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# Hyphema. Part I. Pathophysiologic Considerations

## **Abstract**

Hemorrhage in the anterior chamber of the eye, or hyphema, results from a breakdown of the blood-ocular barrier (BOB) and is frequently associated with inflammation of the iris, ciliary body, or retina. Hyphema can also occur by retrograde blood flow into the anterior chamber via the aqueous humor drainage pathways without BOB breakdown. Hyphema attributable to blunt or perforating ocular trauma is more common than that resulting from endogenous causes. When trauma has been eliminated as a possible cause, it is prudent to assume that every animal with hyphema has a serious systemic disease until proven otherwise.

## **Disciplines**

Medicine and Health Sciences | Ophthalmology | Veterinary Medicine

## **Comments**

Dr. Komáromy was affiliated with the University of Pennsylvania from 2003-2012.

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## FOCAL POINT

- ★ Hyphema is frequently associated with iridocyclitis and generally indicates severe intraocular or systemic disease.

## KEY FACTS

- A thorough diagnostic evaluation should be initiated when hyphema is present, p. 1064.
- Hyphema generally results from a breakdown of the blood-ocular barrier, p. 1064.
- The diagnostic differentials for hyphema do not differ substantially from those for hemorrhage into other areas of the body, p. 1065.
- When trauma has been eliminated as source of hyphema, the diagnostic and therapeutic approach is directed by results of the physical and ophthalmic examinations, p. 1065.

# Hyphema. Part I.

## Pathophysiologic Considerations

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**ABSTRACT:** Hemorrhage in the anterior chamber of the eye, or hyphema, results from a breakdown of the blood-ocular barrier (BOB) and is frequently associated with inflammation of the iris, ciliary body, or retina. Hyphema can also occur by retrograde blood flow into the anterior chamber via the aqueous humor drainage pathways without BOB breakdown. Hyphema attributable to blunt or perforating ocular trauma is more common than that resulting from endogenous causes. When trauma has been eliminated as a possible cause, it is prudent to assume that every animal with hyphema has a serious systemic disease until proven otherwise.

**H**ypHEMA is defined as hemorrhage within the anterior chamber of the eye (Figure 1). In contrast, the accumulation of leukocytes in the anterior chamber is termed *hypopyon*. The etiopathogenesis of hyphema is multifactorial, but ultimately the final common pathway is breakdown of the blood-ocular barrier (BOB) and subsequent intraocular hemorrhage that is often associated with inflammation. Many of the mechanisms that cause intraocular hemorrhage may also result in hemorrhage in other parts of the body. This article focuses on hyphema as a "red flag" for sight-threatening ocular or life-threatening systemic hemorrhagic disease.

When hyphema is present, a thorough diagnostic evaluation similar to that indicated for any third-compartment hemorrhage (e.g., hemoabdomen, hemothorax) should be initiated. Attentive clinicians will recognize the importance of a thorough diagnostic workup before or during the initial treatment of hyphema. Death attributable to systemic or vital organ hemorrhage may occur if the diagnostic workup is incomplete. Part I of this two-part presentation focuses on the many pathophysiologic mechanisms that most frequently result in hyphema, each of which is considered as a separate entity in this article. However, concurrent involvement of more than one mechanism is common. Part II will cover diagnosis and treatment of hyphema.

### BLOOD-OCULAR BARRIER

The BOB, which consists of the blood-aqueous and blood-retinal barriers, prevents erythrocytes and leukocytes and inhibits tissue fluids and proteins from entering nonvascular ocular tissues and compartments. The BOB consists of endothelial

and epithelial tight junctions with variations in their degree of permeability.<sup>1</sup> Dysfunction of the blood–aqueous barrier frequently results in hyphema; breakdown of the blood–retinal barrier generally causes retinal, subretinal, and choroidal hemorrhage but infrequently results in hyphema. The posterior lens capsule and zonules limit but do not completely prevent movement of blood from the anterior chamber to the vitreous and vice versa.



Figure 1—Hyphema in a dog.

Because the intraocular pressure (IOP) is normally higher than the pressure in the aqueous humor drainage pathways (the scleral venous plexus), retrograde blood flow into the anterior chamber is prevented. IOP lower than the pressure in the scleral venous plexus may predispose to hyphema via retrograde blood flow into the anterior chamber.

### **PATHOPHYSIOLOGIC APPROACH**

With the exception of severe intraocular disease, the diagnostic differentials for hyphema do not differ substantially from those for hemorrhage in other areas of the body (e.g., hemothorax, hemoabdomen); therefore, the diagnostic approach to determine the underlying cause of hyphema is similar. In addition to systemic causes, ocular disorders should be considered. Clinicians must develop a sound understanding of the potential causes of hyphema so they are able to construct a list of differential considerations for each mechanism. The most common mechanisms of hemorrhage that may result in hyphema follow.

#### **Iridocyclitis**

Iridocyclitis (anterior uveitis) is the most common ocular disease associated with a breakdown of the blood–aqueous barrier. Disruption of the blood–aqueous barrier may lead to aqueous flare (predominantly proteins), hypopyon, and/or hyphema, depending on the inciting stimulus and duration of the disease. Most of the pathophysiologic mechanisms of BOB breakdown discussed in the remainder of this article are also possible causes for iridocyclitis. Regardless of the cause, if left untreated, hyphema will eventually result in iridocyclitis when chemotactic triggers recruit inflammatory cells for cleanup.

#### **Trauma**

Hyphema attributable to exogenous causes (blunt or

perforating trauma) is probably more common than that resulting from endogenous causes (see Causes of Hyphema). Blunt trauma to the head seldom results in hyphema because the eyeball is protected by anterior portions of the bony orbit and orbital soft tissues. However, severe blunt trauma to the anterior orbital rim or periorbital soft tissues and eyeball may result in hyphema. In this case, examination and palpation of the periorbital area usual-

ly reveals clinical signs of trauma, such as swelling and bruising of the eyelids and conjunctiva, fracture of the bony orbit, or orbital hemorrhage and resultant orbital mass effect. Bilateral hyphema is seldom caused by mild trauma. When blunt ocular trauma occurs, the sudden rise in IOP associated with ocular indentation causes anterior chamber angle distortion and may result in rupture of iris stromal or ciliary body vessels and subsequent hyphema.<sup>4</sup>

Perforating trauma (e.g., cat scratch, BB pellets) to the eyeball (cornea, sclera) with direct damage to intraocular vasculature is more likely to result in traumatic hyphema than is blunt trauma. Traumatic hyphema can also be associated with proptosis of the globe and may be accompanied by structural damage to the eye, including lens subluxation and dislocation, vitreous hemorrhage, or retinal detachment.<sup>5</sup> Head radiographs help to reveal fractures of the orbit or skull in trauma cases. When exogenous sources of hyphema have been eliminated, the diagnostic approach is further directed by results of physical and ophthalmic examinations.

#### **Thrombocytopenia**

Lack of an adequate number of circulating platelets can result in hyphema and hemorrhage secondary to ongoing capillary microtrauma induced by normal activity or exogenous insult.<sup>6</sup> Thrombocytopenia is typified clinically by petechial hemorrhage of mucosal and cutaneous surfaces. Hyphema and concurrent petechial hemorrhages should prompt clinicians to consider thrombocytopenia as a likely mechanism of disease. Thrombocytopenia may be induced by immune-mediated destruction of platelets, infectious agents (e.g., *Ehrlichia canis*, *platys*, or *risticii*; *Leptospira* species; *Rickettsia rickettsii*), sepsis, splenomegaly, neoplasia, or disseminated intravascular coagulation.

## Causes of Hyphema

### Trauma<sup>2-5</sup>

- Blunt
- Penetrating (with or without foreign body)

### Thrombocytopenia<sup>6-10</sup>

- Decreased platelet production in the bone marrow
  - Drug or chemical toxicity—induced bone marrow hypoplasia (e.g., estrogens, antiinflammatory agents, antibiotics, tranquilizing agents, diuretic agents, dapson, myelosuppressive chemotherapy)
  - Toxic doses of irradiation
  - Chronic infections (e.g., feline leukemia virus [FeLV], *Ehrlichia canis*, *Ehrlichia platys*, canine distemper, parvovirus, heartworm disease)
  - Myeloproliferative disorders (e.g., FeLV, feline immunodeficiency virus [FIV]), lymphoma, tumor metastasis
  - Estrogen-secreting tumors (e.g., Sertoli cell tumor)
  - Myelofibrosis
  - Immune-mediated megakaryocytic hypoplasia or aplasia
  - Chronic renal disease
- Reduced circulating platelet life span
  - Sequestration (e.g., splenomegaly)
  - Immune-mediated platelet destruction
  - Nonimmunologic platelet destruction
    - Microangiopathic thrombocytopenia (e.g., disseminated intravascular coagulation [DIC], tumor microvasculature [hemangiosarcoma, hepatic tumors])
    - Microangiopathic hemolytic anemia
    - Severe vascular injury and vasculitis (see Vasculitis and uveitis)
    - Drug-induced (e.g., heparin)
    - Platelet loss via hemorrhage (usually mild thrombocytopenia)
    - Infectious agents (e.g., *E. canis*, *Rickettsia rickettsii*, *Dirofilaria*)

**Thrombocytopathy** (defects in platelet adhesion, aggregation, or release reactions)<sup>10,11</sup>

- Inherited: von Willebrand's disease and other

hereditary thrombopathias, including breed-specific thrombopathias

- Systemic illness: Uremia, collagen deficiency disease, hepatic disease, pancreatitis, ehrlichiosis (*E. canis*, *E. platys*), FeLV, dysproteinemia, gammopathies, myeloproliferative/myelodysplastic disorders, DIC, lymphoproliferative disorders, multiple myeloma
- Drug-induced: NSAIDs, corticosteroids, diuretic agents, tranquilizers, synthetic colloid solutions (e.g., dextran),  $\alpha$ - and  $\beta$ -blockers and stimulators, hormonal agents (e.g., prostacyclin, estrogen), vinca alkaloids, antibiotics and antiparasitic agents, heparin
- Antibody-mediated platelet dysfunction: Immune-mediated thrombocytopathy, systemic lupus erythematosus

### Coagulopathy<sup>8,10,12-14</sup>

- Inherited
- Acquired

### Vasculitis and uveitis<sup>15-21</sup>

- Infectious: Rocky Mountain spotted fever, ehrlichiosis, leptospirosis, brucellosis, piroplasmosis, leishmaniasis, ophthalmomyiasis interna, ocular filariasis (*Dirofilaria immitis*), tuberculosis, geotrichosis, protothecosis, toxoplasmosis (*Toxoplasma gondii*), FIV, FeLV, feline infectious peritonitis (FIP), canine adenovirus 1, cryptococcosis, blastomycosis, coccidioidomycosis, candidiasis
- Immune-mediated (e.g., uveodermatologic syndrome)
- Neoplasia (e.g., lymphosarcoma, ocular sarcoma, metastatic tumors)
- Lens-induced uveitis
- Episcleritis
- Systemic inflammatory response syndrome: Sepsis, endotoxemia (e.g., pyometra)
- Secondary to keratitis or trauma
- Idiopathic

### Noninflammatory vascular disorders<sup>22</sup>

- Hyperadrenocorticism
- Ehlers-Danlos syndrome

## Causes of Hyphema (continued)

### Hyperviscosity syndrome<sup>9,23-27</sup>

- Mono- or polyclonal gammopathies: Multiple myeloma, lymphoma, leukemia, chronic inflammation, antigenic stimulation (e.g., dirofilariasis), FIV, FIP, ehrlichiosis (*E. canis*, *E. platys*)
- Severe erythrocytosis: Hemorrhagic gastroenteritis, polycythemia vera, erythropoietin-secreting neoplasms

### Systemic hypertension<sup>28-30</sup>

#### Neovascularization of uveal and retinal tissues

- Retinal detachment<sup>16,18,31-33</sup>
  - Primary
  - Secondary: Lenticular disease, infectious diseases (see Vasculitis and uveitis), nonseptic inflammation (see Vasculitis and uveitis), trauma (see Trauma), intraocular neoplasia (see Neoplasia), systemic neoplasia (e.g., multiple myeloma), systemic hypertension (i.e., hypertensive retinopathy; see

Systemic Hypertension section in text), congenital abnormalities (e.g., retinal dysplasia), senile degenerative changes

- Chronic glaucoma<sup>16</sup>
- Intraocular neoplasia<sup>34</sup>
  - Primary: Lymphosarcoma, adenoma and adenocarcinoma, melanoma, posttraumatic ocular sarcoma in cats
  - Secondary: Adenocarcinoma, transitional cell carcinoma, lymphoma, multiple myeloma

### Congenital anomalies<sup>31,35</sup>

- Collie eye anomaly
- Vitreoretinal dysplasia (e.g., in Bedlington terriers, Sealyham terriers, Labrador retrievers)
- Persistent hyaloid artery (e.g., with persistent hyperplastic primary vitreous in Doberman pinschers)

### Anemia

### Thrombocytopenia

Defects in platelet adhesion, aggregation, or release can result in ineffectual platelet function.<sup>11</sup> These defects may be inherited (e.g., von Willebrand's disease); be induced by systemic disorders; or, as in most acquired cases, occur as an idiosyncratic reaction to certain drugs (see Causes of Hyphema). Thrombocytopenia should be suspected in patients with hemorrhagic tendency, prolonged bleeding time, appropriate platelet count, and normal tests of secondary hemorrhage.

### Coagulopathy

Abnormalities of the intrinsic, extrinsic, or common pathways of the clotting cascade may result in clotting abnormalities and subsequent hemorrhage and hyphema. Coagulopathies are typified clinically by large third-compartment or major organ hemorrhages (e.g., body cavity, pulmonary, muscle/deep tissue) and may be inherited or acquired. Although ecchymotic hemorrhages are classically described in coagulopathies, cutaneous hemorrhages are less common in animals with coagulopathies than are thrombocytopenias and thrombocytopenias. Clinical presentation is extremely variable depending on the site of hemorrhage. Secondary signs of anemia (weakness, pallor) are often noted by owners of animals with a coagulopathy.

### Vasculitis

Vascular endothelial cell abnormalities may result in transmural extravasation of blood from vascular channels in the iris and ciliary body, resulting in breakdown of the blood-aqueous barrier and hyphema. Vasculitis may result from primary or secondary immune-mediated destruction of endothelial cells (e.g., immune-mediated vasculitis, toxoplasmosis), infectious diseases (e.g., leptospirosis, Rocky Mountain spotted fever, feline infectious peritonitis), neoplasia, or systemic inflammatory response syndrome (e.g., sepsis). Noninflammatory vascular disorders, including hyperadrenocorticism and Ehler-Danlos syndrome, can also result in hemorrhage.

### Hyperviscosity Syndrome

Diseases that produce excessive globulins or other plasma proteins may result in hyphema because of (1) vascular endothelial cell compromise caused by intravascular sludging of blood with vessel wall necrosis, (2) infiltration of proteins into the vessel wall, (3) inhibition of hemostasis secondary to reduction in clotting factors, and/or (4) coating of platelets by abnormal paraproteins resulting in abnormal platelet aggregation.<sup>23</sup> Funduscopic examination of the contralateral eye may reveal engorged retinal vasculature and retinal hemorrhages. Common causes of hyperviscosity include plasma cell myeloma,

lymphoma, ehrlichiosis, and chronic inflammatory disease. Serum total solids will generally be excessively elevated because of hyperglobulinemia. Hyperviscosity syndrome can also be induced by severe erythrocytosis, such as hemorrhagic gastroenteritis, polycythemia vera, and erythropoietin-secreting neoplasms.

### Systemic Hypertension

Hyphema attributable to systemic hypertension is most common in old cats and dogs and is often caused by chronic renal insufficiency. Systemic hypertension affects only the arterial vascular system. Chronic high arterial pressure may result in arteriosclerosis and autoregulatory arteriolar vasospasm. Arteriolar disease causes ischemia and capillary permeability changes (with leakage of plasma proteins) and eventually hemorrhage. In our experience, most cases of hyphema from vascular hypertension are attributable to retinal detachment (see Neovascularization of Uveal and Retinal Tissues section) and most likely occur in response to choroidal vascular hypertension. Hyphema may be less commonly caused by tearing of retinal vasculature that occurs during retinal detachment. Other common causes of vascular hypertension include hyperthyroidism, hyperadrenocorticism, hyperaldosteronism, and pheochromocytoma.

### Neovascularization of Uveal and Retinal Tissues

Although the presence of blood vessels is necessary in most tissues, neovascularization or angiogenesis of tissues can cause severe disease. The surfaces of the retina and iris are vulnerable to symptomatic neovascularization.<sup>36</sup> Possible causes for neovascularization are ischemia (including long-standing retinal detachment), intraocular neoplasia, and inflammation.<sup>36</sup> Vascular proliferation on the anterior iris surface (rubeosis iridis) leads to the formation of a pre-iridal fibrovascular membrane, which can involve the peripheral iris and iridocorneal drainage angle and result in obstruction of aqueous humor outflow. Angiogenesis, a complex process that includes degradation of extracellular matrix and endothelial cell proliferation, is stringently regulated by numerous proangiogenic and antiangiogenic factors. Examples of growth factors that stimulate endothelial cell proliferation include fibroblast growth factors, insulinlike growth factors, transforming growth factor- $\beta$  (TGF- $\beta$ ), and vascular endothelial growth factor (VEGF).<sup>36</sup> The newly grown vessels are exceedingly fragile, leak readily, and can potentially result in hemorrhage and hyphema.<sup>37</sup>

### Retinal Detachment

Long-standing retinal detachment stimulates production of growth factors that induce vascular endothelial

cell and fibroblast proliferation and subsequent fibrovascular membrane formation.<sup>36</sup> The most frequent site of fibrovascular membrane formation in eyes with chronic retinal detachment is overlying the anterior iris surface (pre-iridal fibrovascular membrane).<sup>16</sup> Acute hyphema may occur if the retinal vasculature tears when the neurosensory retina detaches from the underlying retinal pigment epithelial cells. Clinicians must determine the cause of the retinal detachment because life-threatening systemic disease may be the underlying abnormality (see Causes of Hyphema). In our experience, spontaneous (idiopathic) retinal detachment is rare in dogs and cats and an underlying cause is usually present.

### Chronic Glaucoma

Pre-iridal fibrovascular membranes are also frequently detected in eyes with chronic (end-stage) glaucoma.<sup>16</sup> It is likely that hyphema attributable to chronic glaucoma occurs secondary to tearing and leakage of the fragile pre-iridal microvasculature.<sup>16</sup>

### Intraocular Neoplasia

Growth of a neoplasm larger than 2 to 3 mm<sup>3</sup> requires development of a microvascular network to facilitate delivery of nutrients and oxygen and removal of catabolites.<sup>38</sup> Primary and metastatic intraocular neoplasms of the anterior uveal tissues are highly vascular. These neoplasms secrete vascular growth factors (e.g., VEGF, TGF- $\beta$ ) that stimulate formation and rapid growth of vessels to support and sustain tumor growth.<sup>38</sup> Newly developed capillaries of neoplasms are prone to hemorrhage because they have incomplete basement membranes, are leaky, and



## A Look Back

*The more common causes of intraocular hemorrhage were known 20 years ago. Since then, new infectious causes of hyphema, such as feline immunodeficiency virus, have been detected. Research over the past 20 years has demonstrated many mediators of neovascularization and intraocular inflammation. The methodologies for diagnostic workup have improved with the advent of B-mode ultrasonography, computed tomography, and magnetic resonance imaging. However, the primary management issues of hyphema have remained unchanged. A few new treatment options have been added, such as tissue plasminogen activator and topical carbonic anhydrase inhibitors. Unfortunately, the prognosis for maintaining vision in an eye with hyphema has generally remained the same over the past 20 years.*



often fracture.<sup>16,38</sup> Animals with hyphema attributable to intraocular neoplasia are usually in late middle age or older; however, we have diagnosed ciliary body hemangiosarcoma and iris melanoma in dogs as young as 7 months of age. Most primary intraocular neoplasms are unilateral, and thus hyphema attributable to primary intraocular neoplasia is unilateral. Bilateral primary intraocular neoplasms are reported infrequently.<sup>39</sup> Secondary or metastatic intraocular neoplasia (e.g., lymphoma) may affect one or both eyes and may therefore result in unilateral or bilateral hyphema.

### Congenital Ocular Anomalies

Hyphema in young animals should prompt clinicians to consider congenital ocular malformation as a likely cause. Collie eye anomaly, which is recessively inherited, is characterized by defects of the choroid and sclera attributable to abnormal mesodermal differentiation.<sup>31</sup> In severe cases of vitreoretinal dysplasia (e.g., in Bedlington terriers, Sealyham terriers, Labrador retrievers, or springer spaniels), retinal folding is sufficient to permit complete retinal detachment.<sup>31,35</sup> Retinal detachment and subsequent hyphema may occur with collie eye anomaly and vitreoretinal dysplasia. Persistent hyaloid artery occurs sporadically in dogs and is caused by failure of the fetal hyaloid vasculature to regress.<sup>35</sup> Rupture of a persistent hyaloid artery leads to hemorrhage into the vitreous body, with blood passing into the anterior chamber.<sup>35</sup>

### Anemia

According to our experience and a previous report,<sup>40</sup> severe acute anemia (e.g., severe tick or flea infestation) can cause hyphema when hemoglobin rapidly drops below 5 mg/dl. Insufficient oxygen supply may cause endothelial cells to die, which leads to leaking of blood vessels.

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