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## Brief Report

# Venous Nicking Without Arteriovenous Contact

## The Role of the Arteriolar Microenvironment in Arteriovenous Nickings

Michel Paques, MD, PhD; Aurélie Brolly, MD; Jonathan Benesty, MD, PhD; Nicolas Lermé, PhD; Edouard Koch, MD, PhD; Florence Rossant, PhD; Isabelle Bloch, PhD; Jean-François Girmens, MD

**IMPORTANCE** Arteriovenous nickings (AVNs) in the retina are the cause of retinal vein occlusions and are also surrogates of cerebrovascular aging. The prevalent mechanistic model of AVNs stating that arteries crush veins remains somewhat unchallenged despite the lack of evidence other than fundus photographs. Here, we observed that venous nicking may be observed in the absence of physical contact with an arteriole.

**OBSERVATIONS** This observational study, conducted from January 2013 to September 2014, included 7 patients showing remodeling of a venous segment close to a retinal arteriole without arteriovenous overlap were imaged by adaptive optics imaging. Affected venous segments showed a variable association of nicking, narrowing, deviation, and opacification. Venous segments were deviated toward the arterioles in 6 of the 7 cases. The degree of venous narrowing ranged from 40% to 77%, while at these sites, the width of the intervascular space ranged from 16  $\mu\text{m}$  to 42  $\mu\text{m}$ . Similar features were identified in typical AVNs.

**CONCLUSIONS AND RELEVANCE** Arteriovenous nickings do not necessarily involve an arteriovenous compression. Instead, the topology of venous changes suggests a retractile process originating in the intervascular space. These findings have important implications for the understanding of retinal vein occlusions and of cerebrovascular aging.

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Arteriovenous nickings (AVNs) may cause branch retinal vein occlusion,<sup>1</sup> and their prevalence correlates with arterial pressure<sup>2</sup> and with lacunar stroke.<sup>3</sup> Thus, AVNs are surrogates of the retinal and cerebral microcirculations. However, despite its clinical importance, the pathophysiology of AVNs has received limited attention. This may be because there is a general acceptance of the concept postulating that the vein is crushed by the bypassing artery. This belief persists despite the fact that histologies have consistently reported that venous changes were related to perivascular changes described either as glial proliferation,<sup>4</sup> glial edema,<sup>5</sup> or extracellular deposits.<sup>6</sup> Furthermore, clinical studies of AVNs using high-resolution imaging have failed to evidence external compression of veins<sup>7</sup> or parietal thickening of arterioles.<sup>8</sup>

Clinical studies of AVNs are impaired by the extreme variability of their presentation and the difficult access of the arteriovenous interface. In this regard, of interest are cases of venous remodeling occurring where an artery and a vein are close yet not overlapping<sup>8,9</sup> because the arteriovenous interface is directly observable. Here, we analyzed such cases using high-

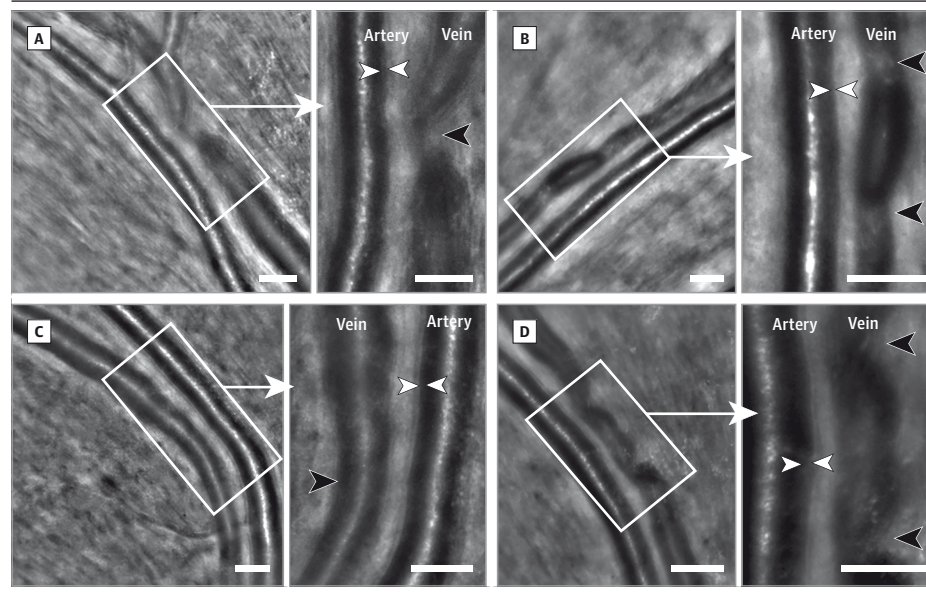
resolution imaging to better understand the relationship between the arteriovenous interface and venous changes.

### Methods

This institutional clinical study, conducted from January 2013 to September 2014, was carried out according to the principles outlined in the Declaration of Helsinki. Approval of the Ethics Committee of the Saint-Antoine Hospital (Paris, France) was obtained. Seven adult patients showing venous remodeling proximal to arterioles were recruited. Each patient received full oral and written information and gave written consent prior to inclusion.

Infrared and 488-nm reflectance imaging and optical coherence tomography were obtained using combined scanning laser ophthalmoscope-optical coherence tomography (Spectralis; Heidelberg Engineering). Adaptive optics (AOs) infrared fundus images were obtained with a commercially available flood imaging AO camera (rtx1 camera; Imagine Eyes) using a previously described procedure.<sup>8</sup> The AO camera illumi-

Figure 1. Adaptive Optics Images of Arteriovenous Interfaces of Venous Nickings



In each panel, the magnification is shown to the right of the original adaptive optics image. The arteriolar wall (between white arrowheads) does not enter in contact with the venous lumen. The black arrowheads indicate peak venous narrowing (bars = 125  $\mu$ m; see also eFigure 1 in the Supplement).

nates the fundus with a noncoherent light delivered by a superluminescent diode at 840 nm, covering a  $4^\circ \times 4^\circ$  area (ie, approximately 1.2 mm  $\times$  1.2 mm in emmetropic eyes). For image acquisition, the gaze of the left eye was oriented with an external target, which allowed the exploration of the fundus of the right eye up to approximately  $30^\circ$  from the disc.

Arteries and veins were semiautomatically segmented from AO images using a custom software running under Matlab (Mathworks).<sup>10</sup> The segmentation algorithm is based on the detection of 4 curves parallel to the central reflection, which are refined using a deformable model incorporating a parallelism constraint. Graphic representations of the venous diameter and of the width of the intervascular space (ie, the distance between the venous lumen and the outer limit of the arteriolar wall) along a given venous segment were generated.

## Results

Seven cases of focal venous remodeling without arteriovenous crossing from 7 patients were documented. Their mean age was 65.9 years (range, 54-80); 3 were women; and 4 had arterial hypertension. Three were fellow eyes of branch retinal vein occlusion. Part of the data from case 4 was previously reported.<sup>8</sup> The regions of interest were located along temporal arcades, up to 3 mm from the disc. The affected vessels had a diameter of 100  $\mu$ m to 150  $\mu$ m. There was unequivocal deviation of the vein toward the arteriole in 6 of the 7 cases. Adaptive optics imaging allowed a high-power view of the arteriolar wall, the arteriovenous interface, and the venous morphology (Figure 1 and eFigure 1 in the Supplement). Nicking of the vein at the side opposite to the arteriole was noted in 3 cases (1, 4, and 5). Adaptive optics imaging could delineate the area between the outer boundary of the arteriole and the venous lumen. At sites of maximal narrowings, the reduction of

venous diameter ranged from 40% to 77%, while the width of the intervascular space ranged from 16  $\mu$ m to 42  $\mu$ m (Figure 2; eFigure 1 in the Supplement).

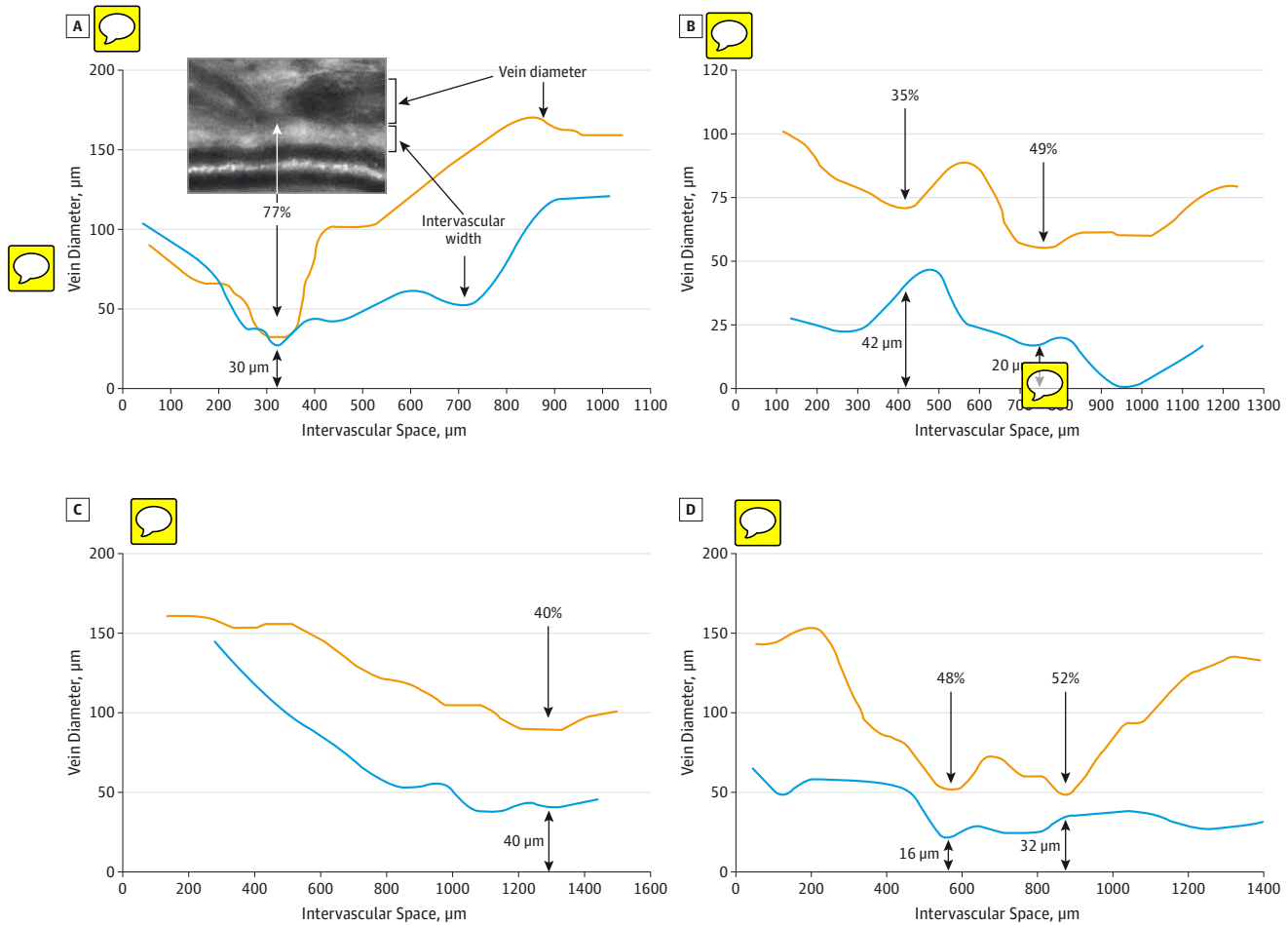
We then examined AO images of common presentations of AVNs (that is, within arteriovenous crossing) to search for similar venous changes. For this, we retrospectively examined AO images of AVNs occurring at arteriovenous crossings from other eyes to determine whether similar changes may be present (Figure 3). Focal narrowing, venous dragging toward the arteriole, and paravascular opacification in AVNs were present; some combined several of these features.

## Discussion

There has been a longstanding yet unsubstantiated consensus among clinicians about the compressive nature of the arteriovenous conflict underlying AVNs. Our findings support the conclusions of histology and in vivo studies suggesting that the paradigm of arterial crushing as the cause of venous nicking stems from a misinterpretation of fundus photographs.<sup>4</sup> We indeed found here that veins close to arterioles, but without detectable arteriovenous contact, may undergo marked phenotypical changes comprising nicking, narrowing, opacification, and/or dragging. Nicking of the venous wall on the side opposite to the arteriole, venous dragging toward the arteriole, and the presence of an arteriovenous gap up to 40  $\mu$ m do not fit easily with the hypothesis of an arterial compression. Similar findings were retrospectively evidenced in AVNs occurring with arteriovenous overlap from other patients, which suggest that classic AVNs may also imply indirect arteriovenous interaction.

Our findings suggest that the interaction between arteries and veins leading to AVNs is mediated by the paravascular milieu. Such hypothesis of an indirect arteriovenous interac-

Figure 2. Morphometric Analysis of Arteriovenous Interfaces



Variations of lumen diameter (orange lines) and of interspace (blue lines) were measured along venous segments. The black arrows point to venous narrowings.

tion has been previously proposed.<sup>11</sup> Our results suggest that retraction of the interspace plays a key role in venous changes; however, this somewhat conflicts with histology findings, which would rather imply its expansion. Therefore, the various ophthalmoscopic presentations of AVNs may result from the combined effects of hypertrophy and retraction of the interspace. The common adventitia and/or the inner limiting membrane may provide a scaffold transmitting retractile forces. The lower mechanical resistance of veins would explain their predominant deviation.

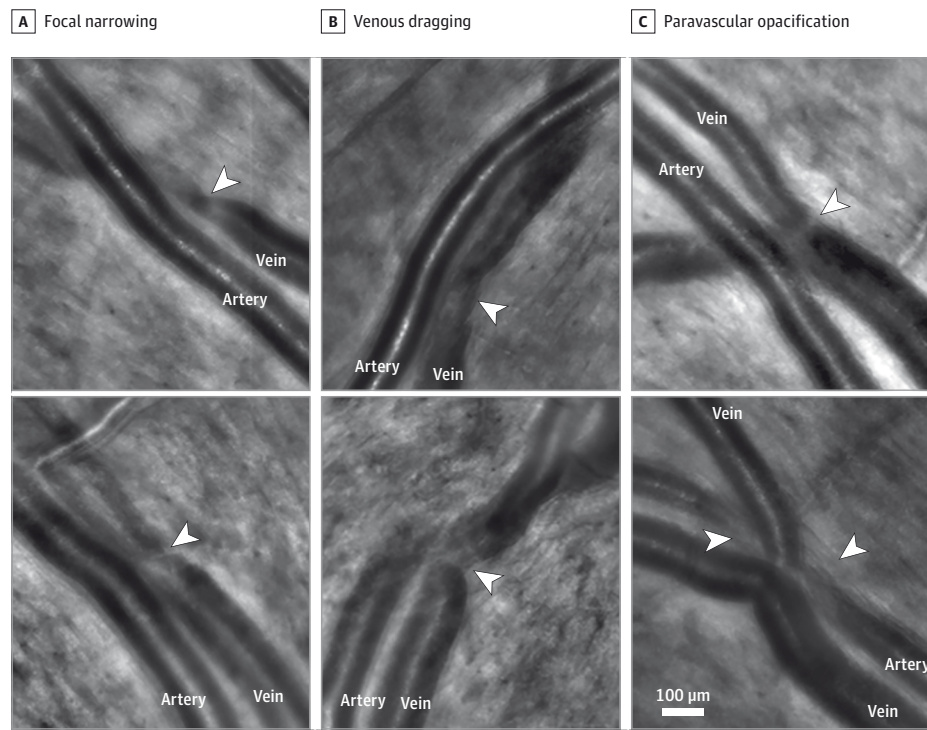
The process that initiates such arteriovenous interaction remains to be characterized. Molecular compounds in the circulation and/or derived from the metabolism of arteries may leak into the arteriolar microenvironment and modify glial, microglial, and/or venous metabolism. The factors mediating such arteriovenous interaction may either be immunomodulators or vasomodulators. It is known that AVNs are related to biological markers of inflammation<sup>12</sup> and that veins are responsive to vasoactive compounds.<sup>13</sup> Chronically increased venous tone could induce rearrangement of the scaffold of smooth muscle cells of veins, similarly to what is observed in

arterioles during arterial hypertension.<sup>14</sup> The role of venous flow turbulence in this process is unclear because laminar flow may be present even in severe venous narrowings (eFigure 2 in the Supplement).

There is indirect evidence that AVNs may regress,<sup>15</sup> suggesting that AVNs have a dynamic component. Therefore, further investigations may address the natural history of AVNs. Histology of arteriovenous crossings may address glial cells, the arrangement of intracellular actin networks, and/or the extracellular matrix. The presence of vasoactive or inflammatory metabolites, in particular small and/or lipophilic molecules,<sup>11</sup> which may cross the blood-retinal barrier, may also be explored. It is unclear whether experimental studies will be contributive because we have as of yet failed to identify AVNs in rodent and nonhuman primate eyes (M.P.; unpublished data; 2013). Given the proximity of the central artery and vein within the optic nerve, it is plausible that central retinal vein occlusion may be related to a similar interaction. It may also be of interest to document whether similar changes occur in the brain.



Figure 3. Adaptive Optics Images of Classic Arteriovenous Nickings (With Arteriovenous Crossings)



The arrowheads show the site of focal narrowing (A), dragging of the vein toward the artery (B), and paravascular opacification (C).

## Conclusions

In summary, this study found that arteriovenous nickings do not necessarily involve an arteriovenous compression. In-

stead, the topology of venous changes suggests a retractile process originating in the intervacular space. These findings have important implications for the understanding of retinal vein occlusions and cerebrovascular aging.

### ARTICLE INFORMATION

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**Study concept and design:** Paques, Benesty, Lermé, Rossant.

**Acquisition, analysis, or interpretation of data:** Paques, Brolly, Koch, Bloch, Girmens.

**Drafting of the manuscript:** Paques, Brolly, Benesty, Rossant.

**Critical revision of the manuscript for important intellectual content:** Paques, Lermé, Koch, Bloch, Girmens.

**Obtained funding:** Paques.

**Administrative, technical, or material support:** Benesty, Lermé, Koch, Rossant.

**Study supervision:** Paques, Bloch.

**Conflict of Interest Disclosures:** All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Dr Paques is a consultant for Imagine Eyes, the manufacturer of the adaptive optics camera used in

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