

1 **Laws of physics help explain capillary non-perfusion in diabetic retinopathy**

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19 Running title: Physics in capillary non-perfusion in diabetic retinopathy

20 Key words: diabetic retinopathy, capillary, microcirculation, rheology, shunts, preferential
21 vessels, ischemia, physics, LaPlace law, Hagen-Poiseuille law.

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23 Conflict of interest: All the authors declare no conflict of interest.

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25 **ABSTRACT**

26 **Purpose:** The purpose is to use laws of physics to elucidate the mechanisms behind
27 **capillary nonperfusion in diabetic retinopathy. In diabetic retinopathy, loss of pericytes**
28 **weakens capillary walls and the vessel dilates. A dilated capillary has reduced resistance to**
29 **flow, therefore increased flow in that vessel and decreased in adjoining capillaries. A**
30 **preferential shunt vessel is thus formed from the dilated capillary and the adjacent**
31 **capillaries become non-perfused.**

32 **Methods:** We apply the laws of Laplace and Hagen-Poiseuille to better understand the
33 **phenomena that lead to capillary nonperfusion. These laws of physics can give a foundation**
34 **for physical or mathematical models to further elucidate this field of study.**

35 **Results:** The law of Laplace predicts that a weaker vessel wall will dilate, assuming
36 **constant transmural pressure. The Hagen-Poiseuille equation for flow and the Ostwald-de**
37 **Waele relationship for viscosity predict that a dilated vessel will receive a higher portion of**
38 **the fluid flow than the adjoining capillaries. Viscosity will decrease in the dilated vessel,**
39 **furthering the imbalance and resulting in a patch of nonperfused capillaries next to the**
40 **dilated “preferential” shunt vessel.**

41 **Conclusion:** Physical principles support or inspire novel hypotheses to explain poorly
42 **understood phenomena in ophthalmology. This thesis of pericyte death and capillary**
43 **remodelling, which was first proposed by Cogan and Kuwabara, already agrees with**
44 **histological and angiographical observations in diabetic retinopathy. We have shown that it**
45 **is also supported by classical laws of physics.**

46 The pathophysiology of diabetic retinopathy and the vascular changes have been
47 investigated using several different technological approaches, but we are still far away from a
48 comprehensive understanding of this process. One of the seemingly paradoxical observations is
49 the occurrence of capillary nonperfusion with hyperperfused shunt vessels and adjacent capillary
50 occlusion in the same retinal area (Figure 1). This might at first glance suggest the presence of
51 opposite causal factors in the disease process.

52 The histological studies of Cogan and Kuwabara discovered some of the early changes in
53 diabetic retinopathy.^{1,2} They demonstrated death of pericytes in the retinal capillaries and the
54 appearance of nonperfused ‘ghost’ vessels in the capillary bed. They described ‘preferential
55 channels’ which are shunt vessels (Figure 2). These preferential channels are dilated capillaries
56 that transcend or are adjacent to patches of non-perfused capillaries in the retina.

57 The histological picture points directly to the pathophysiological mechanism. Pericytes
58 die due to hyperglycaemia. Pericytes (mural cells) are contractile cells and strengthen the
59 capillary wall.³ When they perish, according to the law of Laplace, the wall strength is reduced
60 and the vessel dilates due to the intravascular-tissue pressure difference. All of this was elegantly
61 stated by Cogan and Kuwabara¹: “The pathogenesis of diabetic retinopathy thus revolves about a
62 loss of tone in the capillaries, and this loss permits flow through certain channels—a process that
63 is characteristic of diabetes. It has been previously suggested that the mural cells are responsible
64 for the tonic control of the retinal capillaries. The mural cells presumably guarantee the uniform
65 distribution of blood through all normal capillaries of the elaborate plexus fed by single
66 arterioles. With diabetes these mural cells characteristically disappear”. “In diabetes
67 circulation continues through the endothelial lined capillaries but flow is no longer under the
68 tonic control of mural cells and shunts develop. Although these shunt vessels arise from

69 preformed capillaries, they are often interpreted clinically as neovascularization.” “The
 70 relationship of these shunts to the acellular capillaries which have been bypassed shows clearly
 71 in flat mounts so long as the plexus of vessels is not too dense.”

72 The purpose of the current article is to use principles of physics to further examine the
 73 hypothesis by Cogan and Kuwabara.

74

75 **Physics**

76 In a capillary net, one capillary has suffered loss of pericytes (mural cells), its wall has
 77 weakened and dilates according to the law of Laplace. The dilated capillary has a larger
 78 diameter, d , and therefore a lower resistance to flow (figure 3). This affects the local distribution
 79 of blood flow, which is best explained using the Hagen-Poiseuille equation for flow of a shear-
 80 thinning fluid along a tube of length L which follows the Ostwald-de Waele relationship for
 81 viscosity:⁴

$$82 \quad Q = \frac{\pi d^3}{8(3 + \frac{1}{n})} \left(\frac{\Delta P}{4K} \frac{d}{L} \right)^{\frac{1}{n}}$$

83

84 In this equation Q is the flow rate along a tube, ΔP the pressure difference between the
 85 artery and vein (effectively the same for capillaries near one another), K is the viscosity
 86 parameter and n is the power law index. Blood flow in capillaries is relatively slow so losses
 87 against viscous friction dominate. Blood is a shear thinning fluid⁵: n is < 1 so the blood becomes
 88 more viscous as the flow slows down, and at low flow rates it can experience jamming where
 89 blood cells effectively get stuck⁶ (this is not predicted by the Ostwald-de Waele relationship).

90 Conversely, if d increases for the same pressure drop the viscosity decreases and even more
91 flows along the dilated vessel. If one sets $n = 1/2$, the flow rate is proportional to d^5 : a 10%
92 increase in d gives a 60% increase in Q .

93

94 Dilation of one capillary will thus promote redistribution of flow between neighbouring
95 capillaries. As the flow rate in a capillary drops the blood cells will tend to aggregate and jam.
96 This is a vicious cycle that only stops when the surrounding capillaries have been rendered
97 bloodless, *i.e.* nonperfused, and turn into the ghost capillaries described by Cogan and
98 Kuwabara^{1,2} (Figure 2).

99

100 This is an example of a manifold flow problem. It explains the co-existence of
101 preferential shunt channels and capillary non-perfusion in the capillary bed in diabetic
102 retinopathy. It explains why capillary non-perfusion occurs in relatively well-defined patches and
103 at the same time why they are limited and do not engulf the entire retinal circulation.

104

105 **Alternative hypotheses**

106 Other hypothesis on the development of capillary nonperfusion in diabetic retinopathy,
107 have suggested an embolic mechanism.⁷ White blood cells have been pointed out at the culprit
108 and proposed that they stick in some capillaries, occluding the vessel.^{8,9} If this were the case, we
109 would expect the nonperfusion to be somewhat equally scattered at random over the entire
110 capillary bed and in isolated capillaries as there would be no reason to expect adjacent vessels to
111 be more susceptible than others. Indeed, the nonperfusion patches would not be expected if this

112 was the mechanism nor does it provide any explanation for the preferential shunt vessels.
113 Recently, Lechner et al¹⁰ simply stated that: “Retinal capillaries become progressively non-
114 perfused in the diabetic retina as a direct result vasodegeneration”. Histological studies have
115 shown that this vascular occlusion can be related to basement membrane thickening¹¹ and
116 ingrowth of Müller cells from the surrounding perivascular retina.^{12, 13} Additionally, studies in
117 experimental animals suggest the involvement of granulocyte plugs in the development of
118 capillary occlusion^{7,8} but these observations are by lack of a good animal model for diabetic
119 retinopathy. This is a cardinal feature of diabetic retinopathy as observed in post-
120 mortem specimens but also in long-term diabetic animal models.

121

122 **Conclusion**

123 The laws of physics provide us with a foundation to understand nature and this includes the
124 human animal and its diseases. Thorough study of classical physics will undoubtedly provide
125 clearer and novel understanding of many eye diseases and their treatment. A theoretical approach
126 is a prerequisite for sound hypotheses that can subsequently be put to scientific study and clinical
127 trial. Lack of a theoretical approach has long been a weakness of ophthalmology, which is too
128 data driven and all too willing to accept ‘black box’ explanations when it comes to
129 pathophysiology or treatment mechanisms. We should learn from physics and other fields that
130 have made great strides with a proper mixture of theory and practical study.

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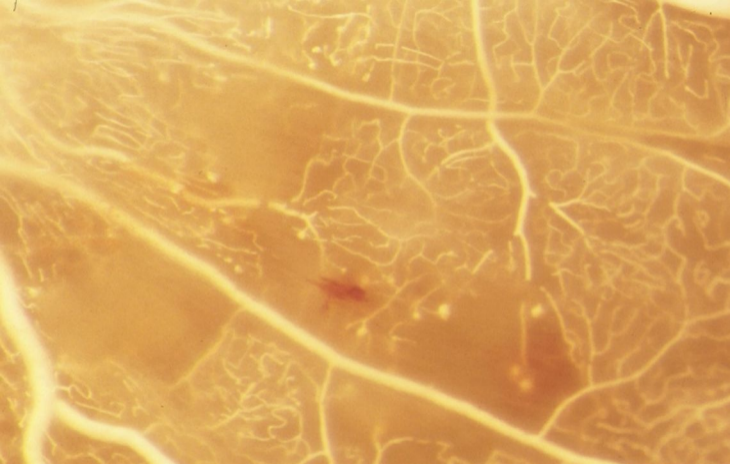
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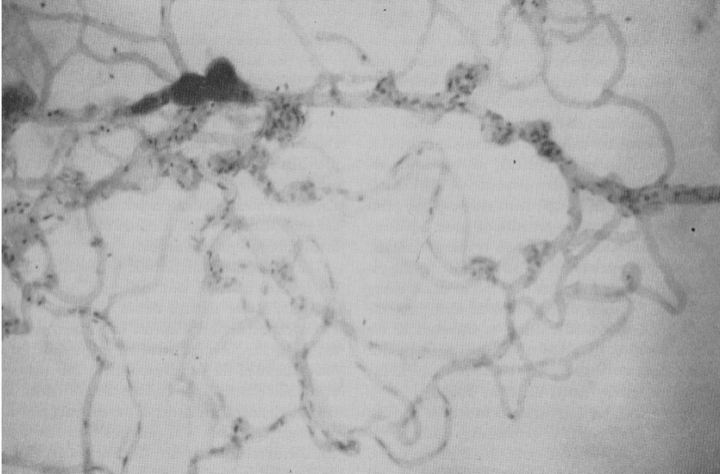
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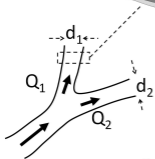
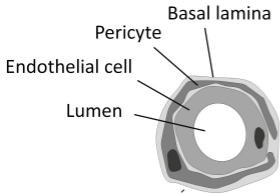
178 **Figure 1** Human retina with a cast of the vascular tree post mortem. Microaneurysms are seen to
179 bound areas of capillary occlusion traversed by larger patent vessels. The red dot represents a
180 small haemorrhage in the nerve fibre layer.

181 **Figure 2** Shunt capillaries with microaneurysms from the retina of a diabetic patient with
182 moderate retinopathy.¹ Note that the shunt vessel has an increased cellularity while the adjacent
183 occluded capillaries are acellular. 80X. Reproduced with permission (pending) from the
184 publisher of Diabetes.

185 **Figure 3** Schematic drawing where one capillary suffers pericyte death, weakening of the wall
186 and subsequent dilatation. Blood flow is increased in the dilated vessels and reduced in the
187 adjoining vessel. A vicious cycle leaves the vessel void of all blood flow as a non-perfused
188 capillary. The dilated one becomes a preferential shunt vessel.

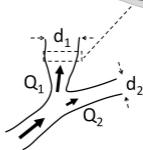
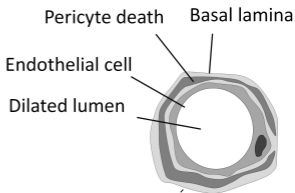






Blood flow $d_1 \sim d_2 \rightarrow Q_1 \sim Q_2$
 $Q = Q_1 + Q_2$

Normal



Blood flow $d_1 > d_2 \rightarrow Q_1 \gg Q_2$
 $Q = Q_1 + Q_2$

Diabetic retinopathy