Based on the photographic appearance,[13] three different features were extracted from each shunt vessel: (1) The branching level (first, second, third, or larger) from the optic disk of the vessel of origin of the shunt (the arteriole in A-V connections and the peripheral leg of V-V connections), (2) the ratio between the average diameter of the shunt and the most proximal (or only) venule it drained to, and (3) the diameter of the venule, which was measured from the point of drainage and proximally towards the optic disk over a distance as long as possible larger than 50 pixels (450 μm), but never exceeding 100 pixels (900 μm).

Table. The Clinical Characteristics of the Studied Patients (Mean ± SD).

Age (y)	39.1 ± 8.2
Duration of diabetes (y)	18.4 ± 13.3
T1D/T2D (*n*)	27/13
Visual acuity	0.68 ± 0.4
MAP (mm Hg)	99.5 ± 11.4
BMI	28.6 ± 10.1
HbA1c (mmol/mol)	71.4 ± 19.6

MAP, mean arterial pressure.

Statistical Analysis

Repeated-measures 1-way ANOVA was used to test for differences in saturations among arterioles, venules, and the studied vascular abnormalities. The analysis was repeated with

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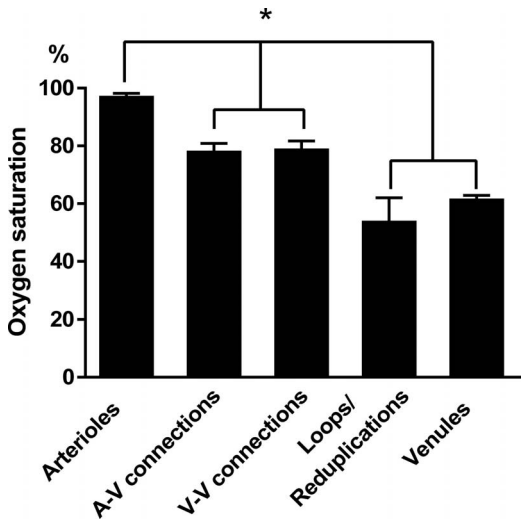

FIGURE 1. The average oxygen saturation in the peripapillary arterioles and venules from all the studied patients and from the different types of shunts. *Error bars*: SEM.

the diameter of the vessels at the site of measurement of oxygen saturation as a covariate, which showed no significant contribution to the difference in saturation (analysis of covariance [ANCOVA], $P = 0.79$).

Linear regression was used to test for changes in the saturation along the course of the A-V and V-V connections, inserting blank values corresponding to the segments where the software had skipped the measurement of oxygen saturation.

Multiple regression was used to test whether the saturation in the vascular abnormality could be explained by the four factors: the category of vascular abnormality, branching level and diameter ratio between vascular abnormality and draining venule.

RESULTS

The average oxygen saturations in the studied vessel types are shown in Figure 1. The overall saturation in the studied abnormal vessels was (mean ± SD) 73.7% ± 15.7%, but differed significantly among the different vessel types ($P < 0.0001$). There was no significant difference between the oxygen saturation (mean ± SD) in the IRMAs that appeared to connect arterioles with venules (A-V connections; 78.6% ± 11.8%, $n = 22$) and to connect venules with venules (V-V connections; 79.2% ± 9.0%, $n = 12$; $P > 0.999$). However, the saturations in A-V and V-V connections, separately and together (78.7% ± 10.4%), were significantly lower ($P < 0.0002$) than the saturation in the arterioles (97.4% ± 5.2%, $n = 40$) and significantly higher ($P < 0.0001$) than that in the omega loops and reduplications (54.2% ± 19.3%, $n = 6$). Additionally, the saturation in loops and reduplications was not significantly different ($P = 0.1$) from that of the venules (61.8% ± 6.8%, $n = 40$).

Figures 2 to 4, respectively, show examples of a studied A-V connection, a V-V connection, and the oxygen saturation along the latter from the peripheral to the central connection with the larger venule. The oxygen saturation (color) is seen to alternate along the course of the vessels. The linear regression showed that the oxygen saturation decreased significantly along six A-V connections (r^2 range, 0.004–0.34) and four V-V connections (r^2 range, 0.01–0.23), increased significantly along two A-V connections (r^2 range, 0.03–0.09) and four V-V

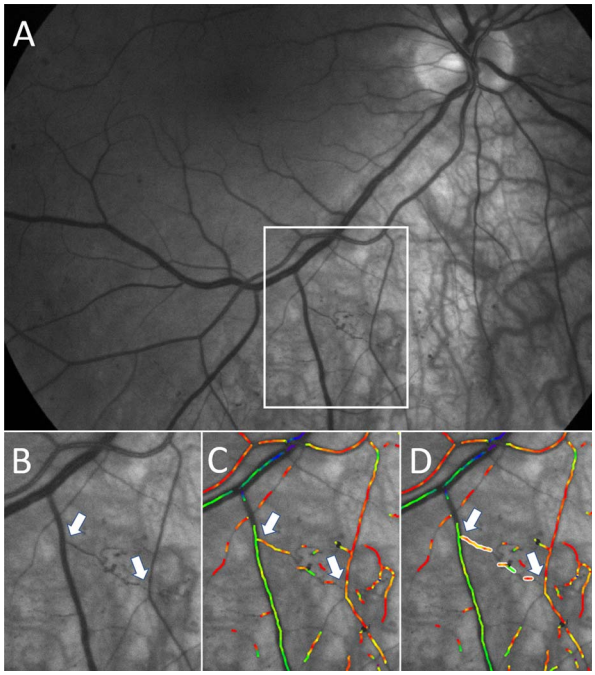

FIGURE 2. Example of an A-V connection. (**A**) Fundus photograph with a rectangle delimiting the area of interest containing the studied vessel. This area is showed in higher magnification in (**B**). The course of the studied vessel can be traced from the arteriole (*right arrow*) to the venule (*left arrow*). (**C**) The color coding of oxygen saturation performed by the oximetry software ranging from high (*red*) to low (*blue*) saturations. (**D**) Marking in white of the segments in the shunt where oxygen saturation was sampled.

connections (r^2 range, 0.06–0.21), and was unchanged along the remaining 18 of these connections (r^2 range, 0.0001–0.03). The slopes of the linear regressions of oxygen saturation along the studied IRMA vessels are plotted in Figure 5.

Figures 6A and 6 B show an example of a venous loop with venous saturation (blue). Figures 6C and 6D show a venous loop connected to a neovascularization in which the oxygen saturation was arterial (red). The multiple regression showed that the included variables could explain 46% of the variation in oxygen saturation, but only a classification of an abnormal vessels as a loop or reduplication contributed significantly ($P < 0.02$) to explaining the oxygen saturation.

DISCUSSION

Shunting of blood to bypass areas of vascular occlusion is a prominent feature of diabetic retinopathy, but the funduscopic appearances of shunt vessels differ at different branching levels of the retinal vascular system. In the microcirculation, dilated and hyperpermeable shunts can be seen as IRMAs, indicating that retinopathy has entered a more advanced stage.[14–16] IRMA vessels are seen to border areas where the capillaries are occluded secondary to structural changes in the vascular walls or because of compression from swollen retinal tissue, such as in cotton wool spots.[17–19] In the larger retinal venules, slowly evolving occlusions may lead to the formation of shunts with an appearance as omega loops or reduplications.[4] These abnormalities may indicate that the disease is in progression to proliferative diabetic retinopathy and may even be the site of origin of preretinal neovascularizations.[3]

The understanding of the role of the different types of vascular abnormalities for the development of diabetic

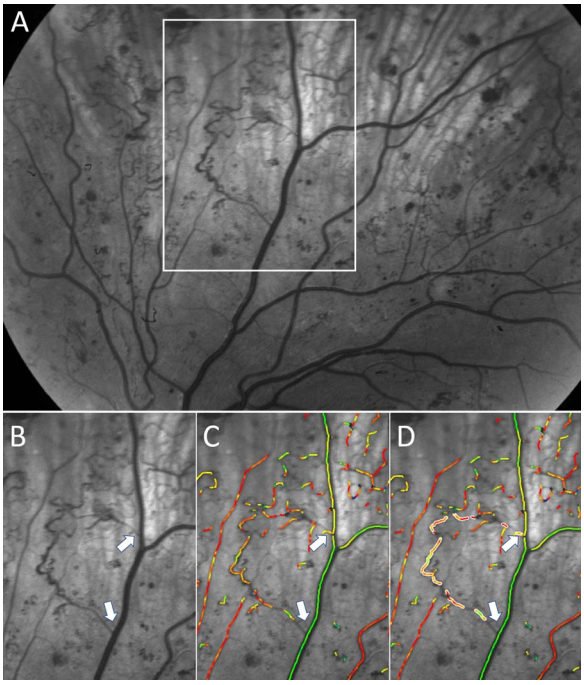

Figure 3. Example of an intraretinal (V-V) connection between two locations on the same venule. (**A**) Fundus photograph with a rectangle delimiting the area of interest containing the studied vessel. This area is shown in higher magnification in (**B**). The course of the studied vessel can be traced from the upper to the lower arrow at the left side of the larger venule. (**C**) The color coding of oxygen saturation performed by the oximetry software ranging from high (*red*) to low (*blue*) saturations. (**D**) Marking in white of the segments where oxygen saturation was sampled.

retinopathy might be facilitated by studying the oxygen saturation in the blood perfusing these vessels. This parameter can be studied by dual wavelength retinal oximetry.[6] The oxygen saturations measured by this method may be affected by the linear velocity of the blood,[20] which contributes to the variation of measured oxygen saturations that may be up to 5%.[21] A test–retest variability assessment was not done in the current study and hence the coefficient of variation of the measurements are unknown. However, the differences in oxygen saturation observed between the different types of vascular abnormalities in the present study are too large for this source of bias to have affected the conclusions. Funduscopic observations of IRMAs sometimes reveal these vessels to connect arterioles with venules and sometimes venules with venules, but the present findings of a similar oxygen saturation in these different appearances of IRMAs suggests that a distinction of these vascular abnormalities based on their connections to larger vessels may not be warranted. The fact that the oxygen saturation in IRMAs was between that of arterioles and venules implies that these vascular abnormalities acted as A-V shunts, but that arteriolar contributions to shunts appearing to connect venules with venules have been too small to be resolved. This is supported by the shifting oxygen saturations along the course of the vessels that may represent contributions from side branches supplying arterial or venous blood that are not discernible on the fundus photographs. This also may explain the lack of overall change in oxygen saturation along the majority of these vessels. In the absence of shifting contributions from side branches the oxygen saturation could be expected to decrease with the direction of the blood flow due to metabolic consumption as was observed in some of the studied A-V and V-V connections. However, the observed changes in oxygen saturation included increases and decreases along the connections and, thus, indicated that the direction of the flow could be from the peripheral to the central leg of the connection, and the reverse, probably reflecting diversities in the hydrostatic pressure gradients driving the blood in these vessels. Fluorescein angiography had been obtained in two of the studied patients, but the frame interval of more than 1 second was not sufficient to resolve the filling of the shunts. A more detailed study of the direction and velocity of the blood in IRMA vessels might potentially be performed by video angiography. This also might disclose dynamic changes in flow of relevance for understanding the development of diabetic retinopathy.[5,22,23] The interpretation of the findings also should consider that the oxygen saturations were measured at daytime and depended on light exposure of the retina for the capture of oximetry images. This may disregard effects of a higher retinal metabolism and oxygen consumption during darkness.[24–26] These effects observed in normal individuals may be different in retinal vascular disease and, therefore, require further investigation in diabetic patients.[27–29]

Based on measurements of oxygen saturation in the present and previous studies,[7–10] it appears that IRMAs and neovascularizations in diabetic retinopathy connect arterioles with venules and thereby share the feature of bypassing vascular segments with capillary occlusion.[30–32] The subsequent increase in the hydrostatic pressure in the remaining patent vessels can be assumed to be the driving force for the

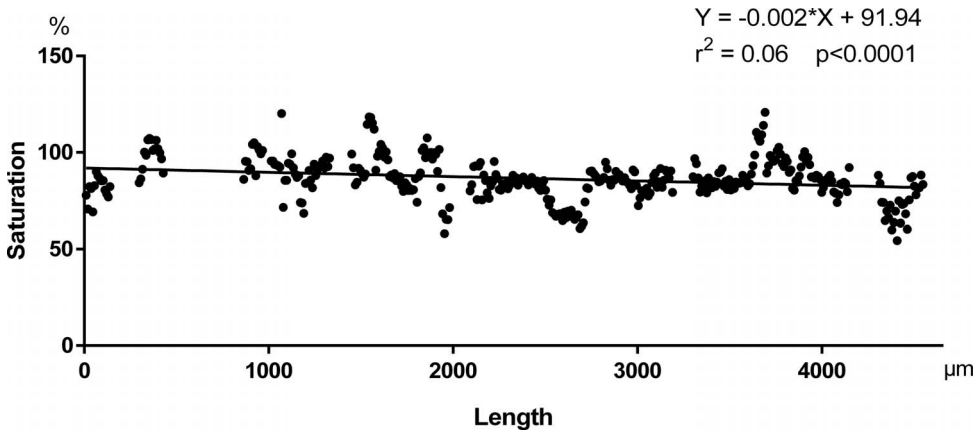

Figure 4. Oxygen saturation measurements along the V-V connection shown in Figure 3. The variations in oxygen saturation along the course of the vessel may be due to contributions from side branches with higher and lower oxygen saturation.

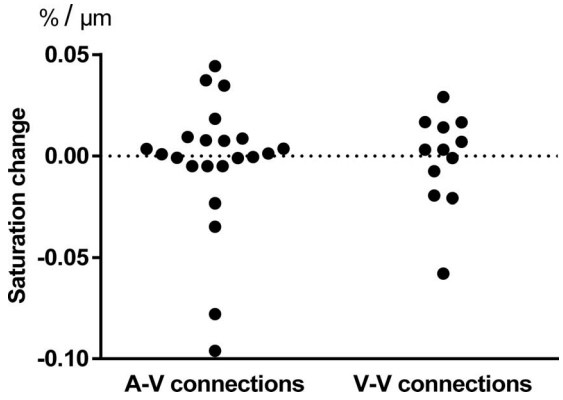

FIGURE 5. The slopes from the linear regression lines of change in oxygen saturation per micrometer along the shunt of intraretinal A-V and V-V connections.

development of shunt vessels in which increasing flow can be expected to result in reduced oxygen extraction and a consequent increasing oxygen saturation. This can explain the sequence of occurrence of vascular shunts that initially present as IRMAs with a moderate shunting capacity and a consequent intermediate oxygen saturation, that may be followed by the development of preretinal neovascularizations with a higher shunting capacity and oxygen saturation.[7] The fact that the blood shunted to the venules will not be fully deoxygenated can explain the increasing venous oxygen saturation observed with increasing diabetic retinopathy grade.[10,11] This suggests that the oxygen saturation in larger retinal venules potentially could be an indicator of the degree of shunting to bypass capillary occlusion in diabetic retinopathy.

The important role of capillary occlusion in the development of diabetic retinopathy is supported by findings that retinal function is reduced in these lesions,[33] whereas other vascular disturbances, such as breakdown of the blood–retina barrier, has no appreciable effect on visual function if not accompanied with edema.[19] On postmortem specimens, it has been shown that the occluded capillaries in diabetic retinopathy contain ingrown retinal Müller cells,[34,35] which may represent the end stage of a chain of events involving the vascular walls and perivascular retina.[30] Investigation of the relationship between these pathologic events will be important to understand the development of diabetic retinopathy.

The background for the development of omega loops and reduplications on larger retinal venules remains to be explained. These lesions develop to bypass a slowly evolving occlusion of a larger retinal venule[4] and seem to have no role for bypassing an occluded capillary bed, except when these vessels become sites of origin of neovascularizations and the observation of an arterial oxygen saturation indicates A-V shunting of the blood. The fact that the classification of vascular abnormalities as loops and reduplications was the only studied variable that could predict the oxygen saturation supports that this lesion type has a special role in the development of diabetic retinopathy that remains to be elucidated.

Altogether, our findings confirmed that a main role of vascular abnormalities in diabetic retinopathy is to act as shunts that bypass areas of capillary occlusion. The progression from preproliferative diabetic retinopathy with IRMAs to proliferative diabetic retinopathy with neovascularizations may reflect a need for increasing the shunting capacity to bypass larger areas of capillary occlusion. Therefore, the increase in the oxygen saturation of retinal venules observed with increasing severity of retinopathy may reflect the extent of capillary occlusion. The potential of retinal oximetry for assessing the severity of diabetic retinopathy should be investigated further.

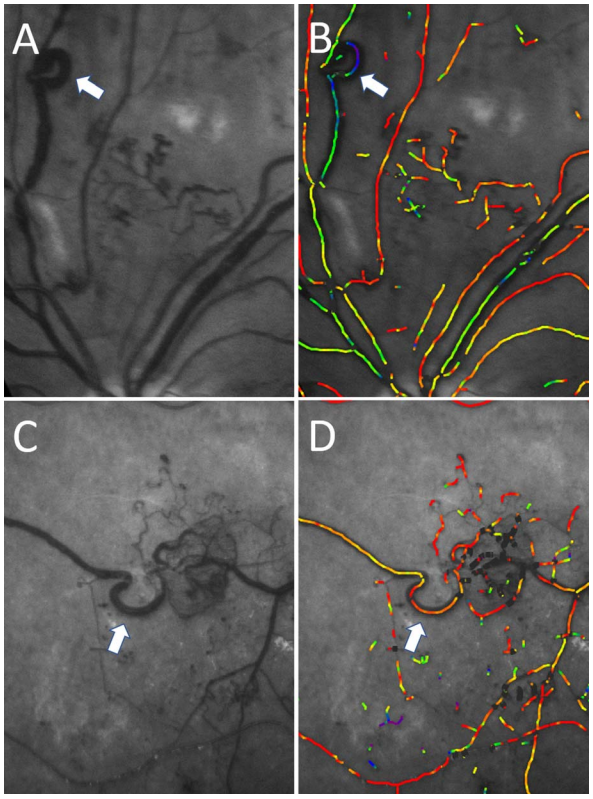

FIGURE 6. Omega loops on larger venules. (**A**) Fundus photograph with an omega loop (*arrow*) on a larger venule superior from the optic disk. (**B**) Color coding of vessels showing venous (*blue*) oxygenation in the loop. (**C**) Fundus photograph with an omega loop (*arrow*) on a superior temporal venule associated with a neovascularization. (**D**) Color coding of the vessels showing arterial (*red*) oxygenation in the loop. Most of the vessels in the neovascularization are too thin to be resolved by the oximetry software.

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