

Retinopathy of Prematurity

(Retrolental Fibroplasia)

Retinal vascular development • Neovascularization • Tractional injury

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Learning objectives

- Explain how interruption of normal retinal vascularization predisposes the preterm infant to ROP.
- Link oxygen exposure, VEGF suppression, subsequent hypoxia and pathologic angiogenesis.
- Recognize the morphologic basis of macular dragging and tractional retinal detachment.
- Apply the ICROP3 descriptors and distinguish observation from treatment-requiring disease.
- Explain why scheduled screening and prolonged follow-up prevent avoidable blindness.

Retinopathy of prematurity: The central lesion

- A vasoproliferative disorder of incompletely vascularized retina in premature infants.
- Abnormal vessels develop at the border of vascularized and avascular retinal tissue.
- Fibrovascular proliferation can contract, deform the macula and detach the retina.
- Retrolental fibroplasia refers historically to severe cicatricial sequelae.

ROP is a developmental vascular disease

Premature delivery

Retinal vessel growth is unfinished when extrauterine life begins.

Vascular growth arrest

The avascular retinal periphery remains metabolically vulnerable.

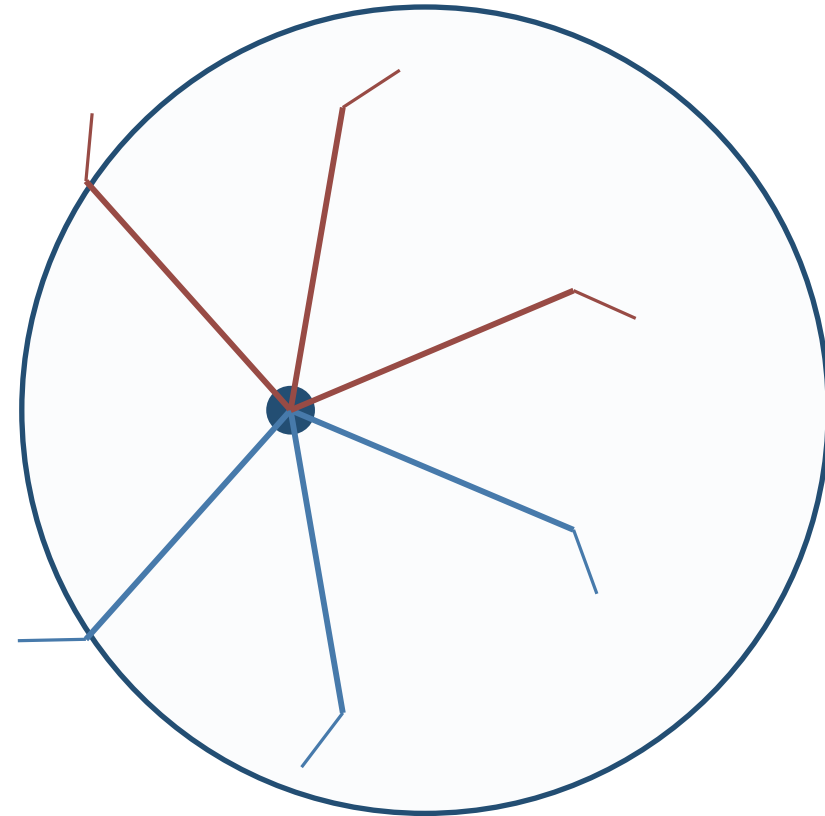
Proliferative response

Later hypoxic drive produces aberrant angiogenesis and traction.

The initiating problem is interrupted development—not a primary retinal infection.

The retina must vascularize before it matures

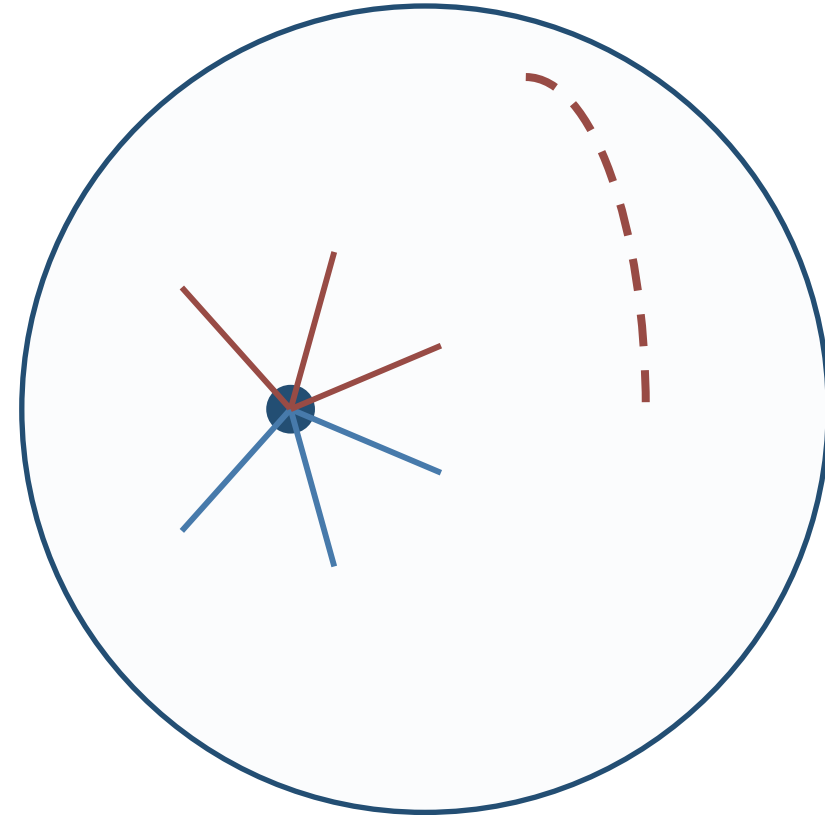
- Retinal vessels extend outward from the optic nerve region toward the periphery during gestation.
- The peripheral retina remains avascular until later in development.
- A very preterm birth exposes incomplete vessels to extrauterine oxygen and nutritional changes.



Schematic — retinal view

Why the temporal periphery is especially vulnerable

- Temporal retinal vascularization normally completes later than nasal vascularization.
- Immature peripheral vessels are highly susceptible to growth arrest and regression.
- The retina beyond the vascular front becomes an avascular substrate for later VEGF-driven proliferation.



Schematic — retinal view

Four structures explain the visual consequences

Optic disc

Central site where retinal vessels enter and spread toward the periphery.

Temporal retina

Late-vascularizing retinal periphery, emphasized in the Robbins description.

Macula and fovea

Central visual region lying temporally to the optic disc.

Vitreoretinal interface

Surface along which neovascular tissue may proliferate and exert traction.

Prematurity and low birth weight are major risk markers

- The degree of retinal immaturity increases as gestational age decreases.
- Lower birth weight and unstable neonatal course identify infants with greater disease risk.
- Oxygen exposure is a modifiable factor, not an exclusive cause of all ROP.
- Screening decisions require a standardized clinical program, not symptoms alone.

Supplemental oxygen: Essential but biologically active

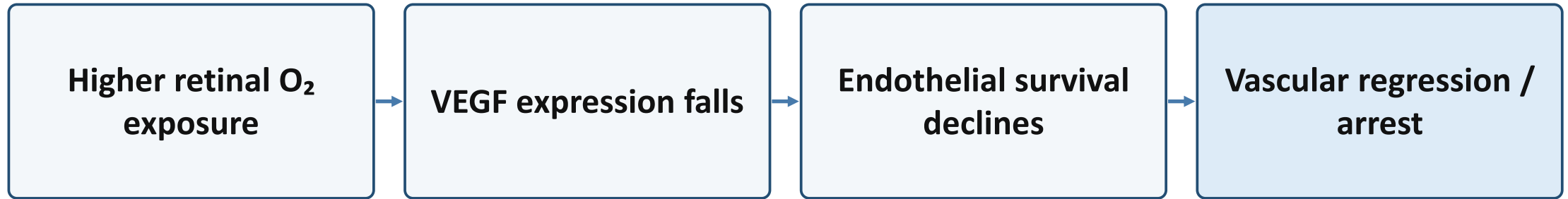
- Oxygen support treats potentially life-threatening neonatal respiratory insufficiency.
- Relative hyperoxia suppresses signals needed for normal retinal vessel growth.
- Unrestricted oxygen should not be conflated with carefully monitored neonatal oxygen therapy.
- Clinical oxygen targets must balance retinal injury against mortality and other neonatal risks.

Two temporally distinct phases



- The first phase creates or maintains avascular retina.
- The second phase generates proliferative lesions at the vascular–avascular interface.

Phase I: Relative hyperoxia suppresses angiogenesis



- Endothelial apoptosis and vasoconstriction in immature retinal vessels.
- The net consequence is inadequate physiologic capillary expansion.

VEGF is a survival and growth signal

Physiologic VEGF

Supports vascular development in the immature retina.

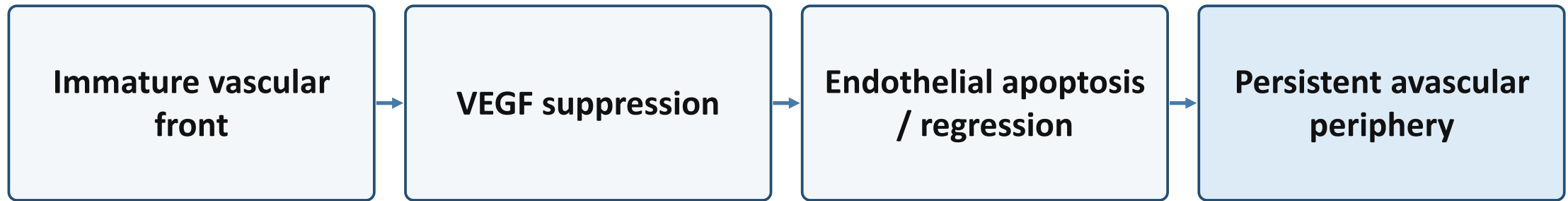
Oxygen-rich environment

Suppresses VEGF expression and can reduce endothelial survival.

Ischemic retina

Later restores and increases VEGF, stimulating abnormal sprouting.

Endothelial loss explains the avascular retina



- The lesion is not merely dilation of mature retinal vessels.
- An altered vascular front creates the territory that later becomes hypoxic.

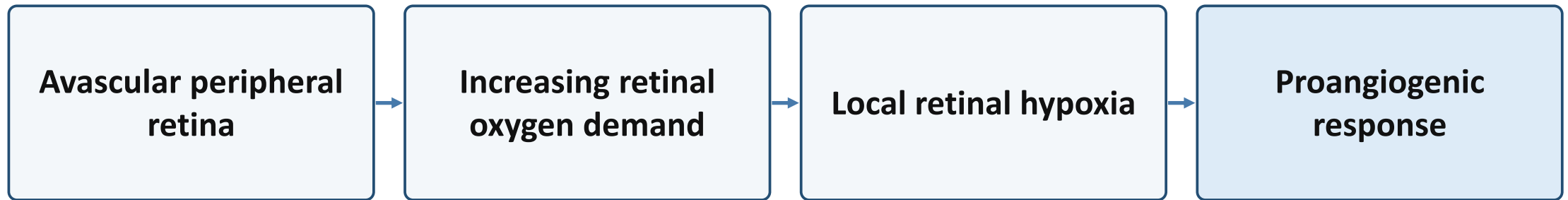
The avascular region is not metabolically inert

- Neural retinal development continues even when vascular extension has stalled.
- Increasing oxygen requirements can outpace oxygen delivery to peripheral retina.
- This mismatch produces the hypoxic stimulus for pathologic angiogenesis.

Phase I and phase II are linked causally

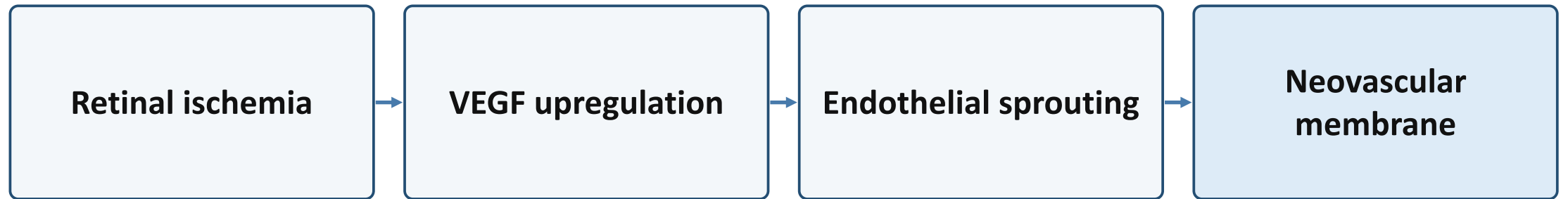
Phase I: Vascular arrest	Phase II: Proliferative response
Relative hyperoxia / growth-factor suppression	Relative retinal ischemia / hypoxia
VEGF availability is reduced	VEGF expression rebounds
Immature capillaries regress or fail to grow	Aberrant new vessels develop
Peripheral avascular retina persists	Fibrovascular proliferation produces traction

Phase II begins when oxygen demand exceeds supply



- The immature retina responds to ischemia by increasing VEGF.
- The resulting neovascular growth is structurally different from orderly vascular maturation.

VEGF rebound drives the proliferative lesion



- VEGF links tissue oxygenation to vascular phenotype.
- Anatomic location and subsequent membrane contraction determine the structural harm.

Normal vascular growth differs from pathologic sprouting

Physiologic development	ROP-associated proliferation
Orderly expansion of vascular territory	New vessels proliferate at an abnormal interface
Supplies retinal metabolism	Often fails to normalize peripheral vascularization
No fibrovascular traction	May organize into contractile fibrovascular tissue
Supports retinal structure	Can distort or detach neural retina

IGF-1 is an additional permissive growth factor

Preterm metabolic setting

Serum IGF-1 levels may be low after very early birth.

Early vascularization

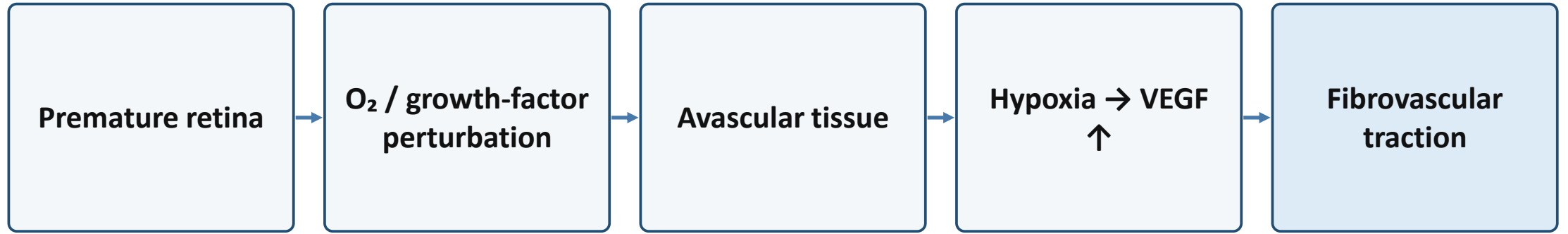
Adequate IGF-1 supports normal VEGF-mediated vascular development.

Later progression

Developmental changes in IGF-1 and VEGF modify angiogenic capacity.

IGF-1 is supplementary mechanistic context, not a routine diagnostic test for ROP.

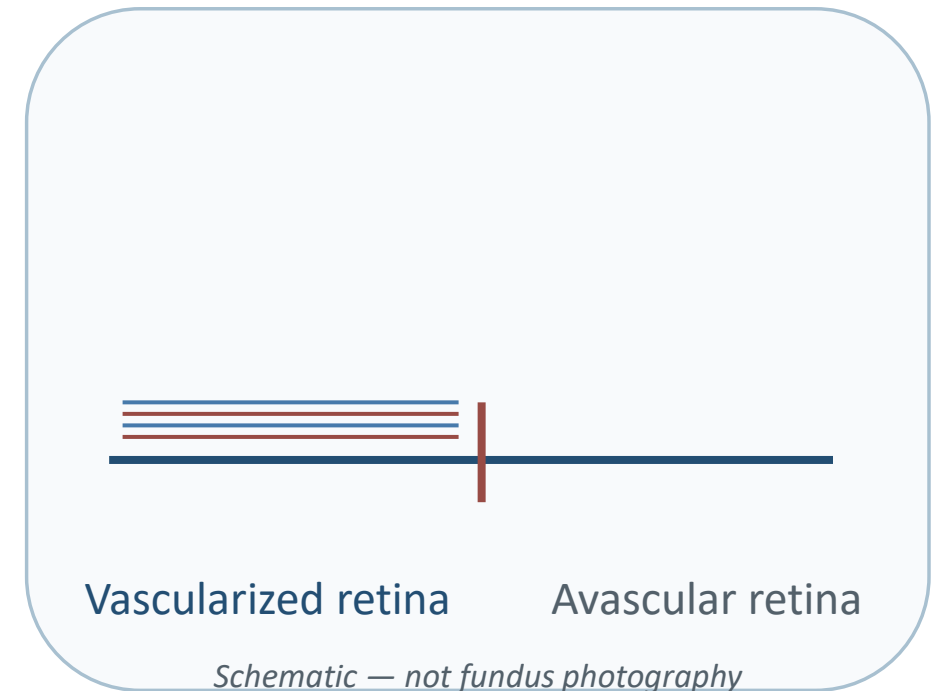
Integrated pathogenic sequence



- This is the explanatory pathway connecting prematurity to retinal distortion.
- Disease severity also depends on where proliferation occurs and how much traction develops.

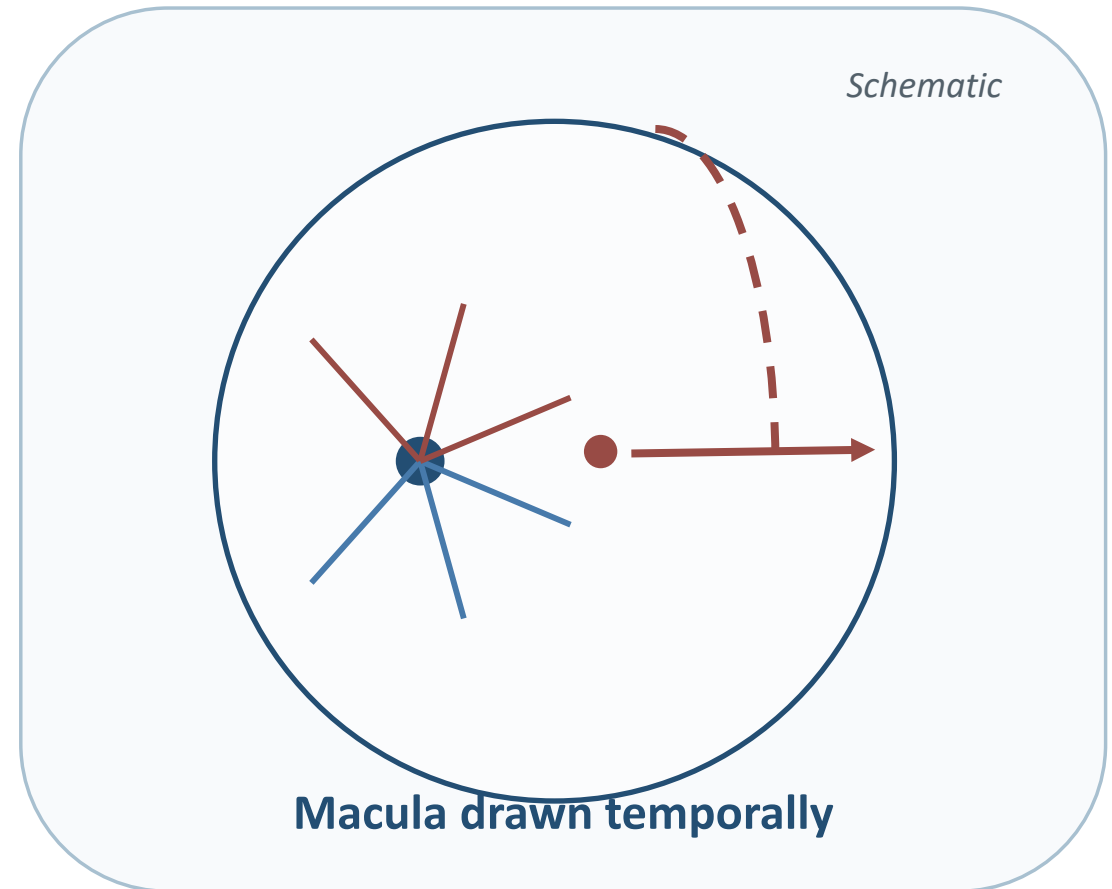
The vascular–avascular junction is the diagnostic site

- The advancing vascular front is the interface between perfused and avascular retina.
- Abnormal vascular tissue at this border defines acute morphologic stages.
- Progression is evaluated by retinal location, appearance, vascular activity and extent.



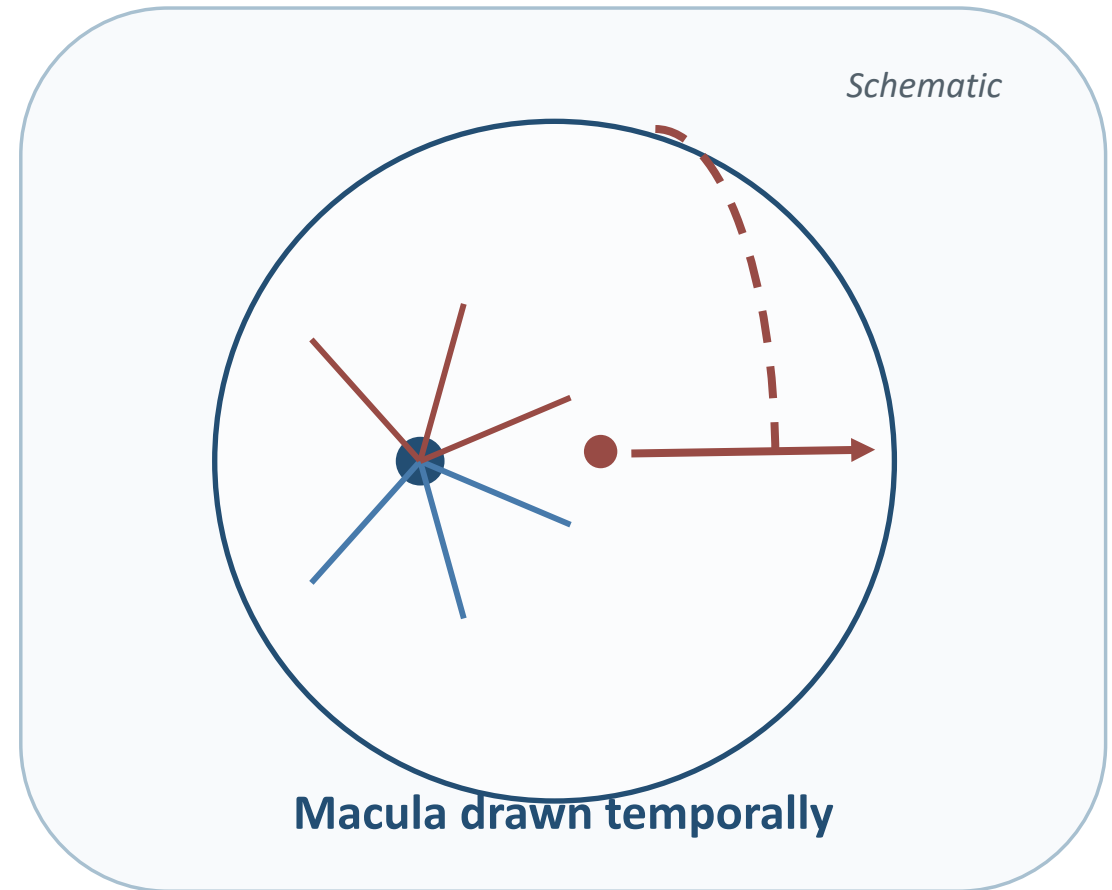
Why neovascular tissue becomes a tractional membrane

- Abnormal vessels coexist with fibrous and glial components in proliferative membranes.
- Organization and contraction transmit force to adjacent neural retina.
- The clinical consequence depends on where the membrane adheres and how it contracts.



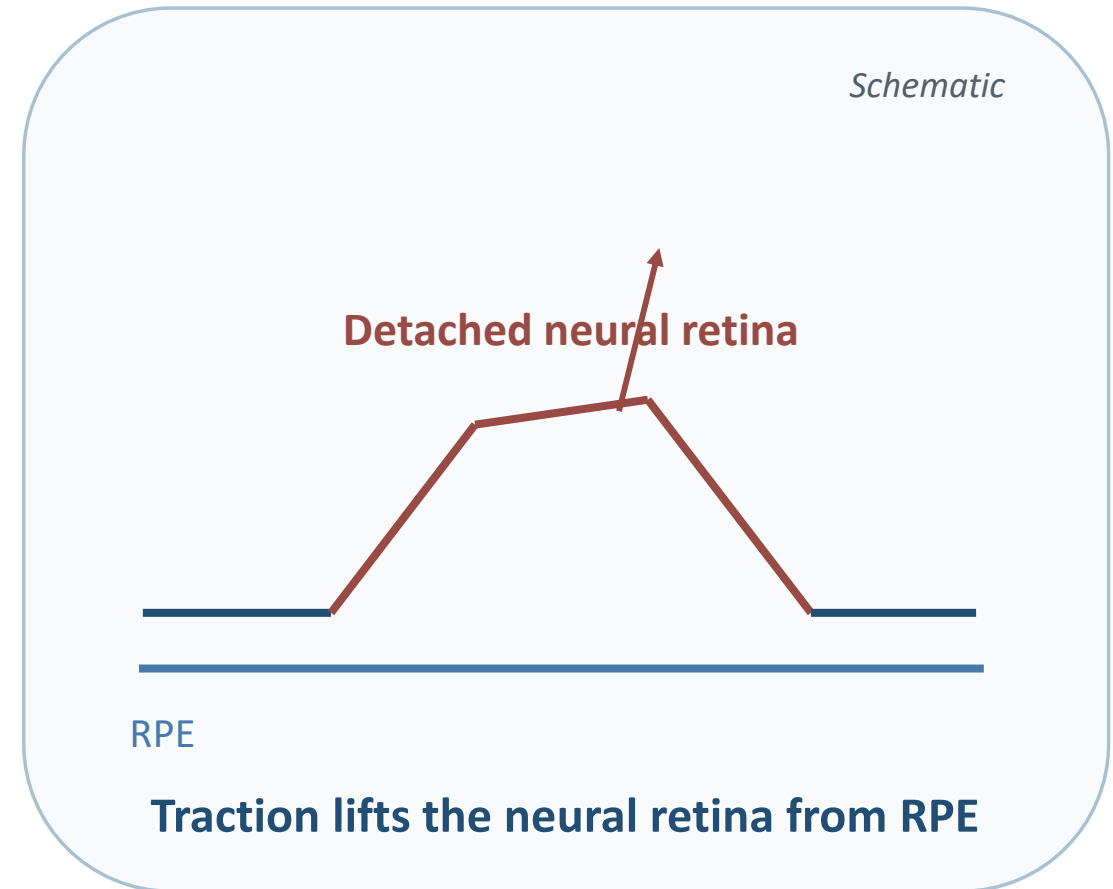
Macular dragging: The key Robbins description

- Peripheral fibrovascular tissue contracts toward its point of attachment.
- Traction pulls the temporal retina and displaces the macula laterally.
- Displacement distorts the normal geometry of central vision.



Traction may progress to retinal detachment

- Contractile fibrovascular tissue exerts a mechanical lifting force.
- Neurosensory retina separates from the retinal pigment epithelium.
- If traction is severe, macula-involving or total detachment compromises vision.



Retrolental fibroplasia describes advanced scarring

- The historical term emphasizes fibrovascular and cicatricial tissue behind the lens.
- It corresponds to severe late structural disease, rather than the full modern spectrum of ROP.
- Current diagnostic communication uses retinopathy of prematurity and explicit ICROP3 descriptors.

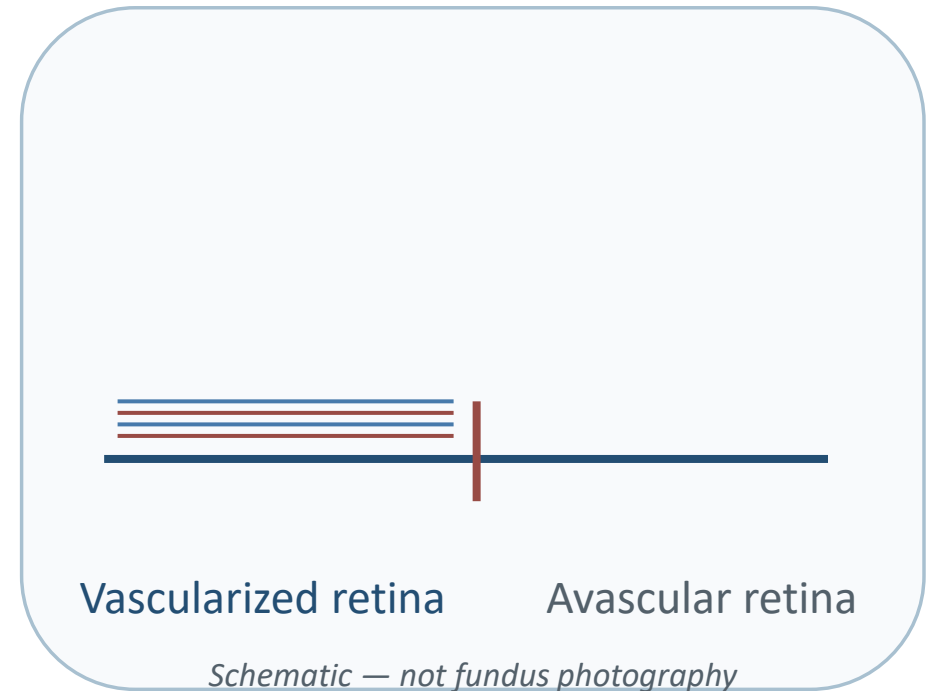
Morphology: A sequence of tissue responses



- These clinical stages describe morphology rather than mutually obligatory time points.
- Aggressive ROP may evolve rapidly without a typical staged course.

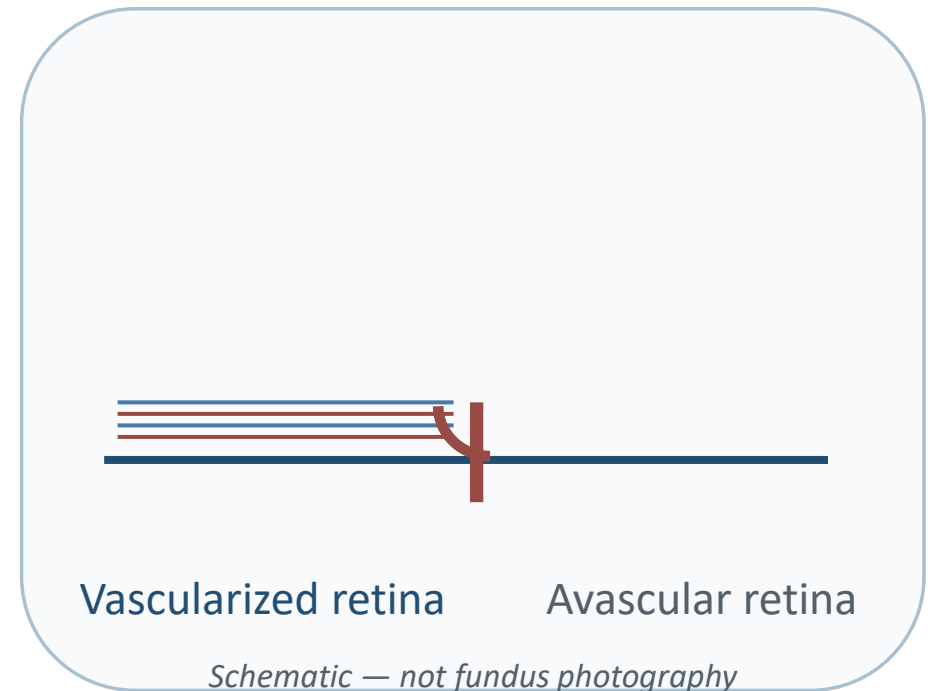
Stage 1: A demarcation line

- A thin line separates vascularized and avascular retina.
- There is no elevated ridge and no extraretinal neovascular proliferation.
- Stage alone is insufficient: Zone and posterior vascular changes modify risk.



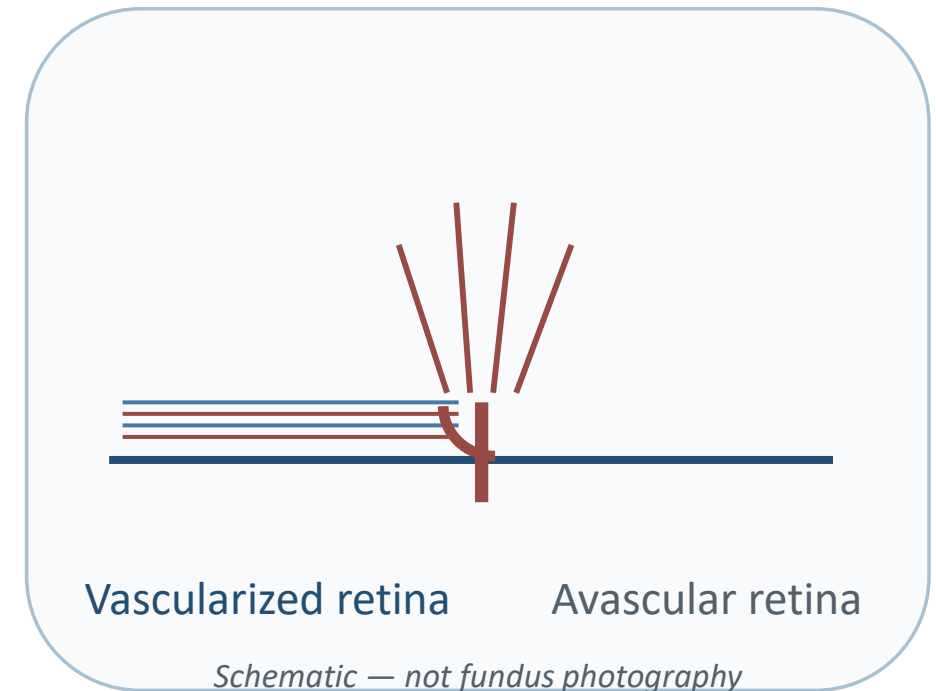
Stage 2: A raised ridge

- The junction becomes elevated above the retinal surface.
- Abnormal vessels may be apparent near the ridge.
- Conflating a ridge with clear extraretinal neovascularization overstates the stage.



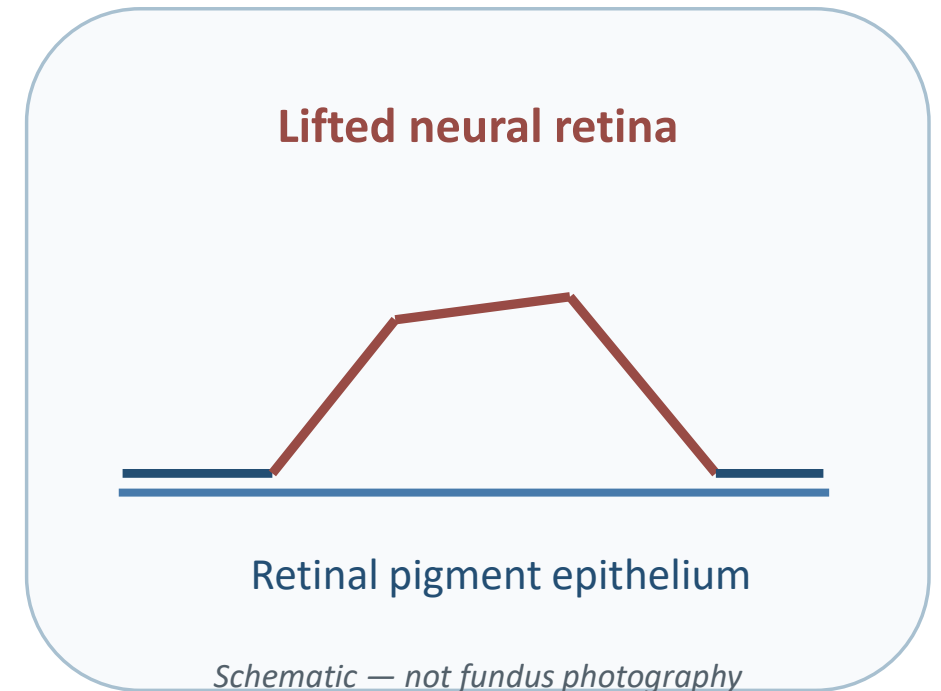
Stage 3: Extraretinal neovascular proliferation

- Neovascular tissue extends at or beyond the vascular–avascular junction.
- ICROP3 recognizes classic extraretinal proliferation and a flat neovascular variant.
- Fibrovascular organization creates the mechanical substrate for traction.



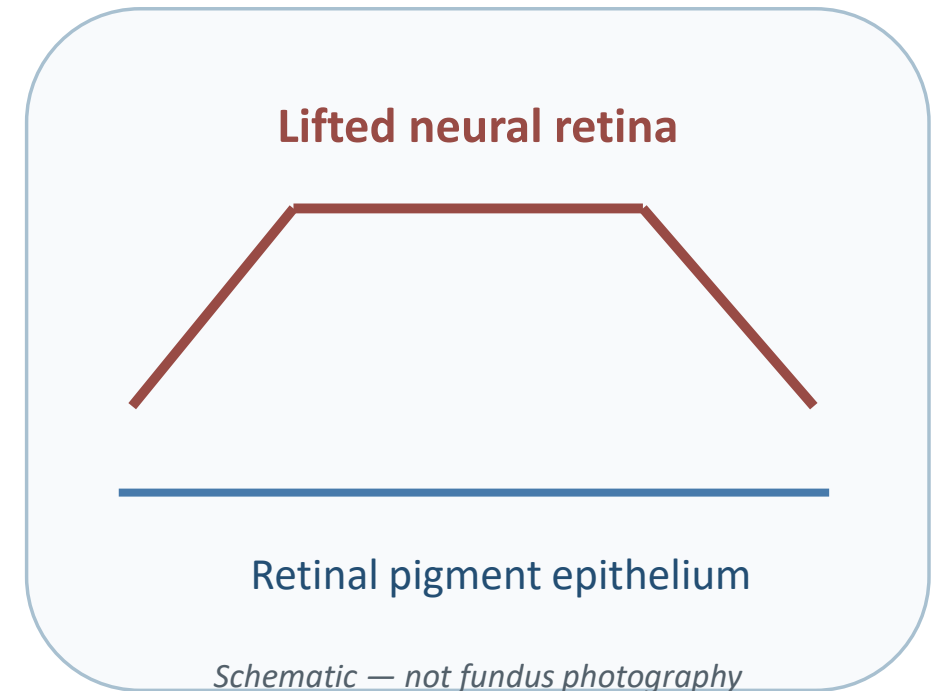
Stage 4: Partial retinal detachment

- Traction detaches part, but not all, of the retina.
- Stage 4A: The fovea remains attached.
- Stage 4B: The fovea is detached, indicating central retinal involvement.



Stage 5: Total retinal detachment

- The retina is totally detached, often with marked distortion.
- ICROP3 further subdivides stage 5 by fundus visibility and anterior segment abnormalities.
- Advanced cicatricial disease has a poorer functional outlook than earlier treatable disease.



Severe disease threatens visual function by anatomy

Macular ectopia

Tangential traction displaces the macula and impairs retinal alignment.

Foveal detachment

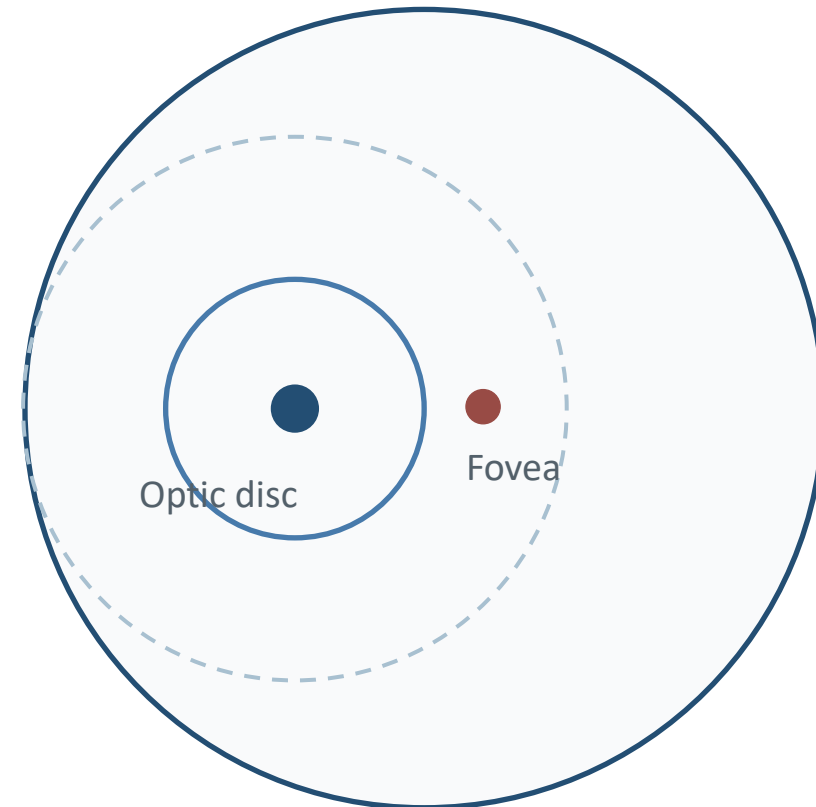
Separation of central neurosensory retina places fine vision at risk.

Total detachment

Extensive distortion and loss of attachment can cause profound impairment.

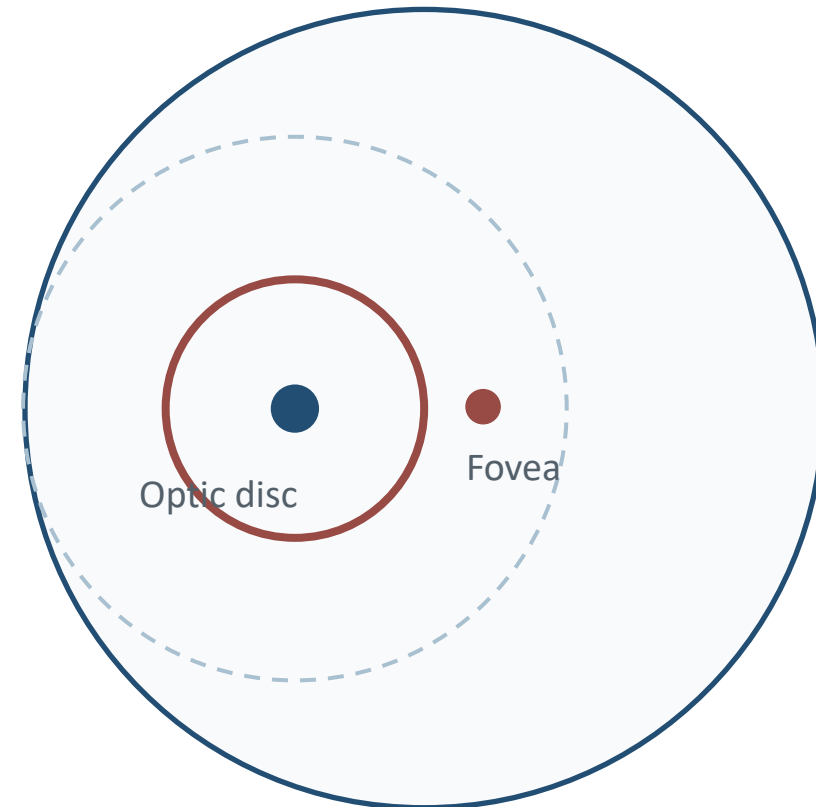
Anatomic zone modifies the clinical meaning of stage

- ICROP3 defines three zones centered on the optic disc.
- Posterior (zone I) disease is generally more concerning than peripheral disease of equal stage.
- Report location together with stage and vascular activity.



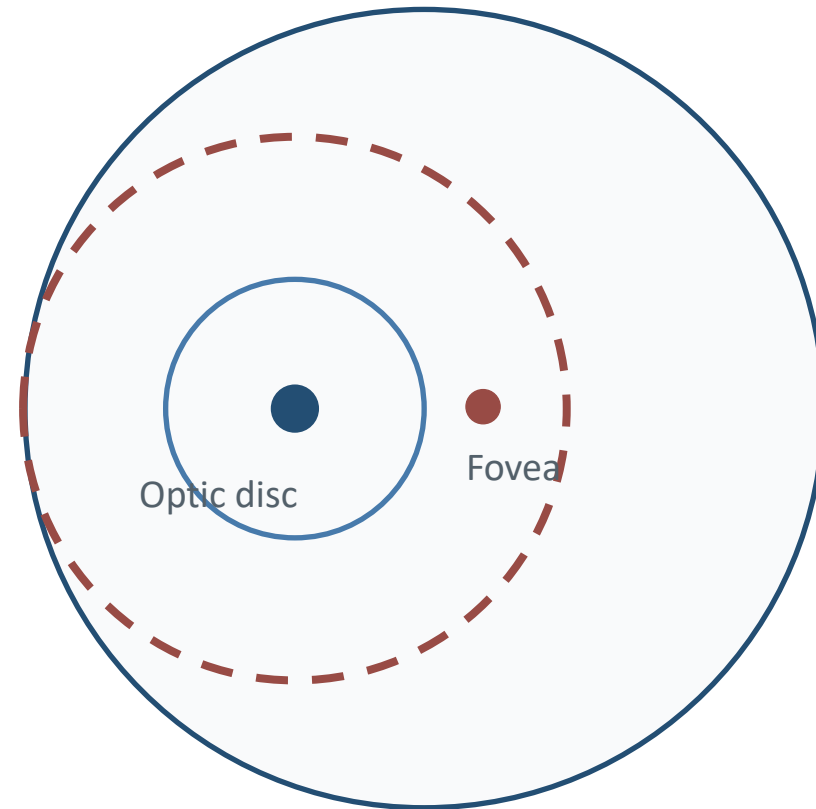
Zone I: The posterior retina

- Zone I is a circle centered on the optic disc.
- Its radius is twice the distance from disc center to foveal center.
- Disease here has high clinical importance, even when overt ridge formation is limited.



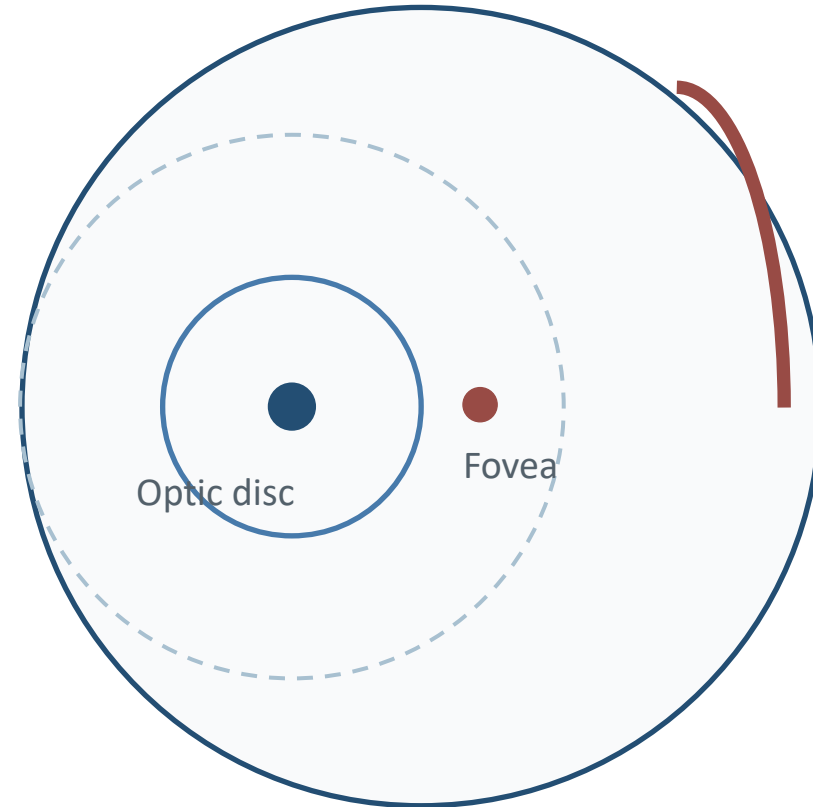
Zone II: The midperipheral retina

- Zone II extends beyond zone I to the nasal ora serrata.
- ICROP3 also identifies posterior zone II for more precise localization.
- Zone II stage 2 or 3 with plus disease meets ETROP type 1 criteria.



Zone III: Residual temporal crescent

- Zone III is the remaining temporal peripheral crescent.
- It is usually the last region to vascularize.
- A peripheral zone does not by itself define disease severity or follow-up completion.



Posterior zone II and notch improve localization

Posterior zone II

ICROP3 defines a 2-disc-diameter zone just anterior to the zone I border.

Notch

A 1–2 clock-hour incursion of a lesion into a more posterior zone.

Clinical reporting

Record the most posterior zone involved and qualify a notch explicitly.

Plus disease indicates abnormal posterior vessels

Descriptor	Posterior vascular appearance
Normal	No abnormal dilation or tortuosity
Preplus	Dilation and/or tortuosity greater than normal but insufficient for plus
Plus	Marked posterior vascular dilation and tortuosity
ICROP3 principle	These changes form a continuum rather than binary biologic states

Plus disease changes management priority

- Marked posterior pole venous dilation and arteriolar tortuosity indicate vascular activity.
- A plus designation must be assessed together with zone and stage.
- Posterior vascular abnormalities are not synonymous with fibrovascular traction.
- ICROP3 emphasizes graded severity and careful photographic comparison.

Aggressive ROP is a rapidly progressive phenotype

- Aggressive ROP (A-ROP) may progress without recognizable conventional stages.
- Severe vascular abnormalities and pathologic neovascularization develop rapidly.
- ICROP3 replaces the older term aggressive-posterior ROP because occurrence is not confined to the posterior retina.
- It warrants urgent expert assessment and close management.

A complete ROP description is multidimensional

Location and extent

Zone; Circumferential clock-hour distribution; Posterior notch if present.

Morphologic stage

Stage 1, 2, 3, 4A/4B or 5 (with relevant stage 5 subdivision).

Activity and evolution

Normal / preplus / plus;
Aggressive phenotype;
Regression or reactivation.

Never describe ROP using only a stage number.

ROP can regress without reaching detachment

- Mild disease may regress with subsequent physiologic vessel maturation.
- Regression may be spontaneous or follow retinal ablation or anti-VEGF treatment.
- ICROP3 distinguishes complete from incomplete regression.
- Residual avascular retina and late complications must be recorded.

Type 1 ROP identifies treatment-requiring disease

ETROP type 1 criterion	Clinical interpretation
Zone I, any stage with plus	Treat
Zone I, stage 3 without plus	Treat
Zone II, stage 2 or 3 with plus	Treat

ETROP type 1 is a treatment threshold—not an alternative anatomic stage.

Type 2 ROP requires close surveillance

ETROP type 2 criterion	Implication
Zone I, stage 1 or 2 without plus	Observe with planned re-examination
Zone II, stage 3 without plus	Observe with planned re-examination
Progression to type 1	Reassess promptly for treatment

Why type 1 and type 2 cannot be guessed by stage

Same stage, different zone

Stage 3 without plus is type 1 in zone I, but type 2 in zone II.

Same zone, different activity

Zone II stage 3 becomes type 1 when plus disease is present.

Clinical consequence

Zone, stage and plus must be stated together before treatment decisions.

U.S. Screening eligibility: AAP 2018 statement

- Routine screening: Birth weight ≤ 1500 g or gestational age ≤ 30 weeks.
- Selected heavier or more mature infants also require screening when the neonatal course is high risk.
- Eligibility should follow local protocols; Criteria may differ in other countries.
- ROP may be asymptomatic before it becomes vision-threatening.

When is the first screening examination?

- Timing depends on gestational age at birth and postmenstrual age.
- For very immature infants, examination is generally scheduled around 31 weeks postmenstrual age.
- For infants born later within the eligible range, first screening is generally at about 4 weeks of chronological age.
- Use the published age-specific schedule and neonatology–ophthalmology coordination.

Serial examination is the diagnostic strategy



- One normal or mildly abnormal examination does not establish that risk has ended.
- Discharge plans must preserve timely ROP follow-up.

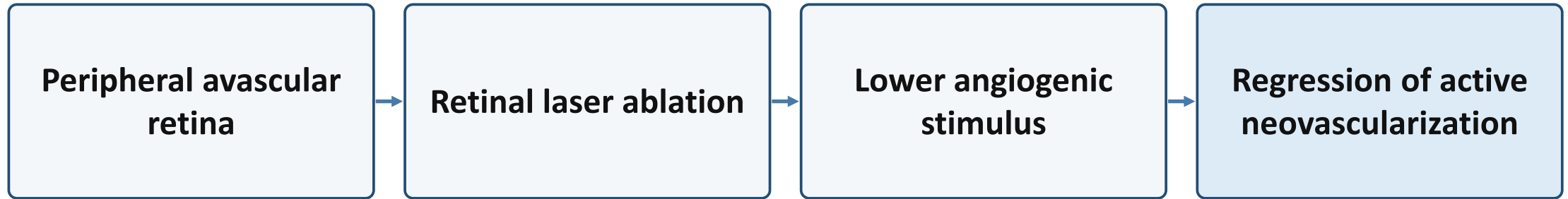
What the examiner should document

Required element	Question answered
Zone / posterior extension	Where is the disease?
Stage / retinal detachment	What lesion is present?
Plus / preplus status	How active are posterior vessels?
Extent, regression, reactivation	How much retina, and is disease evolving?

Prevention requires careful oxygen stewardship

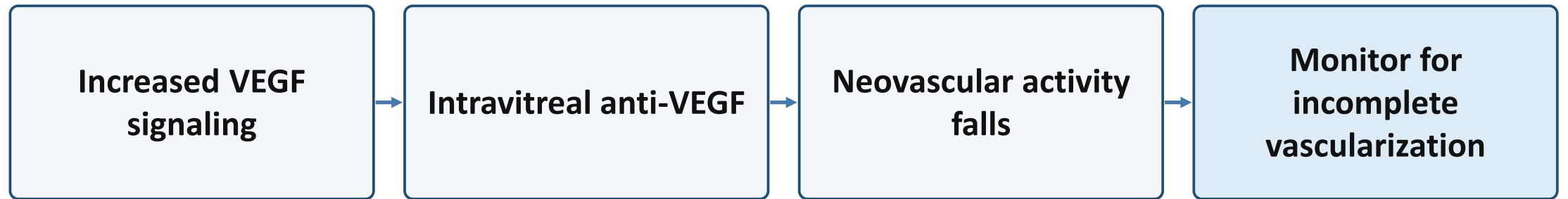
- Avoid unmonitored hyperoxia in preterm infants requiring oxygen.
- Do not assume the lowest oxygen saturation target is safest: Neonatal survival must be considered.
- Standardized oxygen monitoring and coordinated NICU practice reduce avoidable exposure.
- ROP prevention and ophthalmic screening are complementary, not interchangeable.

Laser photocoagulation: Suppress the hypoxic drive



- Ablative treatment removes ischemic retinal tissue contributing to VEGF production.
- Retinal ablation is a structural trade-off and requires an experienced ophthalmologist.

Intravitreal anti-VEGF: Inhibit pathologic signaling



- The therapeutic rationale directly reflects the molecular mechanism.
- Ocular regression does not guarantee permanent disease inactivity or fully vascularized retina.

Laser and anti-VEGF have different follow-up profiles

Laser ablation	Intravitreal anti-VEGF
Peripheral retinal tissue is ablated	No immediate destructive peripheral ablation
Regression through reduced ischemic drive	Regression through VEGF inhibition
Peripheral visual/refractive trade-offs	Delayed reactivation / persistent avascular retina
Follow-up still required	Often more prolonged follow-up required

After anti-VEGF, reactivation is a distinct risk

- Initial vessel regression can be followed by recurrent angiogenic activity.
- ICROP3 recommends explicitly describing reactivated ROP lesions.
- Persistent avascular retina is important even after apparently successful treatment.
- Follow-up must be individualized; Missed appointments can be vision-threatening.

Surgery addresses advanced tractional detachment

- Advanced stage 4 or 5 disease may require vitreoretinal surgical intervention.
- The mechanical objective is to release traction and restore retinal attachment where feasible.
- Anatomic success does not ensure restoration of normal macular function.
- Prevention of advanced scarring is therefore the primary practical priority.

Long-term sequelae extend beyond the neonatal period

Retinal structure

Macular anomalies, peripheral avascular retina, tears and late detachment.

Refraction and alignment

Myopia, strabismus, amblyopia and other visual development difficulties.

Ongoing surveillance

Follow-up for retinal and functional sequelae after regression or treatment.

Case 1: Zone and plus change the decision

A premature infant has stage 3 retinopathy in zone II. The posterior retinal vessels are dilated and tortuous to the degree of plus disease. No retinal detachment is present.

- Classify the retinal findings using ICROP3 terminology.
- Does this eye meet an ETROP treatment threshold?
- What is the major pathobiologic target of therapy?

Case 1: Reasoning and management

- Zone II + stage 3 + plus disease satisfies ETROP type 1 criteria.
- Treatment evaluation is urgent; Prompt retinal laser or appropriate intravitreal therapy is considered by the ophthalmologist.
- VEGF-dependent proliferation at an avascular–vascular interface drives the active lesion.
- Scheduled retinal examination remains necessary after therapy.

Case 2: Apparent regression is not always the end

An infant receives intravitreal VEGF inhibition for severe ROP. The neovascular activity decreases. Weeks later, the retinal periphery remains avascular and abnormal vascular activity is again observed.

- Which ICROP3 term describes renewed active disease?
- Why is a late examination biologically important?
- Which retinal territory may remain vulnerable?

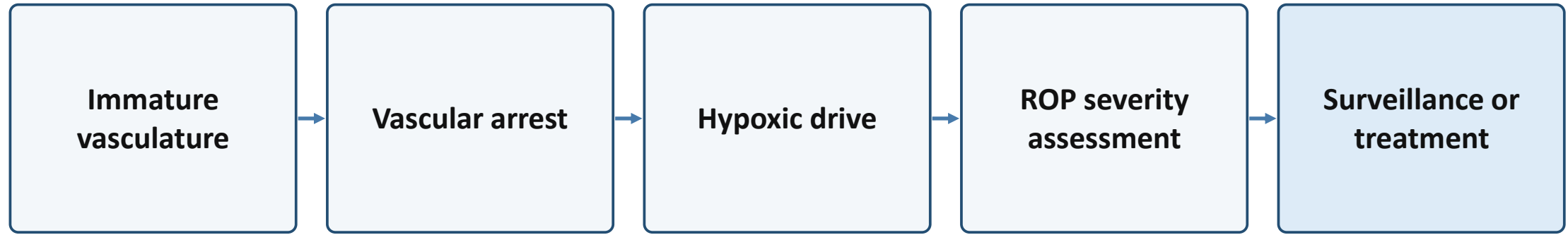
Case 2: Reactivation follows incomplete maturation

- The renewed lesion is described as reactivated ROP, with the appropriate stage when present.
- Persistent peripheral avascular retina can remain a source of later angiogenic stimulation.
- Regression of the initial membrane does not guarantee normal peripheral vascular development.
- Careful continued follow-up is needed to detect recurrence and late complications.

Five common errors in ROP interpretation

- Attributing all risk to oxygen while ignoring extreme retinal immaturity.
- Treating a stage label as sufficient without zone and plus status.
- Confusing fibrovascular traction with simple vascular tortuosity.
- Assuming every stage 1 or 2 lesion must progress sequentially to stage 5.
- Ending surveillance immediately after apparent regression, especially after anti-VEGF.

Mechanism-to-management reasoning



- Early retinal injury explains why babies are screened before visual symptoms develop.
- Monitoring zone, stage and plus detects lesions before irreversible tractional changes.

Core clinicopathologic synthesis

- Prematurity leaves a peripheral avascular retina vulnerable to oxygen-related growth arrest.
- Phase I VEGF reduction impairs vascular survival; Phase II hypoxia induces VEGF-driven proliferation.
- Fibrovascular membrane contraction produces macular dragging and tractional detachment.
- ICROP3 describes anatomic site, morphologic stage, vascular activity and disease evolution.
- Targeted screening, timely type 1 treatment and long-term follow-up protect vision.

Selected primary references

- Robbins, Cotran & Kumar. Pathologic Basis of Disease. 11th ed. 2026. Ch 29, p. 1203; Ch 10, pp. 417–418.
- Chiang MF et al. International Classification of Retinopathy of Prematurity, 3rd ed. Ophthalmology. 2021;128:e51–e68.
- Fierson WM et al. Screening Examination of Premature Infants for Retinopathy of Prematurity. Pediatrics. 2018;142:e20183061.
- Smith LEH. Pathogenesis of retinopathy of prematurity. Semin Neonatol. 2003;8:469–473.

Further reading and evidence context

- Hong EH, Shin YU, Cho H. Retinopathy of prematurity: a review of epidemiology and current treatment strategies. Clin Exp Pediatr. 2022;65:115–126.
- ETROP classification: type 1 and type 2 risk groups guide treatment versus surveillance.
- ICROP3 provides modern nomenclature for posterior zone II, notch, aggressive ROP, regression and reactivation.
- Clinical algorithms and screening cutoffs should be checked against the applicable local protocol.