Angiography and Multifocal Electroretinography Show That Blood Supply to the Pig Retina May Be Both Ipsilateral and Contralateral

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Purpose. We recently presented a transfemoral endovascular coiling technique for inducing experimental retinal ischemia in pigs. Substantial variation was seen in the degree of ischemia. It was hypothesized that the blood supply to the retina may originate from both the ipsilateral and contralateral ophthalmic arteries and that there may be an interconnecting artery between the eyes.

Methods. The external carotid system of 6 pigs was catheterized using a fluoroscopy-monitored, transfemoral, endovascular approach. Vascular occlusion was achieved in the ophthalmic artery using coils. The effect of occlusion was examined using angiography and multifocal electroretinography (mfERG).

Results. During angiography of the ophthalmic artery on one side, contrast filling was seen in the retinas on both sides, suggesting that the ophthalmic artery on one side may supply both retinas. A blood vessel connecting the eyes was visualized. The mfERG recordings indicated that the use of coiling to occlude the ophthalmic artery had greater ischemic effects in eyes that may depend mainly on the ipsilateral ophthalmic artery for blood supply and had smaller ischemic effects in retinas that received blood from both the ipsilateral and contralateral ophthalmic arteries via the interconnecting vessel.

Conclusions. The blood supply to the retina may originate from both the ipsilateral and contralateral ophthalmic arteries in the pig. There is an interindividual variability in the ischemic effect of occlusion depending on the architecture of the vasculature. These findings may be important in the development of new animal models of experimental retinal ischemia because arterial occlusion in one eye may affect the blood supply to the contralateral eye.

Keywords: retinal ischemia, animal model, electroretinography, intra-arterial coiling, retinal vasculature

Retinal ischemia ensues when the retinal circulation is insufficient to meet the metabolic demands of the retina. This is most commonly caused by local circulatory failure resulting from diabetes, vein thrombosis, or arterial occlusion.[1] Experimental animal models of retinal ischemia are required for research to develop treatment that can limit the extent and severity of ischemic injury. A number of animal models have been used to study retinal ischemia. Ischemia can be induced by elevating the intraocular pressure,[2] by vascular ligation,[3–6] by intravenous injection of rose bengal,[7–9] and by laser photocoagulation or transvitreal diathermia.[10,11]

However, many of these commonly used animal models for retinal ischemia have limitations. The clinical relevance of the results obtained in the laboratory depends on the nature of the extrapolation. If an experimental animal model of retinal ischemia can replicate human pathology and if pharmacological treatment can ameliorate this pathology, then it is a logical assumption that such treatment may be effective in the clinical setting and thus merits further investigation. Clearly, the ability to extrapolate the results obtained using an animal model to the clinical situation requires an experimental model that closely resembles retinal ischemia in humans. Pigs have retinal anatomy similar to that in humans.[12] The porcine eye appears to have a typical primate-like architecture and is similar to the human eye regarding both size and retinal blood supply.[12] The pig has also proven to be a suitable animal for experimental analysis of the retina and retinal arteries.[13] If unambiguous retinal ischemia, without confounding factors, can be created in the pig, this may provide an experimental model that closely resembles the pathology in humans.

In 1992, Scheurer et al.[14–16] were successful in catheterizing the external maxillary artery in the pig and injecting microparticles into it before the branching of the ophthalmic artery. However, because the injections were administered in the maxillary artery, which is a large artery supplying substantial parts of the head, ischemia was presumably produced not just in the retina. We recently accessed the retinal circulation by transfemoral endovascular catheterization, inducing retinal ischemia with different degrees of severity by occlusion of the arterial circulation using a balloon catheter and a liquid embolic agent,[17] as well as in a later study[18] by endovascular coiling. One major advantage of occlusion of the retinal circulation using a transfemoral endovascular approach is that it only affects the retinal blood

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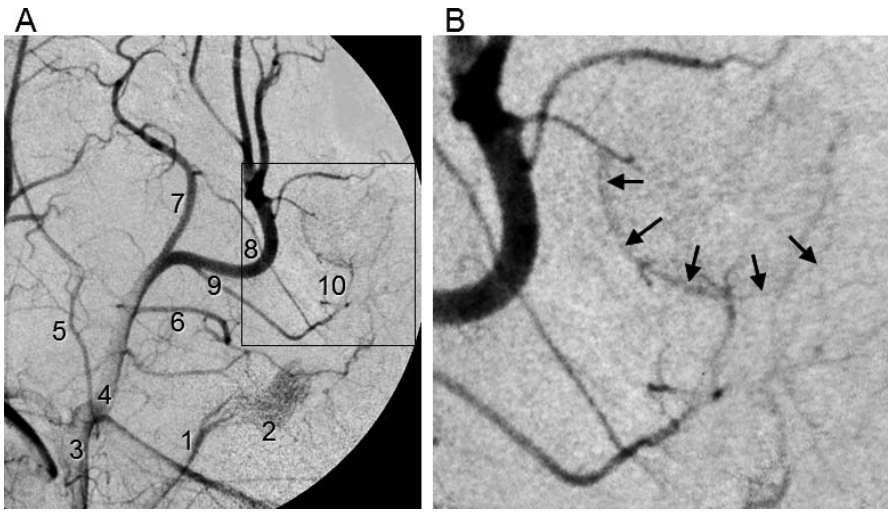

FIGURE 1. Angiogram of the left common carotid artery in a pig. (**A**) shows a lateral view, and (**B**) is an enlargement of the inset in **A**. The ascending pharyngeal artery (**1**) originates as a small side branch from the common carotid artery and feeds the rete mirabile (**2**), which then converges to form the intracranial carotid artery. The external carotid artery (**3**) is a continuation of the common carotid artery. The maxillary artery (**4**) branches from the external carotid artery. The maxillary artery gives off of the lingual (**5**), auricular (**6**), and buccinator (**7**) arteries. The maxillary artery gives rise to the infraorbital artery (**8**). The ophthalmic artery (**9**) branches off of the infraorbital artery. After having accessed the ophthalmic artery, injection of contrast medium will produce a characteristic half-moon–shaped outline of the retina (*arrows* in [**B**]). The ophthalmic artery gives off of the main ciliary artery (**10**), from which the retinal artery branches. Similar angiographies have been presented previously.[17,18]

supply and should not have any other, undesirable effects on the eye, allowing precise and repeatable location of the desired occlusion.

However, we observed a substantial interindividual variability in the degree of ischemia resulting from this kind of arterial occlusion.[17,18] We hypothesized that a variation in the architecture of the vasculature could explain the results. Therefore, the present study was carried out to explore the blood supply of the retina.

METHODS

Animals and Anesthesia

Six domestic Landrace pigs of both sexes, with a mean body weight of 70 kg, were used in the study. Before the surgical procedure, the animals were fasted overnight with free access to water. An intramuscular injection of ketamine (Ketaminol vet, 100 mg/mL; Farmaceutici Gellini S.p.A., Aprilia, Italy), 15 mg/kg of body weight, in combination with xylazine (Rompun vet, 20 mg/mL; Bayer AG, Leverkusen, Germany), 2 mg/kg, was used for premedication. Anesthesia was maintained with 1 to 2 mL of thiopental (Pentothal, 50 mg/mL; Abbott, Stockholm, Sweden) when necessary, in combination with fentanyl (Fentanyl B. Braun; B. Braun Melsungen AG, Melsungen, Germany) at approximately 3.5 μg/kg/h until catheterization was initiated and a vascular sheath was inserted in the femoral artery. Anesthesia was then switched to continuous intravenous infusion of propofol (Diprivan, 20 mg/mL; Astra Zeneca, Södertälje, Sweden) at a dosage of 0.1 to 0.2 mg/kg/min, in combination with fentanyl at approximately 3.5 μg/kg/h. Mechanical ventilation was established in a volume-controlled mode (900B ventilator; Siemens-Elema, Solna, Sweden). The animals were monitored continuously throughout the experiment using electrocardiography and measurements of arterial pH, PO_2, and PCO_2. After the experiments, the animals were given a lethal dose of potassium.

Ethics

All procedures and animal treatments were carried out in accordance with the US National Institutes of Health Guide for the Care and Use of Laboratory Animals and with the ARVO Statement for the Use of Animals in Ophthalmic and Vision Research. The study was approved by the Ethics Committee of Lund University. The animals have also been used for other studies.

Experimental Procedure

Catheterization was performed in each of the pigs. A 6F vascular sheath was inserted into the right femoral artery using a percutaneous approach (Radiofocus Introducer II; Terumo Europe N.V., Leuven, Belgium). A 5F angiographic catheter (Tempo 5 Headhunter; Cordis, South Ascot, UK) was then inserted into the maxillary artery via the external carotid artery using fluoroscopic guidance. Cerebral angiography of the external carotid system was then performed using frontal and lateral projections. The 5F active tracking catheter was then replaced with a 6F guide catheter (Envoy Guide; Cordis), which was inserted into the external carotid artery. The ophthalmic artery was catheterized using a microcatheter (Excelsior SL10; Boston Scientific, Cork, Ireland) and advanced over a guide wire (0.008-inch Mirage; Ev3 Neurovascular, Irvine, CA). The guide wire was removed once the microcatheter was positioned, and a coiling catheter was subsequently inserted. Angiography of the carotid system revealed the anatomical structures described in previous studies[17,18] (Fig. 1).

Occlusion by Coiling

Angiography was performed before coiling. Contrast medium was injected into the internal carotid and ophthalmic arteries, providing proximal and distal angiographs. Thereafter, coils were used to occlude the ophthalmic artery. Each coil consisted of a thin metallic thread contained in a catheter. The coils used were 2 mm × 3 cm, 2 mm × 4 cm, 2 mm × 6 cm, and 2.5 mm × 4 cm (GDC-US [ultrasoft] or GDC-10-Soft-SR; Boston Scientific,

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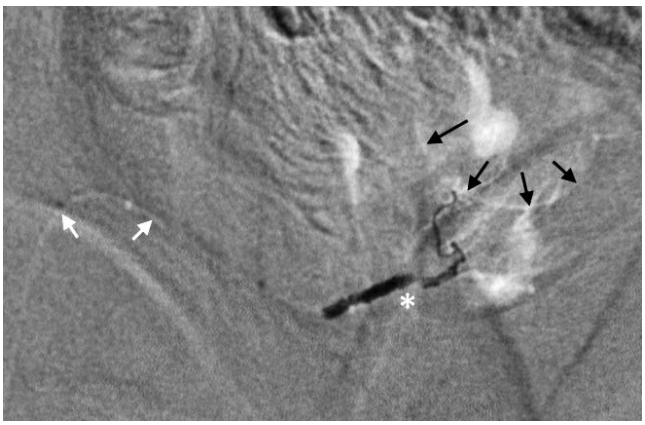

FIGURE 2. Road map image after the coiling procedure. The injection catheter can be seen in the ophthalmic artery (*white arrows*). Coils are positioned in the distal ophthalmic artery, over the branching of the main ciliary artery (*asterisk*). Part of the coil enters the main ciliary artery. The faint white contour of the retina can be seen (*black arrows*).

Natick, MA). The coils are threaded through the catheter and deployed into the blood vessel. Upon exiting the catheter at the desired site, the coil takes on a 3-dimensional structure because of its intrinsic inclination to coil. The coils do not constitute an absolute barrier but lower the blood flow to the point of clot formation, which produces occlusion. The coils were detached from the coiling catheter using an electric device. Occlusion was verified by performing local angiography proximal to the coiling site. If the passage of contrast medium was seen, further coils were inserted until no leakage was observed. Two to ten coils were needed to achieve occlusion. Coiling was performed in the distal part of the ophthalmic artery, over the branching of the main ciliary artery (Fig. 2).

Multifocal Electroretinography

The pig eyes were dilated with topical cyclopentolate hydrochloride (Cyclogyl 1%; Alcon Laboratories, Inc., Fort Worth, TX) to a diameter of 8 to 10 mm. Multifocal electroretinography (mfERG) was performed 1 hour after endovascular artery occlusion to evaluate the retinal function, in line with the International Society for Clinical Electrophysiology of Vision standard mfERG,[19] as described below. The animals were kept in normal room light for 1 hour before and during stimulation. A Burian-Allen bipolar contact lens electrode with built-in infrared emitters (Hansen Ophthalmic Development Laboratory, Iowa City, IA) lubricated with 2% hydroxypropyl methylcellulose (Methocel; Dow Wolff Cellulosics, Bomlitz, Germany) was applied to the eye, and a ground electrode needle was inserted into the skin behind the ear. Recordings were made using the VERIS Science 4.3 system (Visual Evoked Response Imaging System; EDI, San Mateo, CA). The stimulus consisted of a picture of 103 geometric patches (unscaled hexagons), delivered by a

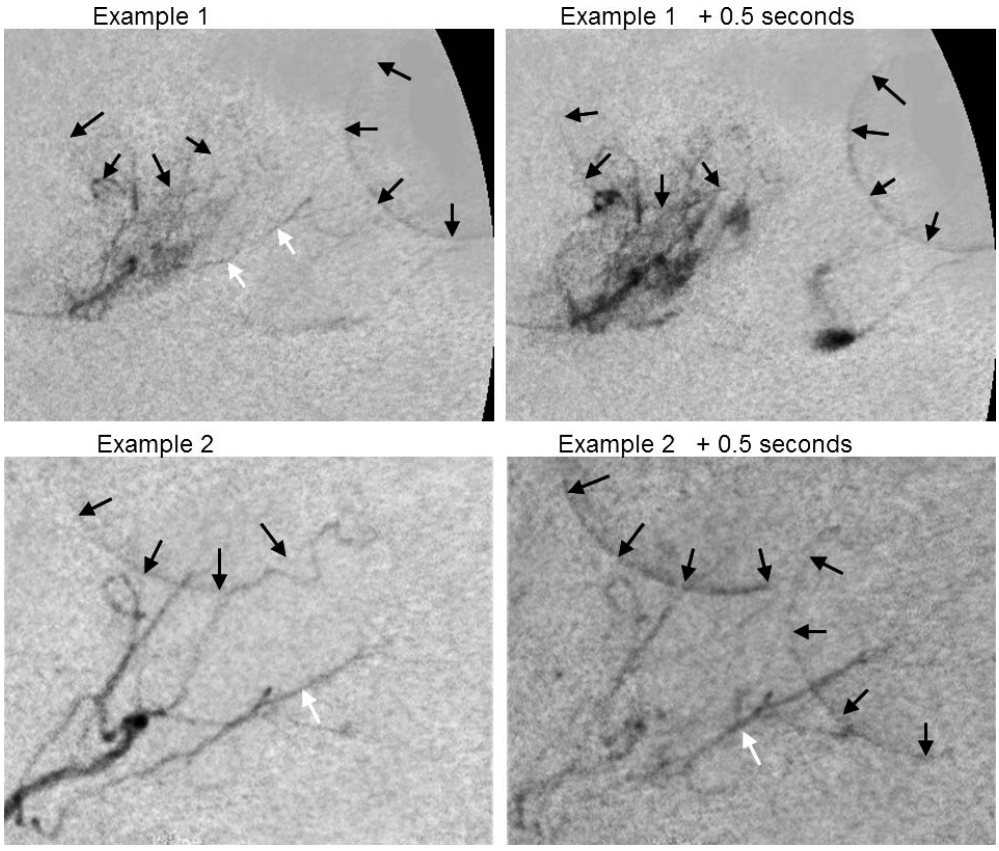

FIGURE 3. Representative angiograms of the pig ophthalmic artery (lateral projection) showing the gradual filling of the retinal circulation in two different pigs. Example 1 shows an angiogram before coiling. Example 2 shows an angiogram after coiling of the contralateral ophthalmic artery. Note that both retinas are filled with contrast medium simultaneously (*black arrows*), presumably because of blood flow from the ipsilateral ophthalmic artery to the contralateral eye. A small interconnecting vessel can be seen (*white arrow*). This blood vessel must branch distally to the location of the tip of the injection catheter, which is positioned in the ophthalmic artery. The right panels show the same projection 0.5 seconds later, demonstrating greater intensity in both retinas.

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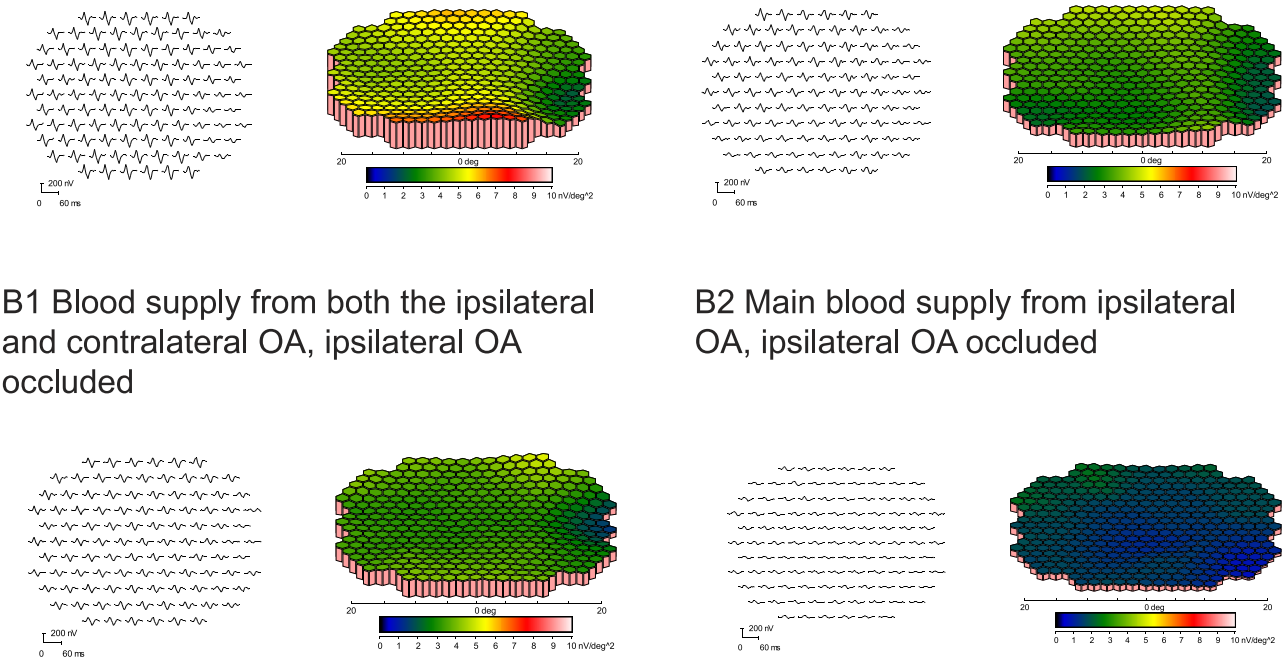

Figure 4. mfERG responses in the retina. The right panels show topographical maps, and the left panels show the individual recordings. (**A1**, **B1**) show recordings from the same pig, and (**A2**, **B2**) show recordings from another pig. (**A1**, **A2**) show recordings from a retina after occlusion of the ophthalmic artery (OA) of the contralateral eye by coiling as follows: In (**A1**), the main blood supply may be from the ipsilateral ophthalmic artery. In (**A2**), blood may be supplied by both the ipsilateral and contralateral ophthalmic arteries. (**B1**, **B2**) show recordings from a retina after occlusion of the ophthalmic artery of the ipsilateral eye by coiling as follows: In (**B1**), blood may be supplied by both the ipsilateral and contralateral ophthalmic arteries. In (**B2**), the main blood supply may be from the ipsilateral ophthalmic artery.

miniature cathode ray tube. The pattern flickers randomly, but each element follows a fixed, predetermined sequence (the m-sequence). The equipment was calibrated according to the manufacturer's instructions regarding both the grid and luminance. The light intensity in the recording area was 0.110 lux. Two additional blank, dark frames were inserted into every m-sequence. The signal gain was 100,000, and the filter range was 3 to 300 Hz with no additional notch filtering. The luminance flickered between light and dark according to a pseudorandom binary m-sequence of 75 Hz, with a mean stimulus luminance of 16.6 candela (cd)/m^2 and a flash intensity of 1.33 cd s/m^2. The spatial averaging was set to 17%, as in the settings for VERIS Science. One iteration of the artifact rejection system included in the VERIS Science software was used. The fundus was visualized in the infrared camera by means of the infrared light from the recording electrode, allowing continual visualization of the retina during the examination. The stimulus pattern was consistently positioned with the optic nerve head in the lower central part of the recording area. The mfERG traces from the visual streak area of two pigs were analyzed using maximum amplitude.

Results

Angiography

The introduction of contrast medium in the ophthalmic artery resulted in almost simultaneous filling of the ipsilateral and contralateral retinas in all six pigs. A small blood vessel (interconnecting artery) could be seen branching distally to the position of the tip of the injection catheter in the ophthalmic artery supplying the retinal circulation of the contralateral eye (Fig. 3, example 1).

After coiling, angiography of the distal parts of the same ophthalmic artery showed that blood flow to both retinas was completely inhibited. Notably, angiography of the distal parts of the contralateral ophthalmic artery resulted in contrast filling of both retinas (Fig. 3, example 2).

Multifocal Electroretinography

The mfERG recordings showed that the use of coiling to create occlusion of the ophthalmic artery had ischemic effects that varied greatly (Fig. 4). In a case of contralateral occlusion in an eye where blood may be supplied from both the ipsilateral and contralateral ophthalmic arteries (via an interconnecting vessel), ischemia seemed to be more pronounced than when the main blood supply is from the ipsilateral side only. In a case of ipsilateral occlusion in an eye where blood may be supplied from both the ipsilateral and contralateral ophthalmic arteries (via an interconnecting vessel), ischemia seemed to not be as pronounced as when the main blood supply is from the ipsilateral side only.

A hypothetical schematic illustrates the blood flow variation based on these results. This is shown in Figure 5.

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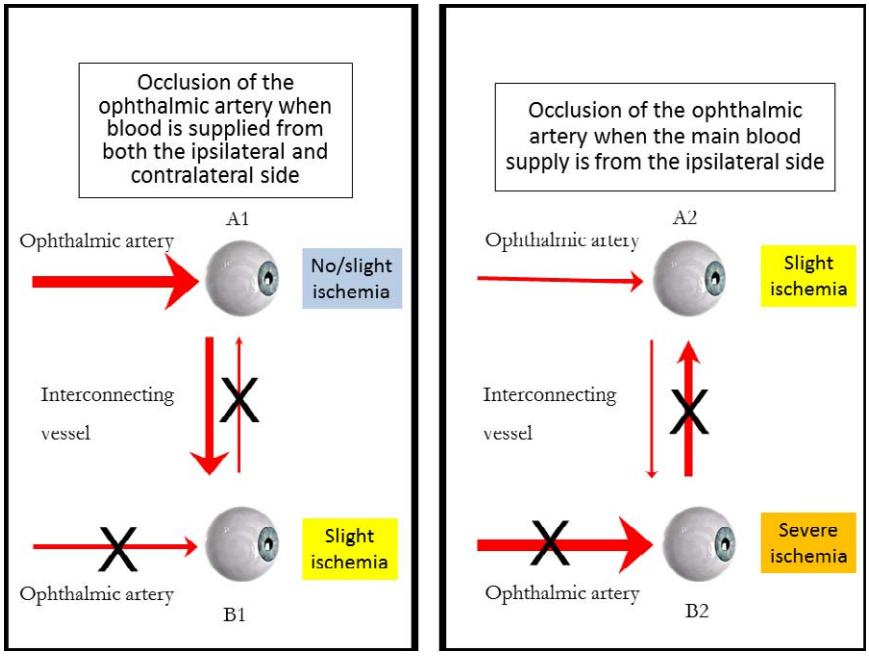

Figure 5. Hypothetical schematic illustration of the angiographies shown in Figure 3 and the blood flow based on the mfERG response shown in Figure 4. The main blood supply to eye (**A1**) is from the ipsilateral ophthalmic artery. When the contralateral ophthalmic artery is occluded (X), there is no (or only slight) ischemia. The blood supply to eye (**B1**) is from both the ipsilateral and contralateral ophthalmic arteries. When the ipsilateral ophthalmic artery is occluded, there is only slight ischemia. The blood supply to eye (**A2**) is from both the ipsilateral and contralateral ophthalmic arteries. When the contralateral ophthalmic artery is occluded, there is slight ischemia. The main blood supply to eye (**B2**) is from the ipsilateral ophthalmic artery. When the ipsilateral ophthalmic artery is occluded, there is pronounced ischemia.

Discussion

We have previously shown that the vasculature of the porcine retina can be accessed for endovascular coiling[17] and that occlusion at different sites in the vasculature created retinal ischemia of variable degrees of severity.[17,18] Endovascular access to the retinal circulation may be useful for creating experimental animal models for retinal ischemia.

In the present study, we show that the blood supply to the pig retina may originate from both the ipsilateral and contralateral ophthalmic arteries and that a small blood vessel connects the eyes. Angiography showed an interconnecting vessel shunting blood to the contralateral retina, even in the presence of a coil in the ophthalmic artery of the contralateral eye. This excludes the possibility that retrograde flow may explain the results. The interconnecting artery presumably originates from a location distal to the tip of the catheter.

Evidence of communication between the vascular systems of the eyes has been reported in other laboratory animals. In 1960, Prince et al.[20] described cross-midline anastomoses of the internal ophthalmic artery in the rabbit. Other possible cross-midline vascular routes in laboratory animals were reported in 1998 by Dondelinger et al.[21] They showed that in the pig the arteries originating from the external carotid artery, including the external ophthalmic artery, anastomose across the midline with the contralateral arteries.[21] They also reported evidence of another possible cross-midline vessel route via the rete mirabile. The right and left retia mirabilia seem to be interconnected near the hypophysis, and the rete mirabile is connected to the external ophthalmic artery through the anastomic artery. The intracerebral circulation is also connected to the ocular circulation via the internal ophthalmic arteries connecting directly to the ciliary artery.[21] The anastomic pathways of the rete mirabile and internal ophthalmic artery could be possible cross-midline routes for the passage of contrast medium when performing angiography of the common carotid. However, when performing angiography of the distal ophthalmic artery, the only possible pathway should be via the anastomoses of the external ophthalmic artery.

The results of the present study may explain the considerable interindividual variability observed in the degree of ischemia resulting from occlusion in our previous studies.[17,18] We speculate that occlusion of the ophthalmic artery by coiling may have greater ischemic effect in eyes that depended mainly on the ipsilateral ophthalmic artery for blood supply. Coiling may have less ischemic effect in retinas that received part of their blood supply from the ipsilateral ophthalmic artery and part from the contralateral ophthalmic artery via the interconnecting vessel. These results suggest that there may be an interindividual variation in the architecture of the vascular system.

Possible variants of blood flow are shown in Figure 5. The presence of collateral circulation may alter the degree of ischemia such that ischemia may be less in the occluded eye (Fig. 5B1), and occlusion of the artery to one eye may alter the blood supply to the contralateral eye, which may result in an ischemic effect in the nonoccluded eye (Fig. 5A2). These findings may be important in the development of new animal models of experimental retinal ischemia. Relevance of extrapolation to the human eye is difficult, but one cannot completely exclude the possibility of a similar collateral network also in humans. It has been shown in humans that experimentally reduced perfusion of one eye may impair the function of the contralateral eye,[22] although no evidence of vascular connection was presented in the study, and similar studies are scarce. The existence of a collateral blood circulation in humans would have clinical importance to modulate the level of ischemic damage to the retina in the event of a vascular occlusion.

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