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Using mathematics to avoid blindness in diabetics (Part 2): eliminating re-emergent diabetic retinopathy caused by blood thinners

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Abstract

Purpose: To report the clinical experiences of author AH, who calculated that modest stepwise lowering of arterial blood pressure can reverse (i) re-emergent diabetic retinopathy (DR) caused by antiplatelet and anticoagulant agents, even in the presence of continued use of the latter necessary agents, or (ii) DR induced by common or severe hypertension and so, (iii) simultaneously treat both of AH's vascular and ocular medical conditions.

Methods: In instances of DR and visual impairment with evidence of exudate formation, blood pressure adjustments were applied, based on mathemat-

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ical models of retinal exudate production developed by one of the authors (AH). Specifically, the model was used to calculate a critical arterial blood pressure below which retinal exudate formation should cease. Antihypertensive agents were then increased gradually until the desired lower target blood pressure was achieved and DR eliminated. Optical coherence tomography (OCT) was used to test for therapeutic effectiveness.

Results: In four different clinical situations, which included blood thinners or hypertension, control of retinal exudate formation and elimination of re-emergent DR was achieved solely by blood pressure lowering and confirmed (with OCT) by return, to normal, of retinal measurements and vision.

Conclusion: While the evidence presented here is derived from clinical examples in one person and not from a statistically justified large study, this approach to the control of retinal exudate formation offers very effective unintrusive management of a common vision-threatening aspect of DR. In particular, this approach avoids laser treatments and the challenging experience of commonly administered intraocular injections. Clinical and mathematical evidence is presented that treatment with abundant vitamin B1 (300 mg) and vitamin D results in partial cure of DR. A cure to DR has not been reported before.

Future perspectives: The reversal of DR and potentially age-related macular degeneration (ARMD), with safe and simple measures, is an incredibly worthy management goal for these two very common conditions. The possibility demands urgent evaluation with what should be zero- or low-risk clinical trials.

Keywords: blood thinners, diabetic retinopathy, hypertension, macular edema, mathematical modelling

1. Introduction

In what follows, blood vessels of the retinal microcirculation (arteriols, precapillaries, capillaries, venules, etc.) will be collectively referred to as "small veins" or just "veins". Increased blood viscosity is widely recognized as a contributing factor to cerebro- and cardiovascular diseases.[1-3] While elevated blood viscosity also has a role in diabetic retinopathy (DR),[1-3] relative reductions in blood viscosity in individuals with DR appear to worsen retinopathy,[4] and contribute toward exudate formation that induces retinopathy and macular edema.[4] The primary author of this paper, Arieh Helfgott (AH), recently experienced re-emergence of DR and macula edema in August 2021 subsequent to commencing clopidogrel and aspirin, which significantly reduce blood viscosity, after being free of symptomatic DR for the past 17 years without laser treatments or bevacizumab injections and while using five concurrent treatments.[5] In that paper, mathematical formulas modelled the exudative process and provided a basis for the medical management, including elevating blood viscosity by stopping blood thinners.[5] AH's recently re-emerged DR due to essential blood thinners, and its successful treatment and management, provided the motivation for writing this paper.

The treatment to eliminate DR is very simple and effective, requiring only the stepwise increase in the dose of antihypertensive medications. We hope that sharing this information with the general public may be beneficial to

those trying to avoid this manifestation of DR and blindness. The paper details procedures for determining the stepwise dose by which antihypertensive medications need to be increased to negate the re-emerging DR and macular edema caused by antiplatelet therapies, such as dual antiplatelet therapy (DAPT), and so eliminate the edema and DR altogether. The reason for documenting this single case is that the outcome of management using simple measures,[5] including antihypertensive treatment as presented below, is so unexpected that it justifies further scientific and medical study, specifically in trials with adequate numbers of subjects. While this work focuses on DR, we do not exclude the possibility that the treatment may also benefit wet age-related macular degeneration.

1.1. Diabetic retinopathy

DR is a serious sight-threatening complication of diabetes, and the leading cause of blindness in working-age adults. Over time, diabetes gradually damages the blood vessels in the retinal microcirculation (arterioles, capillaries, venules, etc.). This damage may eventually lead to formation of abnormal “holes” in retinal blood vessel walls. DR and macular edema occur when the vessels leak fluids (plasma exudate) and blood from the holes into the retina, resulting in hard and soft retinal exudates, macular edema, and hemorrhages. The result is cloudy or blurred vision. DR usually affects both eyes, and, if left untreated, can cause blindness.

Combined clinical and mathematical evidence is presented below that treatment with abundant vitamin B1 (300 mg) and vitamin D results in partial cure of DR. It seems clear that abundant vitamin B1 and vitamin D intake

(below toxic levels) helps "repair" and reduce the diameter of holes in retinal veins (see item 6) in Conclusions and Example D in Results).

Vitamin B1 (thiamine) plays a fundamental role in intracellular glucose metabolism. In human diabetics, the simple link between vitamin B1 deficiency and diabetes complications was originally demonstrated by Thornalley and his team (reviewed in Helfgott *et al.*[5]).[6] They found that vitamin B1 levels in blood plasma concentrations were 76% lower than normal in type 1 diabetics and 75% lower in type 2 diabetics. They also found that type 1 and 2 diabetics expelled vitamin B1 from their bodies at 15 times the normal rate. To keep blood vessels in good health, diabetics with low vitamin B1 levels clearly need additional thiamine intake to return vitamin B1 levels to normal. Since daily nutritional intake of vitamin B1 is only 1 mg, changes to diet would not be enough to have an effect. Accordingly, AH successfully treated his DR with a high dose of 300 mg vitamin B1 daily (Treatment T2 in Helfgott *et al.*[5]) for the past 17 years.

Similarly, evidence is strongly suggestive that significant vitamin D deficiency is present in both type 1 and 2 diabetics compared with non-diabetics, and of a link between vitamin D deficiency and DR severity (reviewed in Helfgott *et al.*[5]). Vitamin D deficiency has also been associated with increased odds of age-related macular degeneration, which is the most common cause of blindness in the elderly. AH successfully treated his DR with a 2,000 IU vitamin D daily (Treatment T3 in Helfgott *et al.*[5]) for the past 17 years.

1.2. Controlled diabetic retinopathy and re-emergence of diabetic retinopathy caused by blood thinners

For the past 17 years, the primary author of this paper, AH, applied five treatments recommended in his 2018 paper[5] to treat and completely eliminate his advanced diabetic retinopathy (ADR). As a result of applying these five treatments, AH was free of ADR with normal retinoscopic appearance, and did not need laser treatment or anti-VEGF bevacizumab injections for the significantly long period of 17 years.

Treatment 4 (T4 in Helfgott *et al.*[5]) recommended stopping intake of blood thinners, such as aspirin or clopidogrel (if permissible), to avoid an increase in exudation and retinal thickness. Blood thinners significantly reduce blood viscosity. For example, the intake of aspirin plus clopidogrel can reduce whole blood viscosity (WBV) by as much as 24.3% (almost a quarter lower) (see Example D in Results), and this in turn could significantly increase the rate at which fluid (exudate) leaks from holes in damaged retinal blood vessels into surrounding retinal tissues. There are, however, medical conditions where avoidance of blood thinners cannot be applied because they must be taken to treat or prevent cerebro- and cardiovascular events. Recently, AH was prescribed aspirin plus clopidogrel as part of treating circulatory problems in the left leg and a diabetic ulcer in a toe of the left foot. He was advised by his vascular surgeon that taking these blood thinners was very important if he did not want to lose his left leg. For the past 17 years, AH did not, of course, take any blood thinners in fulfilment of T4 and was free of DR. However, in less than two weeks after commencing the two blood thinners (aspirin plus clopidogrel), his retinas started swelling and the beginning of macular edema

became noticeable on OCT scans, providing further evidence of the capacity of blood thinners to restart DR!

This was a moment of reassessment because AH had to accept living long-term with blood thinners while finding ways to manage his re-emerging DR. This paper outlines the basis and methodology for AH's medical approach for reducing and ultimately eliminating DR induced by blood thinners while still continuing these indispensable medications. Note that application of this approach resulted in successful and simultaneous saving of both AH's left leg and eyes.

1.3. Mechanics of exudate leakage from abnormal vein holes into retinal tissues

Pressure within small veins is pulsatile, showing periodic cardiac fluctuations that can be quite considerable.[7] In 2018, Helfgott *et al.* (page 46)[5] demonstrated that these periodic cardiac pressure fluctuations can be as high as 6–10 mmHg at the inlet to abnormal retinal vein holes of hypertensive diabetic subjects. These high-pressure pulsations are due to the upstream effects of increased hypertensive pressures in larger central arteries (aorta, etc.).

To analyze the mechanism of plasma exudate leakage into the retina, we introduce two important definitions:

1. $P_{VEIN}(t)$ is defined as the transient (time-varying) pulsatile pressure inside small retinal veins acting at the inlet of abnormal holes in the vein walls.
2. $P_{RET}(t)$ is defined as the pressure in the retinal interstitial space at the retinal end of the abnormal holes. Extravascular pressure $P_{RET}(t)$

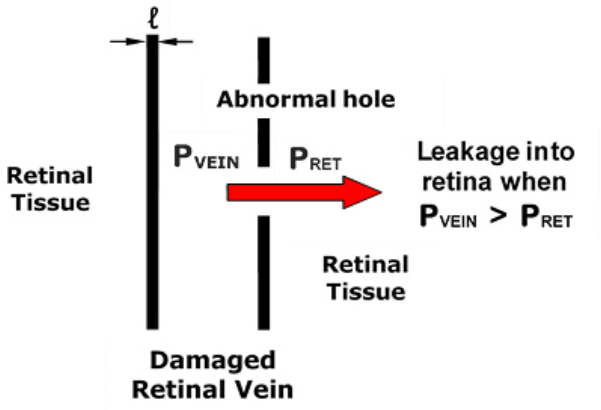

Fig. 1. Diagram illustrating fluid leaking from a tiny abnormal hole in a vein's wall into surrounding retinal tissue. This happens when $P_{VEIN} > P_{RET,}$ that is, when pressure inside the vein exceeds pressure in surrounding tissue just outside the vein. ℓ is the blood vessel's wall thickness and the hole's length.

in retinal tissue surrounding leaking veins can vary with time but is normally fairly constant and slightly subatmospheric.[7] In contrast, intravascular pressure $P_{VEIN}(t)$ varies during the cardiac cycle, being low during diastole and higher during systole. In hypertensive subjects, the transmural pressure drop, $P_{VEIN}(t) - P_{RET}(t)$, provides the driving force for fluid leakage from abnormal holes into the retina, as shown in Figure 1, which graphically illustrates exudate leaking from an abnormal vein hole into surrounding retinal tissue when pressure $P_{VEIN} > P_{RET}$ (inside pressure exceeds outside pressure). The positive transmural pressure difference forces fluid to leak into the retina through the holes. Since $P_{RET}(t)$ is almost constant, transmural pressure difference fluctuations are primarily determined by fluctuations in $P_{VEIN}(t)$, which is thus the major contributor to the transmural pressure difference.

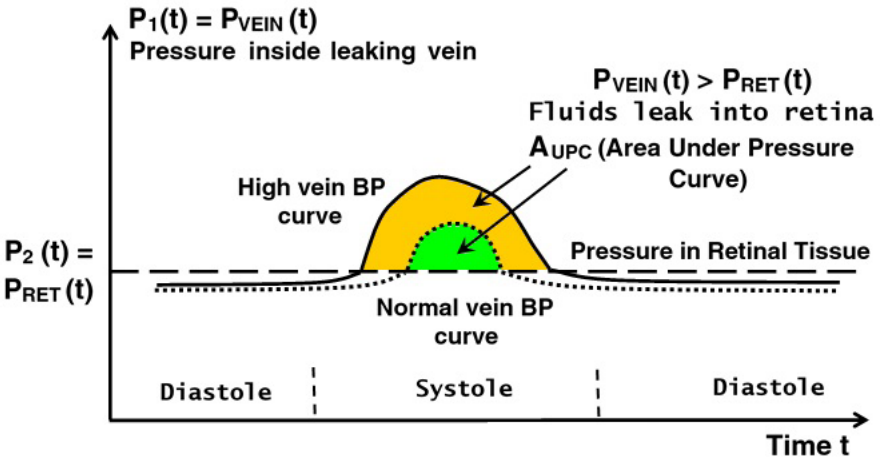

Fig. 2. Diagram showing temporal pressure $P_{VEIN}(t)$ variations inside a damaged small retinal vein during a single cardiac cycle. Pressure rises from low diastolic levels to higher systolic levels, then drops again to low diastolic levels. Fluid starts leaking when P_{VEIN} rises above P_{RET} (pressure in retinal tissue outside vein) and continues leaking until P_{VEIN} drops below P_{RET} (see colored peaks). The longer the leaking lasts, the larger the amount of fluid leaking into retinal tissues. For hypertensive subjects ("High vein BP" curve) the area of the gold-colored peak is significantly larger than the area of the green-colored peak of normotensive subjects ("Normal vein BP"curve).

Note that because venous pressures $P_{\mathbf{VEIN}}(t)$ in microvessels are generally very low, they were traditionally and understandably considered clinically unimportant and were ignored by ophthalmologists (AH experienced this personally). In DR or ADR, however, $P_{\mathbf{VEIN}}(t)$ fluctuation can be as high as 6–10 mmHg, and because it does drive leakage flow through vein holes: it should, therefore, never be ignored!

Figure 2 diagrammatically illustrates temporal pressure $P_{\mathbf{VEIN}}(t)$ variations inside a small vein during a single cardiac cycle. Pressure rises from low diastolic levels to higher systolic levels, then drops back again to low diastolic levels. Because the venous wall is a semipermeable membrane,

leakage occurs only when $P_{VEIN} > P_{RET}$ but does not occur when $P_{VEIN} \leq P_{RET}$ (inside pressure below or equal to outside pressure). Fluid leakage starts the moment P_{VEIN} rises above P_{RET} and continues until eventually P_{VEIN} drops below P_{RET}, at which point leakage stops (see colored peaks in Fig. 2). The longer the leaking lasts, the larger the volume of fluid leaking into the retina will be. For hypertensive subjects ("High vein BP" curve), the gold-colored peak area is significantly larger than the green-colored peak area of normotensive subjects ("Normal vein BP" curve). The area under the vein's pressure curve $P_{VEIN}(t)$ in Figure 2 is denoted by A_{UPC}, and it plays a major role in the ensuing mathematical calculations for lowering blood pressure with antihypertensive medications aimed at eliminating DR.

1.4. Three mathematical formulas required in ensuing calculations previously derived

The starting points of mathematical analysis are three basic formulas derived previously in Helfgott *et al.*[5] The first formula, Equation (8b) in Helfgott *et al.*[5] determines the transient rate of exudate volume $Q_{LEAK}(t)$ leaking from an abnormal hole's exit cross-section into the retina. It is given by the following time-dependent rate relation:

$$Q_{LEAK}(t) = \frac{\pi}{128}\frac{D^4}{\mu \ell}\left[P_{VEIN}(t) - P_{RET}(t)\right] \quad , \quad \text{for} \quad P_{VEIN}(t) > P_{RET}(t) \tag{1a}$$

Here, t is time, $P_{VEIN}(t)$ is transient intravenous pressure, $P_{RET}(t)$ is transient extravenous pressure (retinal tissue pressure), D is the diameter of the hole, μ is the dynamic viscosity of the leaked fluid, and ℓ is the hole-length which

is equal to the vein wall thickness.

Slightly modified Equations (9a) and (9b) in Helfgott *et al.*[5] are obtained by inserting 1/T in front of the integrals. The modified equations determine the volume of a droplet of fluid leaking from the hole's exit cross-section per minute (dot above symbol denotes volume per minute):

$$\dot{V}_{DROPLET}^{LEAK} = \frac{1}{T}\int_0^T Q_{LEAK}(t)\,dt = \frac{\pi}{128}\frac{D^4}{\mu\ell} A_{UPC} \quad , \quad \text{for} \quad P_{VEIN}(t) > P_{RET}(t) \tag{1b}$$

$$\text{in which} \quad A_{UPC} = \frac{1}{T}\int_0^T [P_{VEIN}(t) - P_{RET}(t)]\,dt \quad , \quad \text{for} \quad P_{VEIN}(t) > P_{RET}(t) \tag{1c}$$

Here, T is the duration of a single heartbeat ("cycle length" in cardiology), and A_{UPC} is the area under the vein's pressure curve $P_{VEIN}(t)$ but above retinal interstitial pressure curve $P_{RET}(t)$ (see colored peaks in Fig. 2). Knowledge of A_{UPC} is required because it plays a central role in the design of treatments for eliminating DR, and so formulas for evaluating it are presented in the Methods section.

1.5. Critical volume of a droplet leaking into the retina

We start with an important observation: in hypertensive diabetic subjects suffering from DR or ADR, systole in each heartbeat contributes to exudate accumulation in retinal tissues, and so, with each successive heartbeat, a diabetic subject gets closer and closer to blindness! This is an unusual medical condition in which one's heartbeats act against one's interests. Fortunately, the eye has many pumps capable of removing fluids from the retina. Let symbol Q denote rate of fluid flow (*i.e.*, fluid volume passing per

minute, or per some other unit time). Also, let $Q_{\mathbf{LEAK}}$ and $Q_{\mathbf{PUMP}}$ denote fluid volume leakage rate into the retina through holes in retinal veins and fluid volume removal rate from the retina by retinal pumps, respectively. In normotensive subjects, $Q_{\mathbf{PUMP}} > Q_{\mathbf{LEAK}}$ and the pumps can easily remove excess fluids from the retina because $Q_{\mathbf{PUMP}}$ is larger than the normally low $Q_{\mathbf{LEAK}}$ in normal subjects. This is, however, not so in hypertensive diabetic subjects. In hypertension, $Q_{\mathbf{PUMP}} < Q_{\mathbf{LEAK}}$ and the pumps can no longer cope with the abnormally large leakage rates, and so leaked fluids begin to accumulate in the retina, resulting in unwanted retinal "flooding" and swelling. This is similar to what happens in heavy rains: the amount of water pouring down the streets is so large that street gutters are no longer capable of removing it, resulting in street flooding.

Accordingly, there exists a maximum (critical) value that an increasing $Q_{\mathbf{LEAK}}$ can reach before retinal "flooding" takes place. This critical flow rate is reached when $Q_{LEAK} = Q_{PUMP} = Q_{LEAK}^{CRITICAL}$, in which $Q_{LEAK}^{CRITICAL}$ is defined as the maximal volume of fluid that the pumps are physically capable of removing per minute. In terms of droplet volume, we can write $V_{DROPLET}^{CRITICAL} = Q_{LEAK}^{CRITICAL} = Q_{PUMP}$, in which $V_{DROPLET}^{CRITICAL}$ is the critical volume of a droplet leaking into the retina in one minute from an abnormal hole when $Q_{\mathbf{LEAK}} = Q_{\mathbf{PUMP}}$. Let V_{DROLET}^{LEAK} denote the volume of a droplet leaking from an abnormal hole, then "flooding" of the retina starts the moment the volume of this droplet increases above critical droplet volume, that is, when $V_{DROPLET}^{LEAK} > V_{DROPLET}^{CRITICAL}$ Figure 3 illustrates diagrammatically the leaking of exudate droplets and their removal by retinal pumps. The transition from a DR-free state to DR and ADR is pictorially demonstrated by means of four leaked droplets of increasing volumes, one below

$V_{DROPLET}^{CRITICAL}$, one equal to $V_{DROPLET}^{CRITICAL}$ and two above $V_{DROPLET}^{CRITICAL}$. Retinal flooding starts when fixed-capacity retinal pumps are no longer able to remove excess large volumes of leaked exudate.

All this has important implications in the design of effective blood pressure-lowering treatments for reducing and eventually eliminating DR. First, consider a diabetic subject with controlled DR and an initial droplet volume $V_{DROPLET1}^{LEAK} < V_{DROPLET}^{CRITICAL}$: this patient has some "blood pressure credit" before their droplet volume surpasses $V_{DROPLET}^{CRITICAL}$ and DR re-emerges, that is, the blood pressure can rise by a certain amount before the patient experiences the onset of DR. Coming from the opposite direction, if the patient later has hypertension and uncontrolled DR (with $V_{DROPLET}^{LEAK} > V_{DROPLET}^{CRITICAL}$), there is no need to reduce blood pressure to achieve a return to his initial droplet volume $V_{DROPLET1}^{LEAK}$. Rather, adding moderate stepwise doses of antihypertensive medications to ensure that droplet volume is stepwise reduced to be just below the critical value of $V_{DROPLET}^{CRITICAL}$ is sufficient (and not further down to $V_{DROPLET1}^{LEAK}$), as judged by OCT scans that show diminishing retinal thickness!

1.6. The importance of whole blood viscosity

Blood thinners induce a substantial drop in whole-blood viscosity (WBV). Since this significantly lower WBV plays a central role in causing the re-emergence of DR, it is important to list some known basic facts about viscosity in general and about WBV in particular. Note that there would have been no need to write this paper if the drop in WBV was much smaller!

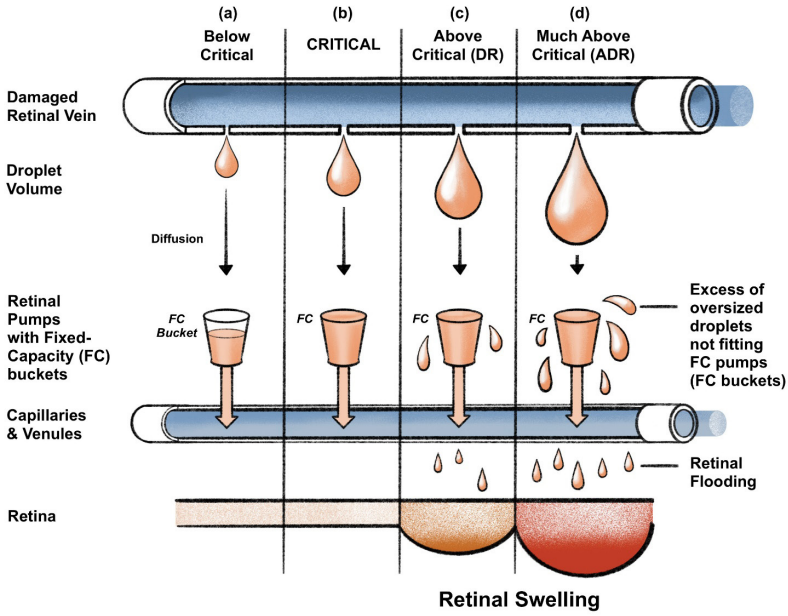

Fig. 3. Diagram illustrating four droplets of exudate [(*a*), (*b*), (*c*), (*d*)] leaking during cardiac systole from tiny abnormal holes in retinal vein walls into surrounding retinal tissue and then *cleared completely* [(*a*), (*b*)] or cleared incompletely [(*c*), (*d*)] by microscopic retinal pumps of fixed capacity (FC). The fixed capacity of a pump is defined as the maximum volume of exudate that the pump is capable of removing from retinal tissues in one minute. This also defines the critical (maximum) volume that a droplet can increase to in one minute, $V_{DROPLET}^{CRITICAL}$, for the pump to be capable of removing it completely. That is, the *critical volume of a droplet* $V_{DROPLET}^{CRITICAL}$ equals the pump's fixed capacity (see text for more details). The fixed capacity of each FC pump is indicated in the diagram by a bucket of fixed capacity (FC bucket), the volume of which equals the maximal volume of exudate that the pump can remove in one minute. All four FC buckets shown in the drawing are of the same critical volume. Note that, after a leaked droplet enters surrounding retinal tissues, it reaches a retinal FC pump by passive diffusion. An FC pump can completely remove a droplet if its volume is below or equal to the critical volume $V_{DROPLET}^{CRITICAL}$. Larger droplets, as occur in (*c*) and (*d*), *i.e.*, DR (diabetic retinopathy) or ADR (advanced diabetic retinopathy), respectively, can only be partially removed. In (*a*), the droplet volume is below critical volume $V_{DROPLET}^{CRITICAL}$, and so the FC bucket is only partially full and the pump can easily remove the entire droplet from retinal tissues. In (*b*), the droplet volume equals exactly the critical volume $V_{DROPLET}^{CRITICAL}$, and so the FC bucket is completely full and the pump has the capacity to completely clear the entire droplet from retinal tissues. In (*c*), the droplet volume is above critical volume $V_{DROPLET}^{CRITICAL}$, and so the FC pump no longer has the capacity to completely remove it, resulting in the excess from the oversized droplet "spilling" into retinal tissues and causing retinal "flooding" and swelling (edema). This example corresponds to DR. In (*d*), the droplet volume is much above critical volume

$V_{DROPLET}^{CRITICAL}$, and so the FC pump is even less able to remove it, resulting in the large excess from the oversized droplet "flooding" retinal tissues and causing significant retinal swelling. This example corresponds to ADR, in which holes in veins have become larger and also increased in number until the blood vessels eventually become so abnormal and full of leaking holes that they lose significant functionality. New blood vessels begin to grow (proliferative retinal neovascularization) that are leakier than ordinary leaking retinal blood vessels, leaking blood into the back of the eye and impairing vision or causing blindness.

Over the past few decades, much has been written about WBV. The excellent book by Caro *et al.*[7] provides a detailed description and analysis of the subject. The recent text by Klabunde[8] provides a good summary of WBV's main features. Whole blood is a two-phase suspension of formed elements [red blood cells (RBCs), white blood cells (WBCs), and platelets] suspended in plasma. The plasma itself is an aqueous solution containing numerous low-molecular weight organic and inorganic materials in low concentration, and approximately 7% by weight of proteins (mainly albumin and fibrinogen). Attention will be focused particularly on RBCs, because they are the only cells which significantly influence the mechanical properties of whole blood. The mechanical property of blood of principal interest to us here is its viscosity. Typical units of viscosity are:

1 Pascal•second [Pa•s] = 1 Newton•second / square metre [Nsm^{-2}] = 1000 centiPoise [cP].

Viscosity is an intrinsic property of any fluid and is related to the internal friction between adjacent fluid layers (laminae) sliding past one another. This internal friction contributes to the resistance to flow of the fluid. There exists an inverse relationship between flow velocity and viscosity: the

greater the viscosity, the smaller the velocity of fluid flow, meaning that, at a given driving pressure, flow velocity will be reduced at higher viscosities and increased at lower viscosities.

The interactions between fluid layers depend on the chemical nature of the fluid, and whether it is homogeneous or heterogeneous in composition. For example, water is a homogeneous fluid, and its viscosity is determined by molecular interactions between water molecules. Water is a Newtonian fluid because, under non-turbulent conditions, its viscosity is independent of flow velocity (*i.e.*, viscosity does not change with changes in velocity). Water, blood plasma, air, alcohol, glycerol, and thin motor oil are all examples of Newtonian fluids over the range of velocities encountered in everyday life. In contrast, the viscosity of non-Newtonian fluids changes with velocity and shear rate (defined in Section, 1.6.1): viscosity is higher at low velocities and lower at high velocities. Ketchup, for example, becomes runnier when shaken and is thus a non-Newtonian fluid. Many salt solutions and molten polymers are non-Newtonian fluids, as is whole blood and many commonly found substances, such as custard, toothpaste, starch suspensions, cornstarch, paint, melted butter, and shampoo.

1.6.1. Blood viscosity at different shear rates

Shear rate is defined as the velocity difference between two parallel fluid laminae (or planes) sliding past each other, divided by the distance between the laminae. The unit of shear rate is 1/second (velocity/distance). Because whole blood is a non-Newtonian fluid, its viscosity depends on shear rate. At low shear rates its viscosity is higher, whereas at high shear rates its viscosity

is lower. At low shear rates, blood cells aggregate, and this induces a sharp increase in viscosity, whereas at higher shear rate blood cells disaggregate, deform, and align in the direction of flow, and this induces a reduction in viscosity.

1.6.2. No-slip condition in blood flow

Because it is viscous, at a solid boundary (*e.g.*, blood vessel wall) blood will have zero velocity relative to the wall, a state labelled the "no-slip condition" in blood flow. Conceptually, one can think of the blood particles as stuck to the wall surface past which the blood flows. More specifically, blood particles in close contact with the wall do not move along with the flow because adhesion is stronger than cohesion. At the blood-wall interface, the force of attraction between the blood particles and solid wall particles (adhesive forces such as electrostatic forces) is greater than the force of attraction between the individual fluid particles themselves (cohesive forces). This force imbalance brings down the blood velocity to zero at the wall. The importance of the no-slip condition in dislodging or producing clots that eventually cause strokes is discussed in Section 1.6.3.

1.6.3. Shearing stresses in flowing blood

Shearing stresses induced in blood that is flowing through arteries play a very important role in cerebro- and cardiovascular disease. Unlike solids, blood at rest cannot resist shearing stresses (shearing forces per unit area). Under the action of sheering stresses, whole blood deforms continuously, however small the stresses are. The resistance to the action of shearing

stresses appears only when blood is in motion, but not at rest. For blood, the shear stress depends on the shear rate and on its viscosity, μ, which is the property of blood to resist the growth of deformation (*i.e.*, shear rate) caused by shear stress. To a good approximation, shear stress in blood is proportional to the shear rate, with μ being the coefficient of proportionality:

$$\text{Shear Stress} = \text{Coefficient of Viscosity } (\mu) \times \text{Shear Rate} \qquad (2)$$

Equation (2) shows that high shear stresses can occur when the coefficient of viscosity μ is large or when shear rate is high or both. The importance of this in cerebro- and cardiovascular disease is as follows. Consider, as an example, arteries with partial occlusions caused by blood clots or fatty plaque buildup (atheroma). In this example, high shear stresses can apply sufficiently large forces to dislodge some of the clots or to tear off parts of plaques and result in strokes. The no-slip condition plays an important role in these dislodgements. Recall that, when viscous blood comes in contact with a solid wall, it adheres to it by, for example, electrostatic forces, and so its velocity at the wall is zero. But the shear rate is not zero. It can be very substantial when neighboring laminae flowing close to the wall move at very large velocities with respect to the wall. Hence, when the blood flows past a clot or plaque in an artery, it adheres to it by electrostatic forces and large shear stresses are then applied to it. If μ and/or shear rates are high enough, the dislodgement of clots or the tearing off of parts of a plaque will result.

The risk of clot dislodgement or tearing off of parts of a plaque is diminished after commencement on blood thinners. Blood thinners significantly reduce

whole blood viscosity μ. The reduction in μ can, for example, be as large as 24.3% (almost a quarter reduction in magnitude of μ) when both aspirin and clopidogrel are taken simultaneously (see Example D in Results section). By Equation (2) above, a reduction of 24.3% in μ will result in a 24.3% reduction in wall shear stresses capable of dislodging clots, or ripping off parts of a plaque, which is a significant reduction! In summary, blood thinners are very effective in controlling cerebro- and cardiovascular disease by inducing very substantial reductions in viscosity and corresponding shear stresses. However, at the same time, they may also cause re-emergence of DR.

1.6.4. Viscosity and osmotic pressure of plasma

Plasma is a pale yellow, transparent fluid, which is obtained by removing the cells from blood that has been prevented from coagulating. In contrast to whole blood, normal plasma is a Newtonian fluid, meaning that there is an immeasurably small influence of shear rate on plasma viscosity in the physiological range. Typical values for the viscosities of normal human plasma and serum at 37°C are 1.1 to 1.2 cP, and they are independent of a person‘s age and gender. The plasma exudate leaking from retinal vein holes can therefore be treated in calculations as a Newtonian fluid!

The osmotic pressure of plasma affects the mechanics of the circulation in several ways. An osmotic pressure difference across the cell membrane of an RBC will cause a shift of water and a change of the RBC volume. For example, a reduction of the concentration of sodium chloride external to RBCs will cause them to swell. In the extreme, there would be a spherical RBC that would be much stiffer than the normal disc-shaped cell because of

its inability to deform without stretching its membrane. The change both in RBC shape and flexibility will affect the mechanical properties and viscosity of whole blood, as explained in Section 1.6.5. Furthermore, a change in plasma osmotic pressure will alter the hematocrit (the volume of RBCs in whole blood) by redistributing water between the intravascular and extravascular spaces. This, in turn, will alter the mechanics of whole blood.

Although plasma is mostly water, it also contains other molecules such as electrolytes, proteins (*e.g.*, albumin and fibrinogen), and other macromolecules. Because of molecular interactions between these different components of plasma, it is not surprising that Newtonian plasma has a higher viscosity than water. Plasma at 37°C is about 1.8 times more viscous than water at the same temperature. The addition of the formed elements, RBCs, WBCs, and platelets, to plasma further increases the viscosity of blood. RBCs have the greatest effect on blood viscosity. With hematocrit defined as the ratio of RBC volume to total blood volume, at a normal hematocrit level of 40%, the relative viscosity of blood is about 4. Relative viscosity increases non-linearly with hematocrit levels. Increasing hematocrit levels from 40% to 60% (a 50% increase) increases the relative viscosity from 4 to 8 (a 100% increase).

1.6.5. Deformability of red blood cells and its profound effect on blood viscosity

The primary role of a RBC and its hemoglobin is to carry oxygen from the lungs to all body tissues and then make the return trip, taking carbon dioxide back to the lungs to be exhaled. Hemoglobin is both an oxygen carrier and a

carbon dioxide carrier. Virtually all the hemoglobin in blood (about 15 g/100 ml) is contained as a liquid solution within RBCs. Each RBC consists of a very thin membrane and a liquid interior, which is an almost saturated solution (approximately 32% by weight) of hemoglobin. The viscosity of the fluid interior is about 6 cP, which is nearly five times greater than that of blood plasma, and it plays an important role in RBC deformability and flexibility (discussed below). This may be altered in some diseases, such as sickle cell anemia, when the hemoglobin may become crystalline and consequently the RBC becomes stiffer.

Intact RBCs have no internal structure, their contents are liquid (no nucleus or mitochondria), and their shapes are determined by the properties of their membranes. RBCs have the unique ability to undergo large deformations reversibly when subjected to external forces (axial forces or tangential shear forces), which allows them to pass through capillaries that are narrower than the diameter of a resting RBC. RBCs are highly flexible biconcave discs, typically 6–8 μm in diameter and 2–3 μm thick, and their deformation can involve a change in cell curvature, a uniaxial deformation, or an area expansion. Note, however, that a biconcave RBC can deform into an infinite variety of shapes without changing its volume or surface area, that is, without stretching its membrane.

The RBC cell membrane contains a very thin phospholipid bilayer of about 7.5 nm in thickness. Consequently, it has negligible stiffness to bending, compared with its stiffness on stretching. Because the interior of the RBC is liquid, it is able to offer viscous resistance to deformation, but not bending resistance, and this makes the RBC very flexible. The deformability

and flexibility of RBCs play an important part in determining the WBV. At a given shear rate and for a range of hematocrits exceeding a given value, the viscosity of a suspension of hardened RBCs considerably exceeds that of a suspension of normal RBCs.[7] Similar findings are obtained with RBCs that have been sphered, and which are therefore less flexible, and also with the stiffer cells of patients with sickle cell anemia.[7] For blood flow at high shear rates, normal RBCs align with the direction of flow by deforming into an elliptical shape via a "tank tread-like" motion of the cell membrane around its hemoglobin liquid interior. Rigid RBCs, on the other hand, cannot properly deform into an ellipse and remain perpendicular to blood flow, consequently increasing vascular resistance.

1.6.6. Blood viscosity in diabetics with and without diabetic retinopathy and in non-diabetics

The rank order of WBV in diabetic populations is diabetes-with-retinopathy > diabetes-without-retinopathy > non-diabetics, as reported in the following studies. WBV at high and low shear rates of 100 sec^{-1} and 0.94 sec^{-1}, and several of its major determinants (hematocrit, plasma fibrinogen) were measured in 38 insulin-treated diabetics and in 38 non-diabetic control subjects by Lowe *et al.*[9] Diabetics without fundoscopic retinopathy had higher mean WBV than controls at both high shear (7.07 cP vs 6.75 cP) and low shear rates (21.2 cP versus 18.7 cP). These differences persisted after correction for standard hematocrit and were associated with increased plasma viscosity (1.41 cP versus 1.34 cP, $p < 0.025$) and plasma fibrinogen (2.9 g/L versus 2.5 g/L). Diabetics with retinopathy had higher mean WBV than diabetics without

retinopathy, again at both high shear (7.53 cP vs 7.07 cP) and low shear rates (24.3 cP vs. 21.2 cP), and had higher hematocrit. In another study, in 26 diabetic patients (11 with and 15 without retinopathy) and in 25 non-diabetic control subjects,[10] WBV, plasma viscosity, and plasma fibrinogen were significantly higher in diabetics than in controls and RBC deformability was significantly reduced.

Irace *et al.*[3] also demonstrated a direct relationship between blood viscosity and blood glucose in non-diabetic subjects and suggested that, even within glucose values considered completely normal, individuals with higher blood sugar levels have increased blood viscosity comparable to that observed in prediabetic subjects.

While it is generally accepted that blood viscosity is increased in diabetic patients,[1-3,9,10] the reasons for this are still not fully understood. It has been suggested that the increase in osmolarity could cause diuresis, and consequently, increased hematocrit and viscosity.[12] These and other hemorheological parameters (fibrinogen, RBC aggregation, etc.), therefore appear to play an important role in the pathogenesis of severe diabetes complications as well as in cerebro- and cardiovascular diseases more generally.[11-14]

1.6.7. High whole-blood viscosity increases thromboembolic risk and plays an important role in cerebro- and cardiovascular diseases

Elevated levels of WBV can cause blood stagnation and subsequent pathological thrombotic events that result in the development of ischemic strokes or other cardiovascular diseases. Several clinical and epidemiologic studies have demonstrated an association between high WBV and the occurrence

of major thromboembolic events.[11,12] Furthermore, there is evidence to show that WBV is significantly higher in cases of lacunar or cardioembolic strokes.[13] Finally, as increased RBC aggregation is a reflection of inflammation, hyperviscosity has been shown to be a marker of inflammatory activity.[2] Thus, because of its role in hemodynamics, thrombosis, and inflammation, laboratory measurement of WBV could provide useful information for diagnostics and therapy of cerebro- and cardiovascular disease. Regrettably, however, laboratory facilities for measuring WBV on a routine basis are currently not available to physicians in Australia and in many other countries.

Thankfully, thromboembolic risks associated with high WBV levels can be greatly diminished with treatments such as statins or antithrombotics, such as aspirin and clopidogrel, which can reduce WBV by a significant 24.3% (Example D in Results) and even more (with warfarin).

1.6.8. Blood thinners, aspirin, and/or clopidogrel substantially reduce whole-blood viscosity

Aspirin has been demonstrated to lower WBV. Though various mechanisms have been proposed, aspirin-induced changes to RBC cell membrane deformability were shown to decrease RBC rigidity, and thus decrease WBV.[14] In 2008, Vekasi *et al.*[15] demonstrated a relationship between aspirin use and lowered blood viscosity in patients with DR. Thus, stopping aspirin intake leads to an increase in blood viscosity μ, which in turn reduces the rate of fluid leakage $Q_{\mathbf{LEAK}}(t)$ from vein holes into the retina. The reduced leakage rate is due to the inverse relationship between $Q_{\mathbf{LEAK}}(t)$ and μ, defined in Equation (1a) above, specifically, the higher the viscosity, the lesser the rate (and volume) of fluid

leaking into the retina from holes in damaged veins. Similarly, in a study of 70 subjects with abnormally high blood viscosity and ultrasound evidence of subclinical atherosclerosis, Ciuffetti *et al.*[16] reported that treatment with clopidogrel 75 mg daily for at least three weeks significantly reduced WBV levels from 5.38 cP to 4.84 cP at high shear rates of 94.5 sec^{-1}, and from 27.52 cP to 22.55 cP at low shear rates of 0.94 sec^{-1}. In 2018, Zhang *et al.*[17] reported that combined treatment with clopidogrel 75 mg and aspirin 100 mg daily for one year reduced WBV from 42.0 cP to 31.8 cP in a group of 40 patients with confirmed coronary heart disease (angina pectoris). This corresponds to a significantly large 24.3% [(42.0 – 31.8) / 42.0] drop in WBV!

2. Methods

In this section, a mathematical model of re-emerging DR and a medical approach for its elimination are developed. The re-emerging DR has its origins in the hefty drop in WBV caused by blood thinners. The aim of the new approach is to eliminate re-emerging DR by lowering blood pressure with stepwise increases in doses of antihypertensive drugs while continuing indispensable blood thinners.

To determine how large the volume of an exudate droplet has become after commencement on blood thinners, we first calculate the percentage increase in volume of the droplet leaking into the retina from a vein hole. Then, by applying stepwise blood pressure-lowering treatments, the enlarged volume of the droplet is reduced stepwise until it is below the critical volume, $V_{DROPLET}^{CRITICAL}$. This, in turn, ensures that retinal pumps can then completely eliminate the re-emerging DR over a period of time.

Recal that in what follows, blood vessels of the retinal microcirculation (arterioles, precapillaries, capillaries, venules, etc.) are collectively referred to as “small veins” or just “veins”. All pressures are defined relative to the atmospheric pressure. We first determine the area under the pressure curve, A_{UPC}, corresponding to transmural pressure drop $P_{VEIN}(t) - P_{RET}(t)$.

2.1. Computation of area under the pressure curve A_{UPC}

The starting point of mathematical analysis is with the three basic formulas, Equations (1a), (1b), and (1c), previously derived in Helfgott *et al.*[5] and presented in Section 1.4 of the Introduction. Figure 2 shows that a lowering of blood pressure $P_{VEIN}(t)$ during systole is accompanied by a reduction in the area under the pressure curve, A_{UPC}, defined in Equation (1c). Hence, A_{UPC} will play a central role in the design of blood pressure-lowering treatments for eliminating DR developed below. Computation of A_{UPC} with Equation (1c) poses significant difficulties because it requires knowledge of transmural pressure drop $P_{VEIN}(t) - P_{RET}(t)$, which is the drop in pressure between the inlet and outlet of microscopic abnormal vein holes. Currently, there are no simple procedures for routinely measuring such pressures in the microcirculation. Instead, a good approximation of this transmural pressure drop is derived below, with which the integral in Equation (1c) is evaluated and a new formula for A_{UPC} is obtained. After switching parameters from the microcirculation to the macrocirculation, the new formula for microcirculatory A_{UPC} includes only a single macrocirculatory variable, namely, the average peak systolic arterial blood pressure measured with a cuff around the arm (or by any other method) and then averaged over a period of a few weeks.

A_{UPC} will be approximated here in three increasingly accurate ways. Let $B_{VEIN} < T$ denote the duration ('B' for "Breadth in time") of the systolic part of $P_{VEIN}(t)$ and let P_{VEIN}^{MAX} be peak of $P_{VEIN}(t)$ during B_{VEIN}.

1. A crude approximation of A_{UPC} is obtained by assuming it equals the area of a triangle of base B_{VEIN} and height P_{VEIN}^{MAX}: that is, $A_{UPC} = 0.5 \frac{1}{T} B_{VEIN} P_{VEIN}^{MAX}$.
2. Let $B_{VEIN} = 2b$. Then, a more accurate value of A_{UPC} is obtained by approximating the systolic part of transmural pressure drop $P_{VEIN}(t) - P_{RET}(t)$ with the quadratic polynomial (parabola):

$$P_{VEIN}(t) - P_{RET}(t) = -\frac{P_{VEIN}^{MAX}}{b^2}(t+b)(t-b) \quad , \quad b = \frac{B_{VEIN}}{2} \tag{3a}$$

$$A_{UPC} = \frac{1}{T}\int_{-b}^{b}[P_{VEIN}(t) - P_{RET}(t)]\,dt = \frac{4}{3}\frac{1}{T}B_{VEIN}P_{VEIN}^{MAX} = 0.667\frac{1}{T}B_{VEIN}P_{VEIN}^{MAX} \quad \text{(quadratic approximation)} \tag{3b}$$

3) A significantly more accurate value of A_{UPC} is obtained by approximating the systolic part of $P_{VEIN}(t) - P_{RET}(t)$ with the biquadratic polynomial (4^{th} order polynomial):

$$P_{VEIN}(t) - P_{RET}(t) = \frac{P_{VEIN}^{MAX}}{4b^4}(t+b)(t-b)(t+2b)(t-2b) \quad , \quad b = \frac{B_{VEIN}}{2} \tag{4a}$$

$$A_{UPC} = \frac{1}{T}\int_{-b}^{b}[P_{VEIN}(t) - P_{RET}(t)]\,dt = \frac{19}{30}\frac{1}{T}B_{VEIN}P_{VEIN}^{MAX} = 0.633\frac{1}{T}B_{VEIN}P_{VEIN}^{MAX} \quad \text{(bi-quadratic approximation)} \tag{4b}$$

Approximation (4b) will be used to evaluate A_{UPC} in all calculations underlying the treatment of DR that follow. This requires, however, measurement of microcirculatory parameters B_{VEIN} and P_{VEIN}^{MAX}. Since such measurements at the level of the microcirculation are not currently available on a routine

basis, B_{VEIN} and P^{MAX}_{VEIN} will be calculated from their counterparts in the arterial (ART) macrocirculation, namely, B_{ART} and P^{MAX}_{ART}. Accordingly, let time-dependent arterial blood pressure be denoted by $P_{ART}(t)$, and let $B_{ART} < T$ denote the duration of the systolic part of arterial $P_{ART}(t)$. Then peak arterial blood pressure, denoted by P^{MAX}_{ART}, which is the peak of $P_{ART}(t)$ during B_{ART}, can readily and routinely be measured by a cuff placed around the arm (or by any other similar method). The mathematical relationship between measured P^{MAX}_{ART} and measured B_{ART} can then be readily determined by curve fitting, which then allows calculation of B_{ART} from any cuff-measured P^{MAX}_{ART}.

The duration of arterial systole B_{ART} is known to increase with arterial blood pressure. In 1986, De Scalzi *et al.*[18] reported that normal subjects have significantly lower values of average $\overline{B}_{ART}$ compared to hypertensives [341.7 ± 18.4 ms versus 355.1 ± 15.2 ms ($p < 0.025$)]. Hence, average $\overline{B}_{ART}$ in hypertensives is approximately 4% longer than the $\overline{B}_{ART}$ average in normotensives (355.1 ms /341.7 ms). A difference of 4% can affect the volume of a droplet leaking into the retina from an abnormal vein hole. Fitting a suitable linear trendline to the data series of B_{ART} against P^{MAX}_{ART} found in De Scalzi *et al.*[18] yielded the relationship:

$$B_{ART} = 0.2845 \times (1072 + P^{MAX}_{ART}) \qquad (5a)$$

With Equation (5a), the duration of arterial systole B_{ART} can then be calculated for any measured peak arterial pressure P^{MAX}_{ART}. Since pressure pulsations in the microcirculation correspond to arterial pressure pulsations, it is reasonable to assume that B_{VEIN} equals B_{ART}, and so we can write:

$$B_{VEIN} = B_{ART} = 0.2845 \times (1072 + P_{ART}^{MAX}) \quad (5b)$$

If it is further assumed that for a given subject, and after many heartbeats, peak systolic pressure in the microcirculation, P_{VEIN}^{MAX}, is on average smaller than arterial pressure by a constant factor k_R with respect to macrocirculatory peak systolic pressure P_{ART}^{MAX}, then we can also write:

$$P_{VEIN}^{MAX} = k_R P_{ART}^{MAX} \quad , \quad k_R = \text{constant} \quad (5c)$$

Thus, both microcirculatory variables B_{VEIN} and P_{VEIN}^{MAX} can be determined from the single macrocirculatory peak arterial pressure, P_{ART}^{MAX}, measured with a cuff around the arm. Inserting B_{VEIN} and P_{VEIN}^{MAX} from Equations (5b) and (5c) into Equation (4b), we finally obtain the microcirculatory area under the pressure curve A_{UPC} in terms of single macrocirculatory variable P_{ART}^{MAX}:

$$A_{UPC} = 0.18\, k_R \frac{1}{T} (1072 + P_{ART}^{MAX})\, P_{ART}^{MAX} \quad (6a)$$

The mean of A_{UPC}, which is a potent parameter needed in calculations below, is then simply obtained by taking the mean of both sides of Equation (6a):

$$\overline{A}_{UPC} = 0.18\, k_R\, \overline{f}\, (1072 + \overline{P}_{ART}^{MAX})\, \overline{P}_{ART}^{MAX} \quad (6b)$$

Here, the overbar denotes the means of A_{UPC} and P_{ART}^{MAX}. In the derivation of the means in Equation (6b), it was assumed that the variance of P_{ART}^{MAX} is much smaller than the square of its mean $(\overline{P}_{ART}^{MAX})^2$ (see Appendix). Note that f = 1/T

is the heart rate in beats per minute (bpm). In general, f is determined by many factors unrelated to our small pressure-lowering treatments. In order not to introduce these other factors into our calculations, we have inserted the mean heart rate over a long period of time, $\bar{f}$, into Equation (6b). Note also that the small pressure lowering measures made during treatments have a negligible effect on $\bar{f}$.

2.2. Computation of mean volume of an exudate droplet $\bar{V}_{DROPLET}^{LEAK}$

The volume of a droplet of exudate leaking from an abnormal hole per minute is given by Equation (1b). This equation can also be written in the following simpler form:

$$\dot{V}_{DROPLET}^{LEAK} = \frac{1}{\mu} K A_{UPC} \quad , \quad \text{for} \quad P_{VEIN}(t) > P_{RET}(t) \tag{7a}$$

In this equation, K is a geometric parameter, the value of which depends solely on an abnormal hole's geometrical dimension, and it is defined by:

$$K = \frac{\pi}{128} \frac{D^{\cdot}}{\ell} = \text{constant} \tag{7b}$$

For a given heartbeat, the volume of a leaked droplet of exudate can vary from hole to hole and, for each hole, it can vary from heartbeat to heartbeat. To deal with this variability, we calculate below the more potent average (mean) volume of an exudate droplet leaking into the retina from a total of M holes during N heartbeats. This mean droplet volume will be used to evaluate the effectiveness of blood pressure-lowering treatments in reducing the volume

of the mean droplet and in ultimately eliminating re-emergent DR. In what follows, the mean of a random variable will be denoted by an overbar above its name (*e.g.*, $\overline{X}$).

Because plasma exudate is a Newtonian fluid, the viscosity of which does not vary with shear rate, in all ensuing computations it will be assumed that plasma exudate viscosity μ has a constant value that does not vary from hole to hole. This assumption will also hold for whole blood because there are very small velocity and shear rate changes in the microcirculation. With all holes in retinal blood vessels numbered from 1 to M and heartbeats numbered from 1 to N, let i denote hole number i and j heartbeat j. In terms of i and j, $\dot{V}^{LEAK}_{DROPLET}$ in Equation (7a) takes the form:

$$\dot{V}^{\mathbf{LEAK}}_{\mathbf{DROPLET}}(i,j) = \frac{1}{\mu} K(i) A_{\mathbf{UPC}}(i,j) \quad , \qquad \text{for} \quad P_{VEIN}(t) > P_{RET}(t) \tag{8}$$

In Equations (7a) and (8), both K and $A_{\mathbf{UPC}}$ are independent random variables. This is because K varies solely with the geometrical dimensions of holes and $A_{\mathbf{UPC}}$ varies solely with physiological pressure differences across walls of damaged retinal veins. For these two independent random variables, the mean of their product equals the product of their means.[19]

Hence, the mean volume of an exudate droplet leaking into the retina from M holes in N heartbeats is then obtained from Equation (7a) by simply taking the mean of both sides of this equation (placing overbar above random variables).

$$\overline{\dot{V}}_{DROPLET}^{LEAK} = \frac{1}{\mu}\,\overline{K\,A}_{UPC} = \frac{1}{\mu}\,\overline{K}\,\overline{A}_{UPC} \quad , \qquad \text{for} \quad P_{VEIN}(t) > P_{RET}(t) \tag{9a}$$

In Equation (8), K is a one-dimensional random variable that can only vary from hole to hole, but not from heartbeat to heartbeat. Two-dimensional random variables $\dot{V}_{DROPLET}^{LEAK}$ and A_{UPC} can, however, vary from hole to hole as well as from heartbeat to heartbeat. Accordingly, the three means appearing in Equation (9a) are defined as follows:

$$\overline{\dot{V}}_{DROPLET}^{LEAK} = \frac{1}{NM}\sum_{j=1}^{N}\sum_{i=1}^{M}\dot{V}_{DROPLET}^{LEAK}(i,j) \quad , \qquad \text{for} \quad P_{VEIN}^{i,j}(t) > P_{RET}^{i,j}(t) \tag{9b}$$

$$\overline{A}_{UPC} = \frac{1}{NM}\sum_{j=1}^{N}\sum_{i=1}^{M}A_{UPC}(i,j) \quad , \qquad \text{for} \quad P_{VEIN}^{i,j}(t) > P_{RET}^{i,j}(t) \tag{9c}$$

$$\overline{K} = \frac{1}{M}\sum_{i=1}^{M}K(i) \quad , \qquad \text{for} \quad P_{VEIN}^{i,j}(t) > P_{RET}^{i,j}(t) \tag{9d}$$

Here, the product NM equals the total number of individual exudate droplets leaking into the retina from a total of M holes in N heartbeats. The double sum in Equation (9b) (two-dimensional random variable) equals the total volume of exudate leaking (not accumulating!) into the retina from M holes in N heartbeats (*i.e.*, in NM individual leaking episodes). The important mean volume of an exudate droplet leaking into the retina from M holes in N heartbeats, $\overline{\dot{V}}_{DROPLET}^{LEAK}$, is then simply this total exudate volume divided by NM. Similarly, for two-dimensional A_{UPC}, the mean $\overline{A}_{UPC}$, in Equation (9c) equals the sum of all A_{UPC} occurring in M holes during N heartbeats divided by NM. Finally, the mean of one-dimensional K, *i.e.*, $\overline{K}$, is the sum of all Ks over M holes

divided by M, and this mean does not change from heartbeat to heartbeat.

Equation (9a) indicates the important existence of an inverse relationship between mean droplet volume $\overline{V}^{\mathbf{LEAK}}_{\mathbf{DROPLET}}$ and blood viscosity μ. Note that $\overline{V}^{\mathbf{LEAK}}_{\mathbf{DROPLET}}$ increases hyperbolically, and steeply, as blood viscosity μ decreases due to, for example, mono or dual antiplatelet therapy. This unwanted effect can, however, be reversed and the mean droplet volume reduced by decreasing the dose of blood thinners, which in turn increases blood viscosity μ and reduces $\overline{V}^{\mathbf{LEAK}}_{\mathbf{DROPLET}}$. Equation (9a) also indicates the important existence of a linear relationship between $\overline{V}^{\mathbf{LEAK}}_{\mathbf{DROPLET}}$ and the mean $\overline{A}_{\mathbf{UPC}}$. When blood pressure is high, $\overline{A}_{\mathbf{UPC}}$ is large and so by Equation (9a), mean droplet volume is also correspondingly large. But when blood pressure is reduced with, for example, antihypertensive medications, systolic blood pressure drops and this reduces the magnitude of $\overline{A}_{\mathbf{UPC}}$ which, in turn, causes a reduction in $\overline{V}^{\mathbf{LEAK}}_{\mathbf{DROPLET}}$.

Over a brief period of a few weeks, or even a few months, the geometry of abnormal holes in veins changes little with the passage of time or with changes in medications. Accordingly, $\overline{K}$ will be assumed to be constant during this brief period. However, viscosity μ can change under the influence of, for example, blood thinners in a period of three weeks, and $\overline{A}_{\mathbf{UPC}}$ can change even faster under the influence of different doses of antihypertensive medications. To evaluate how changes in medical treatments affect the magnitude of mean droplet volumes, we need first to calculate $\overline{V}^{\mathbf{LEAK}}_{\mathbf{DROPLET}}$ before and then after a change in treatment. Let subscripts 1 and 2 denote conditions before and after the change, respectively, then μ_1, μ_2, and $\overline{A}_{UPC1}$, $\overline{A}_{UPC2}$ will denote blood viscosity and mean area under the systolic pressure

curve before and after treatment, respectively. Inserting these definitions into Equation (9a) we obtain the two required pre, $\overline{V}_{D1}$, and post, $\overline{V}_{D2}$, mean droplet volumes:

$$\overline{V}_{D1} = \left(\overline{V}_{DROPLET}^{LEAK}\right)_1 = \overline{K}\,\frac{\overline{A}_{UPC1}}{\mu_1} \quad , \quad \text{for} \quad P_{VEIN}(t) > P_{RET}(t) \tag{10a}$$

$$\overline{V}_{D2} = \left(\overline{V}_{DROPLET}^{LEAK}\right)_2 = \overline{K}\,\frac{\overline{A}_{UPC2}}{\mu_2} \quad , \quad \text{for} \quad P_{VEIN}(t) > P_{RET}(t) \tag{10b}$$

The effect of a change in treatment on DR can be assessed by calculating the relative mean droplet volume, which is defined as the ratio of the two droplet volumes $R = \overline{V}_{D2} / \overline{V}_{D1}$. When $R > 1$, mean droplet volume is increasing and DR is worsening, but when $R < 1$, mean droplet volume is decreasing, and DR is diminishing. Dividing Equation (10b) by Equation (10a) we obtain:

The very important ratio of mean droplet volumes R is itself a product of two

$$R = \frac{\overline{V}_{D2}}{\overline{V}_{D1}} = \frac{\left(\overline{V}_{DROPLET}^{LEAK}\right)_2}{\left(\overline{V}_{DROPLET}^{LEAK}\right)_1} = \frac{\mu_1}{\mu_2}\,\frac{\overline{A}_{UPC2}}{\overline{A}_{UPC1}} \tag{11a}$$

ratios: viscosities ratio μ_1 / μ_2, and mean areas under systolic pressure curve ratio, $\overline{A}_{UPC2}/\overline{A}_{UPC1}$. In repetitive calculations, it is convenient to write Equation (11a) in the following three forms:

$$R = R_{\mu} \cdot R_{\mathbf{AUPC}} \tag{11b}$$

$$R_{\mu} = \frac{\mu_1}{\mu_2} \tag{11c}$$

$$R_{\mathbf{AUPC}} = \frac{\overline{A}_{\mathbf{UPC}2}}{\overline{A}_{\mathbf{UPC}1}} = \frac{(1072 + \overline{P}^{MAX}_{ART2})\,\overline{P}^{MAX}_{ART2}}{(1072 + \overline{P}^{MAX}_{ART1})\,\overline{P}^{MAX}_{ART1}} \tag{11d}$$

Equation (11d) was derived from Equation (6b) by first substituting $\overline{P}^{MAX}_{ART2}$ into it to give $\overline{A}_{UPC2}$, and then substituting $\overline{P}^{MAX}_{ART1}$ into it to give $\overline{A}_{UPC1}$, and finally dividing $\overline{A}_{UPC2}$ by $\overline{A}_{UPC1}$. Note that both $\overline{A}_{UPC1}$ and $\overline{A}_{UPC2}$ depend linearly on k_R. In the act of dividing $\overline{A}_{UPC2}$ by $\overline{A}_{UPC1}$, k_R is cancelled. As a result, R_{AUPC} and R itself are independent of k_R.

On occasion, it is important to express $\overline{P}^{MAX}_{ART2}$ in terms of a given calculated value of R_{AUPC} (see Examples B, C, and D in Results). To do this, Equation (11d) was rearranged to give a quadratic equation in arterial blood pressure $\overline{P}^{MAX}_{ART2}$:

$$\left(\overline{P}^{MAX}_{ART2}\right)^2 + 1072\,\overline{P}^{MAX}_{ART2} - R_{\mathbf{AUPC}}(1072 + \overline{P}^{MAX}_{ART1})\,\overline{P}^{MAX}_{ART1} = 0 \tag{11e}$$

Quadratic Equation (11e) was then solved to give required $\overline{P}^{MAX}_{ART2}$ in terms of R_{AUPC} and $\overline{P}^{MAX}_{ART2}$:

$$\overline{P}^{MAX}_{ART2} = -536 + \sqrt{536^2 + R_{\mathbf{AUPC}}(1072 + \overline{P}^{MAX}_{ART1})\,\overline{P}^{MAX}_{ART1}} \tag{11f}$$

In Equation (11b), R is the product of ratio R_{μ} multiplied by ratio $R_{\mathbf{AUPC}}$, and so calculation of R requires prior calculation of these two ratios. Calculation of R_{μ} is straightforward if whole blood viscosities μ_1 and μ_2 can be measured in common pathology laboratory tests. Otherwise, published data of μ_1

and μ_2 can be used. In this paper, R_μ will be calculated from published data. Ratio R_{AUPC} is readily calculated by substituting measured mean peak arterial pressures $\overline{P}^{MAX}_{ART1}$ and $\overline{P}^{MAX}_{ART2}$ into Equation (11d). Ideally, means $\overline{P}^{MAX}_{ART1}$ and $\overline{P}^{MAX}_{ART2}$ should be calculated from peak arterial systolic blood pressures measured over a period of two weeks or three weeks, and then averaged.

The mathematical formulas derived in this section are applied in the Results section to treat DR, demonstrated with retinopathy brought to clinical concern by hypertension, aspirin alone, clopidogrel alone, and aspirin and clopidogrel combined.

3. Results

In this section, mathematical formulas derived in the Methods section are applied to eliminate DR induced by hypertension alone or by blood thinners. It is demonstrated here that large mean droplet volumes can be efficiently reduced in size with stepwise blood pressure-lowering medications until the re-emergent DR is completely eliminated. This allows diabetics to continue indispensable blood thinners while avoiding blindness. The only “price” they pay is a modest increase in their antihypertensive medication!

The form in which Equations (11a), (11b), (11c), (11d), and (11f) are written makes it easier, and more intuitive, to compare and design medical treatments involving viscosity changes versus blood pressure-lowering changes. Four examples (A, B, C, D) of application of Equations (11a), (11b), (11c), (11d), and (11f) are presented below. All four examles are based on the experiences of AH.

3.1. Example A: diabetic retinopathy induced by common or severe hypertension

AH, with controlled DR, developed common hypertension, in which average peak systolic blood pressure increased from $\overline{P}_{ART1}^{MAX}$ = 130 mmHg to $\overline{P}_{ART2}^{MAX}$ = 168 mmHg. Simultaneously, DR and macula edema re-emerged, verified by OCT scans. No blood thinners were being taken.

Questions:

- What was the percentage increase in the patient's mean droplet volume, $\overline{V}_{DROPLET}^{LEAK}$, caused by this rise in blood pressure?
- How can the hypertension-induced DR be brought under control again?

From Equations (11c) and (11d) and then from (11b) we obtain:

$$R_{\mu} = \frac{\mu_1}{\mu_2} = 1 \qquad (\mu_1 = \mu_2 \text{ , no blood thinners})$$

$$R_{AUPC} = \frac{\overline{A}_{UPC2}}{\overline{A}_{UPC1}} = \frac{(1072 + 168) \times 168}{(1072 + 130) \times 130} = 1.333$$

$$R = R_{\mu} \cdot R_{AUPC} = 1 \times 1.333 = 1.333$$

R = 1.333 is the ratio by which mean leaked droplet volume $\overline{V}_{DROPLET2}^{LEAK}$ has increased with respect to original $\overline{V}_{DROPLET1}^{LEAK}$, a hefty 33.3% increase in mean droplet volume caused by hypertension.

The above calculations for R and then the percentage increases were repeated for the same initial $\overline{P}^{MAX}_{ART1}$ = 130 mmHg and for three additional pressures $\overline{P}^{MAX}_{ART1}$ = 158, 148, 138 mmHg, and then summarized in Table 1. Evaluation of R at a number of different blood pressures, $\overline{P}^{MAX}_{ART1}$, is helpful in designing pressure-lowering treatments and in assessing their effectiveness. For example, in Table 1 it can be seen that droplet volume decreases by about 9% for every pressure reduction of 10 mmHg.

Table 1. Percentage reduction in mean leaked droplet volume caused by stepwise lowering of peak systolic blood pressure with antihypertensive medications

$\overline{P}^{MAX}_{ART2}$ **mmHg**	**168**	**158**	**148**	**138**	**130**
R	1.333	1.244	1.156	1.069	1.000
R – 1	33.3 %	24.4 %	15.6 %	6.9 %	0.0 %

$\overline{P}^{MAX}_{ART2}$ = Post-treatment peak systolic arterial blood pressure; R = Ratio by which mean leaked droplet volume $\overline{V}^{LEAK}_{DROPLET2}$ has increased with respect to original $\overline{V}^{LEAK}_{DROPLET2}$ as a result of newly developed hypertension.

It would be possible to eliminate AH's DR by reducing blood pressure back to the original 130 mmHg and so reduce the mean leaked droplet volume back to the original size $\overline{V}^{LEAK}_{DROPLET1}$ of when AH was free of DR. However, there is no need for this because mean droplet volume $\overline{V}^{LEAK}_{DROPLET2}$ needs to be reduced only below the critical size of $\overline{V}^{CRITICAL}_{DROPLET}$ (explained in Section 1.5) and not further. With moderate stepwise increases in antihypertensive medication, AH's blood pressure $\overline{P}^{MAX}_{ART2}$ was gradually reduced to 140 mmHg, and at this blood pressure his DR was eliminated, as verified by OCT scans. Note that

during the process of blood pressure lowering, regular OCT scans every two weeks were needed to verify that macular thickness was reducing and eventually returning to normal. AH had OCT scans performed every two weeks, but periodic scans every three weeks are also satisfactory.

Recall that $\dot{V}_{DROPLET}^{CRITICAL}$ is the critical volume of a droplet leaking per minute into the retina when $Q_{PUMP} = Q_{LEAK}$ (see Section 1.5). Since DR was eliminated when blood pressure was brought down to 140 mmHg, we can write $\overline{\dot{V}}_{DROPLET2}^{LEAK} = \dot{V}_{DROPLET}^{CRITICAL}$ at blood pressure of 140 mmHg, and so "flooding" of the retina stopped the moment the droplet volume decreased to this or below critical droplet volume, that is, when $\overline{\dot{V}}_{DROPLET2}^{LEAK} \leq \dot{V}_{DROPLET}^{CRITICAL}$. At pressure $\overline{P}_{ART2}^{MAX} = 140$ mmHg we have R = 1.086, and so critical mean droplet volume $\dot{V}_{DROPLET}^{CRITICAL}$ is 8.6% larger than the original $\overline{\dot{V}}_{DROPLET1}^{LEAK}$ at pressure $\overline{P}_{ART1}^{MAX} = 130$ mmHg. This means that blood pressure can increase by 10 mmHg (from 130 to 140 mmHg) before retinal "flooding" begins. Thankfully, AH had a "blood pressure credit" of 10 mmHg before his droplet volume surpassed the critical value when DR re-emerged. It also meant that successful elimination of his DR required a smaller increase in dose of his antihypertensive medications!

Finally, it is very important to note here that in severe hypertension such as $\overline{P}_{ART2}^{MAX} = 200$ mmHg, we have $R_{AUPC} = 1.628$ and consequently R = 1.628, which amounts to a monstrous 62.8% increase in mean droplet volume due to severe hypertension. Thus, computational evidence is presented here that severe hypertension dramatically increases the risk of being blinded by DR.

3.2. Case B: aspirin intake and worsening of very mild diabetic retinopathy

With controlled hypertension, $\overline{P}_{ART1}^{MAX}$ = 139 mmHg, and with very mild DR, AH was started on 100 mg aspirin daily, resulting in mild worsening of his DR, as confirmed by OCT scans three weeks after commencement on aspirin. AH experienced minor loss of visual acuity and minor blurred vision attributed to starting aspirin.

Questions:

- What was the percentage increase in the patient's mean droplet volume, $\overline{V}_{DROPLET}^{LEAK}$, caused by the aspirin-induced reduction in his WBV?
- How can worsening DR be brought under control while still taking aspirin?

Because the hypertension was under control and no changes in antihypertensive medications were reported, we can write $\overline{A}_{\mathbf{UPC2}} = \overline{A}_{\mathbf{UPC1}}$. Since facilities for measuring WBVs μ_1 and μ_2 were not available to the patient, published data was used instead. Zhang *et al.*[17] reported that treatment with 100 mg aspirin daily for one year reduced WBV from μ_1 = 42.19 cP to μ_2 = 36.55 cP in a group of 40 patients with confirmed coronary heart disease (angina pectoris). This represents a moderate drop of 13.4% [(42.19 cP – 36.55 cP) / 42.19 cP] in WBV.

Substituting first μ_1 = 42.19 cP and μ_2 = 36.55 cP into Equation (11c) yielded R_μ, then substituting $\overline{A}_{\mathbf{UPC2}} = \overline{A}_{\mathbf{UPC1}}$ into Equation (11d) yielded $R_{\mathbf{AUPC}}$. Inserting calculated R_μ and $R_{\mathbf{AUPC}}$ into Equation (11b) we finally obtain ratio R:

$$R_{\mu} = \frac{\mu_1}{\mu_2} = \frac{42.19\ cP}{36.55\ cP} = 1.1543$$

$$R_{AUPC} = \frac{\overline{A}_{UPC2}}{\overline{A}_{UPC1}} = \frac{\overline{A}_{UPC1}}{\overline{A}_{UPC1}} = 1$$

$$R = R_{\mu} \cdot R_{AUPC} = 1.1543 \times 1 = 1.1543$$

R = 1.1543 is the ratio by which mean leaked droplet volume $\overline{V}^{LEAK}_{DROPLET2}$ has increased with respect to original $\overline{V}^{LEAK}_{DROPLET1}$ as a result of starting the patient on aspirin. This means that aspirin induced a moderate reduction of 13.4% in WBV, which in turn caused a correspondingly moderate increase of 15.4% in the patient's leaked mean droplet volume.

The patient already had very mild DR before starting on aspirin, which means that very mild "flooding" of his retina has already begun because $\overline{V}^{LEAK}_{DROPLET1} > \overline{V}^{CRITICAL}_{DROPLET}$. In this example, the patient does not have "blood pressure credit" as in Example A above. The aspirin-induced 15.4% increase in his mean droplet volume $\overline{V}^{LEAK}_{DROPLET2}$ can be reversed and mean droplet volume returned to its original size $\overline{V}^{LEAK}_{DROPLET1}$ by further increasing antihypertensive medications so that $R_{AUPC} = 1 / 1.1543 = 0.8663$. The target blood pressure $\overline{P}^{MAX}_{ART2}$ corresponding to $R_{AUPC} = 0.8663$ is obtained by substituting $R_{AUPC} = 0.8663$ and $\overline{P}^{MAX}_{ART1} = 139$ mmHg into Equation (11f):

$$\overline{P}^{MAX}_{ART2} = -536 + \sqrt{536^2 + 0.8663 \times (1072 + 139) \times 139} = 122.1\ mmHg$$

Thus, the target of blood pressure-lowering treatments is 122.1 mmHg. Such moderately lower blood pressure of 122.1 mmHg should be easily tolerated on a long-term basis. The combined action of aspirin and of increased-dose antihypertension medication can be assessed with Equations (11c), (11d), and (11b) as follows:

$$R_{\mu} = \frac{\mu_1}{\mu_2} = \frac{42.19\ \text{cP}}{36.55\ \text{cP}} = 1.1543$$

$$R_{AUPC} = \frac{\bar{A}_{UPC2}}{\bar{A}_{UPC1}} = \frac{1}{1.1543} = 0.8663$$

$$R = R_{\mu} \cdot R_{AUPC} = 1.1543 \times 0.8663 = 1.0$$

Hence, R = 1 when blood pressure is lowered to 122.1 mmHg. AH's blood pressure eventually settled at approximately 120 mmHg (below target of 122.1 mmHg). In this way, the unwanted effects of aspirin were completely negated by means of a small increase in the antihypertensive medication, which resulted in R = 0.981 (1.9% below critical droplet volume) at blood pressure of 120 mmHg. This allowed the patient to continue taking aspirin without experiencing further DR.

In summary, aspirin caused a moderate decrease of 13.4% in WBV, which induced a correspondingly moderate increase of 15.4% in his mean leaked droplet volume $\bar{V}^{LEAK}_{DROPLET2}$, and re-emergence of DR and macular edema. The DR was eliminated when blood pressure was brought down to approximately 120 mmHg. At 120 mmHg, R = 0.981 and $\bar{V}^{LEAK}_{DROPLET2} < V^{CRITICAL}_{DROPLET}$, and so "flooding" of the retina stopped. Thus, a small increase in AH's antihypertensive medications was all that was needed to get rid of the DR.

3.3. Example C: clopidogrel intake and worsening of very mild diabetic retinopathy

This example is similar to Example B, but with clopidogrel intake instead of aspirin. With controlled hypertension, $\overline{P}_{ART1}^{MAX}$ = 140 mmHg, and with very mild DR, AH, started on 75 mg clopidogrel daily, resulting in worsening of DR, as confirmed by OCT scans three weeks after starting clopidogrel. AH experienced slight loss of visual acuity and slight blurred vision attributed to clopidogrel.

Questions:

- What was the percentage increase in the patient's mean droplet volume, $\overline{V}_{DROPLET}^{LEAK}$, caused by the clopidogrel-induced reduction in his WBV?
- How can his worsening DR be brought under control while he continues clopidogrel?

Because the patient's hypertension was under control, we can write $\overline{A}_{\mathbf{UPC}2}$ = $\overline{A}_{\mathbf{UPC}1}$. Facilities for measuring WBVs μ_1 and μ_2 were not available to the patient, and so published data was used instead. Ciuffetti *et al.*[16] reported that treatment with clopidogrel 75 mg daily for at least three weeks reduced WBV levels from 5.38 cP to 4.84 cP at high shear rates of 94.5 sec^{-1}, and from 27.52 cP to 22.55 cP at low shear rates of 0.94 sec^{-1} in a group of 70 subjects with abnormally high blood viscosity and ultrasound evidence of subclinical atherosclerosis. In this example, the low shear rate data was applied in calculations. Note that a drop in WBV from 27.52 cP to 22.55 cP represents a significant reduction of 18.1% [(27.52 cP – 22.55 cP) / 27.52cP] in WBV, which

is higher than that of aspirin alone in Example B (13.4%).

Substituting $\mu_1 = 27.52$ cP and $\mu_2 = 22.55$ cP into Equation (11c) yielded R_μ, then substituting $\overline{A}_{UPC2} = \overline{A}_{UPC1}$ into Equation (11d) yielded R_{AUPC}. Inserting calculated R_μ and R_{AUPC} into (11b) we finally obtain the important ratio R:

$$R_\mu = \frac{\mu_1}{\mu_2} = \frac{27.52\ \text{cP}}{22.55\ \text{cP}} = 1.2204$$

$$R_{AUPC} = \frac{\overline{A}_{UPC2}}{\overline{A}_{UPC1}} = \frac{\overline{A}_{UPC1}}{\overline{A}_{UPC1}} = 1$$

$$R = R_\mu \cdot R_{AUPC} = 1.2204 \times 1 = 1.2204$$

R = 1.2204 is the ratio by which mean leaked droplet volume $\overline{V}^{LEAK}_{DROPLET2}$ has increased with respect to original $\overline{V}^{LEAK}_{DROPLET1}$ as a result of starting clopidogrel. This means that clopidogrel has induced a significant reduction of 18.1% in WBV, which in turn, has caused a correspondingly significant increase of nearly 22.0% in the patient's mean leaked droplet volume.

The patient already had very mild DR before starting on clopidogrel, which means that very mild "flooding" of his retina has already begun because $\overline{V}^{LEAK}_{DROPLET1} > V^{CRITICAL}_{DROPLET}$. For this reason, the patient does not have "blood pressure credit" as available in Example A above. The clopidogrel-induced 22.0% increase in his mean droplet volume $\overline{V}^{LEAK}_{DROPLET2}$ can be reversed and mean droplet volume returned to its original size $\overline{V}^{LEAK}_{DROPLET1}$ by simply increasing his antihypertensive medications so that $R_{AUPC} = 1 / 1.2204 = 0.8194$. The target lower blood pressure $\overline{P}^{MAX}_{ART2}$ that corresponds to $R_{AUPC} = 0.8194$ is obtained by substituting $R_{AUPC} = 0.8194$ and $\overline{P}^{MAX}_{ART1} = 140$ mmHg into Equation (11f):

$$\bar{P}_{ART2}^{MAX} = -536 + \sqrt{536^2 + 0.8194 \times (1072 + 140) \times 140} = 116.94\ \text{mmHg}$$

Thus, the target of blood pressure lowering-treatments is 116.94 mmHg, which may still be acceptable to live with on a long-term basis. The combined action of clopidogrel and of increased-dose antihypertension medication can be assessed with Equations (11c), (11d), and (11b) as follows:

$$R_{\mu} = \frac{\mu_1}{\mu_2} = \frac{27.52\ \text{cP}}{22.55\ \text{cP}} = 1.2204$$

$$R_{AUPC} = \frac{A_{UPC2}}{\bar{A}_{UPC1}} = \frac{1}{1.2204} = 0.8194$$

$$R = R_{\mu} \cdot R_{AUPC} = 1.2204 \times 0.8194 = 1.0$$

Hence, R = 1 when blood pressure is lowered to 116.94 mmHg. The patient's blood pressure eventually settled around 115 mmHg (below the target of 116.94 mmHg). The unwanted effects of clopidogrel were thus completely negated with a moderate increase in antihypertensive medications, which at blood pressure of 115 mmHg resulted in R = 0.982 (1.8% below critical droplet volume). This allowed the patient to continue clopidogrel without experiencing further DR.

In summary, clopidogrel has caused a *significant* decrease of 18.1% in WBV, which induced a correspondingly significant increase of 22.0% in mean leaked droplet volume $\bar{V}_{DROPLET2}^{LEAK}$, and re-emergence of DR. The DR was eliminated when the blood pressure was brought down to about 115 mmHg. At 115 mmHg, we have R = 0.981 and $\bar{V}_{DROPLET2}^{LEAK} < V_{DROPLET}^{CRITICAL}$, and so "flooding" of the retina has stopped. Thus, a moderate increase in antihyperten-

sive medications was all that was needed to get eliminate DR induced by clopidogrel.

3.4. Example D: re-emergent DR caused by combined aspirin plus clopidogrel intake

In this example, with both controlled hypertension, $\overline{P}_{ART1}^{MAX}$ = 137 mmHg, and controlled DR for 15 years, AH was given dual antiplatelet therapy (DAPT) of 75 mg clopidogrel and aspirin 100 mg daily. Within ten days after starting DAPT, AH experienced slight changes to vision attributed to re-emerging DR of which he had been free for 15 years. The quick re-emergence of DR caused by DAPT was confirmed by OCT scans three weeks after commencement of DAPT, at which point AH was already experiencing slight loss of visual acuity and slight blurred vision. The reasons for the fast re-emergence of DR will become apparent below.

Questions:

- What was the percentage increase in AH's mean droplet volume, $\overline{V}_{DROPLET}^{LEAK}$, caused by DAPT-induced reduction in his WBV?
- How can AH's re-emerging DR be brought under control while still continuing indispensable clopidogrel and aspirin?

Facilities for measuring AH's WBVs μ_1 and μ_2 were not available, and so the published data of Zhang *et al.*[17] were used instead. Zhang *et al.* reported that combined treatment with clopidogrel 75 mg and aspirin 100 mg daily for one year reduced WBV from μ_1 = 42.0 cP to μ_2 = 31.8 cP in a group of 40 patients

with confirmed coronary heart disease (angina pectoris). Note that a drop in WBV from 42.0 cP to 31.8 cP represents a huge reduction of 24.3% [(42.0 cP– 31.8 cP) / 42.0 cP] in WBV, which is higher than that of clopidogrel alone in Example C (18.1%) and aspirin alone in Example B (13.4%).

Because AH's hypertension was very well controlled with irbesartan (Avapro, Sanofi, Paris, France) 75 mg daily and ramipril (Tritace, Sanofi, Paris, France) 5 mg twice daily during the 15 years prior to starting on DAPT, we can write $\overline{A}_{UPC2} = \overline{A}_{UPC1}$. Substituting $\mu_1 = 42$ cP and $\mu_2 = 31.8$ cP into Equation (11c) yielded R_μ, then substituting $\overline{A}_{UPC2} = \overline{A}_{UPC1}$ into Equation (11d) yielded R_{AUPC}. Inserting calculated R_μ and R_{AUPC} into Equation (11b) we finally obtain ratio R:

$$R_\mu = \frac{\mu_1}{\mu_2} = \frac{42.0\ \text{cP}}{31.8\ \text{cP}} = 1.321$$

$$R_{AUPC} = \frac{\overline{A}_{UPC2}}{\overline{A}_{UPC1}} = \frac{\overline{A}_{UPC1}}{\overline{A}_{UPC1}} = 1$$

$$R = R_\mu \cdot R_{AUPC} = 1.321 \times 1 = 1.321$$

R = 1.321 is the ratio by which mean leaked droplet volume $\overline{V}^{LEAK}_{DROPLET2}$ increased with respect to original $\overline{V}^{LEAK}_{DROPLET1}$ as a result of starting DAPT. Thus, the DAPT-induced reduction in WBV caused an enormous increase of 32.1% in mean droplet volume. With such large mean leaked droplets, being almost one-third larger than prior to DAPT, it is not surprising that "flooding" of AH's retinas started quickly, and within only ten days of starting DAPT!

The 32.1% increase in AH's $\overline{V}^{LEAK}_{DROPLET2}$ can be reversed and mean droplet volume returned to its original size of $\overline{V}^{LEAK}_{DROPLET1}$ by increasing antihypertensive

medications so that R_{AUPC} = 1 / 1.321 = 0.757. This will then eliminate AH's DR because R = 1.321 x 0.757 = 1. The lower target blood pressure $\overline{P}^{MAX}_{ART2}$ at which this occurs is obtained by substituting R_{AUPC} = 0.757 and $\overline{P}^{MAX}_{ART1}$ = 137 mmHg into Equation (11f):

$$\overline{P}^{MAX}_{ART2} = -536 + \sqrt{536^2 + 0.757 \times (1072 + 137) \times 137} = 106.4 \text{ mmHg}$$

Such low blood pressure of 106.4 mmHg may be unpleasant to live with on a daily basis. Fortunately, there is no need to lower the blood pressure as far as this because mean droplet volume $\overline{V}^{LEAK}_{DROPLET2}$ needs only be lowered to just below its critical size of $V^{CRITICAL}_{DROPLET}$, and not further to its original size of $\overline{V}^{LEAK}_{DROPLET1}$ when AH was free of DR. While still continuing DAPT, AH's re-emerging DR was easily brought under control by lowering blood pressure with stepwise increases in the dose of his antihypertensive medication irbesartan as described below. The dose of his second antihypertensive medication, ramipril, remained unchanged.

The stepwise reduction in blood pressure results in stepwise reduction of $R_{\mathbf{AUPC}}$ below 1.0, and so mean droplet volume also reduces correspondingly. For example, after increasing AH's dose of irbesartan by 50 mg daily, his $\overline{P}^{MAX}_{ART2}$ decreased from 137 to 127 mmHg, his $R_{\mathbf{AUPC}}$ decreased from 1.0 to 0.919, and R decreased from 1.321 to 1.214, as the following calculations show:

$$R_{\mu} = \frac{\mu_1}{\mu_2} = \frac{42.0\ cP}{31.8\ cP} = 1.321$$

$$R_{AUPC} = \frac{\overline{A}_{UPC2}}{\overline{A}_{UPC1}} = \frac{(1072 + 127) \times 127}{(1072 + 137) \times 137} = 0.919$$

$$R = R_{\mu} \cdot R_{AUPC} = 1.321 \times 0.919 = 1.214$$

With R – 1 = 21.4%, mean leaked droplet volume $\overline{V}_{DROPLET2}$ has reduced in size by 10.7% (32.1% to 21.4%) compared with the large initial 32.1% increase in $\overline{V}_{DROPLET2}$ caused by DAPT. This improvement corresponds to the 10 mmHg drop in AH's blood pressure induced by a modest 50 mg of additional irbesartan. Since lowering blood pressure proved effective in reducing droplet size, it was then lowered further to eliminate DR altogether.

The above calculations for R and then R – 1 (as a percentage) were repeated with the same initial $\overline{P}_{ART1}^{MAX}$ = 137 mmHg and for three additional lower pressures $\overline{P}_{ART2}^{MAX}$ = 122, 117, 106.4 mmHg, and then summarized in Table 2. In general, evaluating R at a number of different blood pressures, $\overline{P}_{ART2}^{MAX}$, is helpful in assessing a patient's condition and in designing arterial blood pressure lowering strategies. For example, Table 2 shows that droplet volume decreases by about 10.6% for every pressure reduction of 10 mmHg.

Table 2. Aspirin plus clopidogrel % reduction in mean leaked droplet volume after stepwise lowering of peak systolic blood pressure with antihypertensive medication

$\overline{P}^{MAX}_{ART2}$ mmHg	137	127	122	117	106.4
R_{AUPC}	1.000	0.919	0.879	0.840	0.757
R_{μ}	1.321	1.321	1.321	1.321	1.321
$R = R_{\mu} \bullet R_{AUPC}$	1.321	1.214	1.162	1.109	1.000
R - 1	32.1%	21.4%	16.2%	10.9%	0.0%

$\overline{P}^{MAX}_{ART2}$ = Post-treatment peak arterial systolic blood pressure; RAUPC = $\overline{A}_{UPC2}/\overline{A}_{UPC1}$ = Ratio of areas under the pressure curve defined in Equation (11d); Rμ = μ1 / μ2 = Ratio of viscosities defined in Equation (11c); $R = R\mu \bullet R_{AUPC}$ = Ratio by which mean leaked droplet volume $\overline{V}^{LEAK}_{DROPLET2}$ has increased with respect to original $\overline{V}^{LEAK}_{DROPLET1}$ as a result of starting aspirin plus clopidogrel (DAPT), defined in Equations (11a) and (11b)

With modest stepwise increases in the dose of irbesartan, pressure eventually fell to 122 mmHg (shaded column in Table 2) and DR was eliminated, as verified by OCT scans. This required an extra dose of irbesartan 75 mg in addition to the original dose of 75 mg. Thus, the damaging effects of DAPT were completely negated by simply doubling the dose of irbesartan to 150 mg daily, and so aspirin plus clopidogrel could be continued as needed.

Note that, during the process of blood pressure lowering, regular OCT scans every two weeks were needed to verify that macular thickness was diminishing. AH, had OCT scans performed every two weeks, but periodic scans every three weeks are also satisfactory.

Note also that, at a pressure $\overline{P}^{MAX}_{ART2}$ = 122 mmHg, we have R = 1.162 (Table 2), and so critical droplet volume $\overline{V}^{CRITICAL}_{DROPLET}$ is 16.2% larger than the $\overline{V}^{LEAK}_{DROPLET}$ at blood pressure $\overline{P}^{MAX}_{ART2}$ = 106.4 mmHg (when R = 1). This means that AH now had a “blood pressure credit” of 15.6 mmHg (122.0 minus 106.4) before his

droplet volume surpassed the critical value when DR re-emerged.

In summary, DAPT caused a significant reduction of 24.3% in AH's WBV, which induced a correspondingly significant increase of 32.1% in mean leaked droplet volume $\overline{V}_{DROPLET2}^{LEAK}$ and, consequently, re-emergence of DR. DR was eliminated when blood pressure was brought down to 122 mmHg. At this pressure we have $\overline{V}_{DROPLET2}^{LEAK} = V_{DROPLET}^{CRITICAL}$, and so retinal "flooding" came to a halt. At pressure 122 mmHg we have R = 1.162 (Table 2), which means that critical droplet volume $V_{DROPLET}^{CRITICAL}$ is 16.2% larger than the $\overline{V}_{DROPLET}^{LEAK}$ at target blood pressure $\overline{P}_{ART2}^{MAX}$ = 106.4 mmHg (when R = 1). Hence, blood pressure can increase by 15.6 mmHg (from 106.4 to 122 mmHg), or droplet volume can be increased by 16.2%, before retinal "flooding" begins. Thankfully, AH had a "blood pressure credit" of 15.6 mmHg before mean droplet volume surpassed the critical value when DR re-emerged. It also means that successful elimination of AH's DR required a much smaller increase in the dose of irbesartan to negate the effects of DAPT!

The above computations make it possible to conclude this section with the exciting reporting of a partial cure to DR (cures to DR have not been previously reported). More specifically, a partial cure for DR is offered by treatments T2 (vitamin B1, 300 mg) and T3 (vitamin D) recommended in Helfgott *et al.*,[5] which seem to cause a reduction in the diameter and/or number of retinal vein-holes. Seventeen years ago, AH had ADR and zero "blood pressure credit"; now AH has a 15.6 mmHg "blood pressure credit" (demonstrated in Example D above). The passage of 17 years has created this "blood pressure credit", which is only possible if the diameter and/or number of vein holes has been reduced during these 17 years. Note that the diameter of vein holes

needs only be reduced by a small amount to be to be very effective because droplet volume depends on hole diameter to the power of four (D^4) [see Equation (1b)].

4. Discussion

The mathematical formulas derived in the Methods section were successfully applied in the Results section to eliminate DR induced by hypertension or by blood thinners. It was demonstrated that large leaked mean droplet volumes can be efficiently reduced in size with stepwise blood pressure-lowering medications until the re-emergent DR is completely eliminated, as confirmed by the return to normal retinal measurements and vision measured with OCT scans. This allows diabetics to continue indispensable blood thinners while avoiding blindness.

The correct and efficient way to use the mathematical formulas derived in Methods section is demonstrated with four different clinical situations detailed in the Results (Examples A, B, C, D). Note that all calculations can be performed manually or with a spreadsheet. However, to make calculations simpler and quicker, an online calculator is currently being developed to assist ophthalmologists and other medical professionals to quickly execute all required computations involved in stepwise blood pressure lowering-treatments that result in elimination of re-emergent DR, or in control of DR in common/severe hypertension.

This paper presents the convincing finding of successful management of antiplatelet-induced re-emergence of macular edema and DR, and adds biological support for the conflicting role of viscosity in retinopathy. On the

one hand, as discussed above, increased viscosity contributes to vascular disease; on the other, reduced viscosity induces DR and macular edema (this case). Although demonstrated in only one person (mathematician and first author, AH), given the widely recognized serious implications of macular edema, it is remarkable that it has been manageable with only a modest increase in the dosage of antihypertensive agents.

This, however, is less remarkable than, while having had ADR 17 years ago, AH now has near normal vision and retinal examination with no DR in response to using a non-invasive, easily managed, low-risk, and low-cost treatment, as described in his earlier paper.[5] Based on insights from mathematical modeling of retinal vein exudation, Helfgott *et al.*[5] proposed five possible approaches to managing DR:

1. Reducing blood pressure to a sufficient extent to reduce retinal vein blood pressure and thus reduce leakage of exudate.
2. Increasing WBV when possible by safely reduced doses of antiplatelet agents so that leakage exudation is lessened.
3. Taking abundant (300 mg) vitamin B1[20-23] to improve endothelial metabolism,[28,29] thereby reducing the size and/or number of vein holes,
4. Taking abundant vitamin D[24-27] to improve endothelial metabolism,[28,29] thereby reducing the size and/or number of vein holes.
5. Improving blood pressure control by reducing caffeine intake.[30]

The benefits of the approach presented in this paper are:

1. Efficient blood pressure lowering and control (to the extent that the lowered blood pressure can be tolerated) resulting in reduced blood

flow velocities and so reduced likelihood of hemorrhages and atheromatous plaque ruptures.

2. Continued use of thrombus-preventing antiplatelet agents that significantly reduce viscosity.
3. Effective control of DR by means of the lowered blood pressure.

Such jointly effective interventions are rare and welcome in medicine.

These simple measures have led to the reversal of AH's signs of ADR, viz. hemorrhages, hard and soft exudates, microaneurysms, new vessel formation, and macular edema. Reversal is not normally recognized as a feature of DR or ADR, yet this is what AH has demonstrated. The benign treatments identified by AH clearly offer the potential of a major impact in the management of DR for many individuals facing blindness in their future years. A modest change in antihypertensive treatment is usually safe to undertake. Together with thiamine and vitamin D, these simple measures, if known to people with DR, could be safely prescribed without waiting for large scale trials.

The above treatments collectively constitute a potential and hugely cost-effective preventive health approach to a very common problem. Funding studies of the measures should be of the highest priority. In particular, studies are urgently needed to determine what proportion of individuals might benefit from these treatments and their effects on the specific features of DR, such as microaneurysms, hemorrhages (dot, blot, and flame), hard exudates, cotton-wool spots, and venous loops. The evidence required is the quantitation of these features in diabetics while undergoing the treatments. Fortunately, the potential risks of these treatments are either absent or

mild, so studies should be easy. Positive findings would revolutionize the management of DR.

It seems that the suite of measures recommended herein, might also be applied to Age-Related Macular Degeneration (ARMD). Although predominantly affecting the deep retina compared with DR, this disease is also characterized by early "dry" or later "wet" (exudative or neovascular) types, the latter exhibiting neovascularization that leads to hemorrhages and leakage of fluid in the outer retinal layers and, frequently, permanent vision loss. Not unlike DR, low levels of vitamin D are implicated,[31] although the linkage is somewhat contested, and there is also preliminary evidence that higher thiamine and folate may be preventive.[32] Again, not unlike DR, anti-VEGF agents have proven to be beneficial in targeting neovascular lesions and preserving vision.[33] For the reason of these similar features, an evaluation of these non-invasive treatments would be very worthwhile in ARMD, and positive findings might also lead to a revolution in the management of yet another retinal degenerative disease.

5. Conclusions

The main convincing findings reported in this paper are:

1. In diabetics in which DR has been efficiently controlled for many years (effectively non-existent DR), starting blood thinners induces large reductions in whole blood viscosity that can cause re-emergence of DR and macular edema, as verified by OCT scans.
2. There exists a critical mean droplet volume leaking exudate (per minute) from vein holes and denoted by $\dot{V}_{DROPLET}^{CRITICAL}$. The arterial blood

pressure at which this critical volume occurs can be determined from periodic OCT scans when macular thickening comes to a halt.

3. When leaked droplet volume exceeds critical volume, DR and macular edema occur. But when leaked droplet volume is below critical volume, a diabetic patient has “blood pressure credit”, defined as the amount by which arterial blood pressure can rise before critical droplet volume is reached and retinal flooding begins.
4. The re-emergent DR and macular edema can be completely eliminated with lowering of arterial blood pressure to a target lower blood pressure, calculated with Equation (11f). This is true when the patient does not have “blood pressure credit”, and it completely negates the effects of blood thinners.
5. If the patient does have “blood pressure credit”, then blood pressure does not need to be reduced to the low target blood pressure calculated with Equation (11f), it only needs to be reduced to a pressure given by “target blood pressure” plus “blood pressure credit”. This means that successful elimination of DR and macular edema requires a much smaller increase in dose of antihypertensive medication to negate the effects of blood thinners!
6. A partial cure to DR is offered by treatments T2 (abundant vitamin B1, 300 mg) and T3 (vitamin D) recommended by Helfgott *et al.* in 2018,[5] which seem to cause a reduction in the diameter and/or number of retinal vein holes. Seventeen years ago, AH had ADR and zero blood pressure credit. Now, AH has 15.6 mmHg blood pressure credit (Example D in Results). The passage of 17 years has created this blood

pressure credit, which is only possible if the diameter and/or number of vein holes has been reduced during this 17-year period. Note that the diameter of vein holes needs only be reduced by a small amount to be very effective because droplet volume depends on hole diameter to the power of four (D^4) [see Equation (1b)].

7. In the case of DR and macular edema induced by common hypertension, similar blood pressure-lowering treatments as described in Example A above are very effective in eliminating DR and macular edema.
8. Severe hypertension deserves special attention because it dramatically increases the risk of being blinded by DR or ADR. At the end of Example A, it was shown that, when arterial blood pressure rises to 200 mmHg, mean droplet volume increases by a monstrous 62.8% (droplets almost two-thirds larger than prior to hypertension). With such huge droplets, it is only a question of time before blindness sets in!
9. By examples presented in this paper, mean leaking droplet volume is a marker of DR severity. In order of decreasing severity of percent larger droplet volumes, we have: severe hypertension (62.8%), common hypertension (33.3%), DAPT (32.1%), clopidogrel alone (22.0%), and aspirin alone (15.4%).
10. In all cases mentioned above, it is very important to perform periodic OCT scans every two or three weeks to verify that blood pressure-lowering treatments actually reduce macular thickness (and DR). The final increased dose of antihypertensive medication, when macular

thickening comes to a halt, determines the adequate dose for the patient to remain free of DR.

11. Finally, because venous pressures $P_{VEIN}(t)$ in retinal microvessels are generally very low, they were traditionally, and understandably, considered clinically unimportant and were ignored by ophthalmologists. In DR or ADR, however, fluctuation in $P_{VEIN}(t)$ can be as high as 6–10 mmHg (Helfgott *et al.* page 46), and this provides a large enough driving force for causing significant leakage of fluids through retinal vein holes. For this reason, venous pressures $P_{VEIN}(t)$ in retinal microvessels should never be ignored!

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Appendix

To be more specific (Kreyszig[19]), for a random variable X with known mean E(X) (Expectation of X) and known variance Var(X), we have the well-known identity $E(X^2) = Var(X) + [E(X)]^2$. When Var(X) is much smaller than the square of its known mean, $[E(X)]^2$, then to a good approximation, $E(X^2) = [E(X)]^2$. This approximation was used in the derivation of Equation (6b) from Equation (6a), with P_{ART}^{MAX} replacing X. The data series for peak arterial blood pressure P_{ART}^{MAX} found in De Scalzi *et al.*[18] provided support for this approximation. For normotensives, $Var(X) / [E(X)]^2 = 12.4^2 / 128.6^2 = 0.0093$, and for hypertensives it is $22.4^2 / 175.7^2 = 0.0163$