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Demographics and quality of life effects of normobaric oxygen on cohort of patients with retinal vein occlusions

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DEMOGRAPHICS AND QUALITY OF LIFE EFFECTS OF NORMOBARIC OXYGEN ON COHORT OF PATIENTS WITH RETINAL VEIN OCCLUSIONS

by

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DEDICATION

I would like to dedicate this work to my mother, Robin H. Minturn, and my father, John T. Minturn. Without their support, guidance and unwavering belief I would never have been able to do this. Finally, my wonderful fiancé, Megan M. Paskey. Thank you for always supporting me and encouraging me to pursue my dreams.

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DEMOGRAPHICS AND QUALITY OF LIFE EFFECTS OF NORMOBARIC OXYGEN ON COHORT OF PATIENTS WITH RETINAL VEIN OCCLUSIONS

ROBERT J. MINTURN

ABSTRACT

Purpose: This study examined the effects of normobaric oxygen in patients diagnosed with either a Central Retinal Vein Occlusion (CRVO) or Branched Retinal Vein Occlusion (BRVO) who had previously undergone treatment via Anti-VEGF or PRP treatment. The investigation looked into the changes in Macular Thickness (MT) and Visual Acuity (VA).

Methods: This pilot study analyzed patient data from Beth Israel Deaconess Medical Center (Boston, MA) that had been diagnosed with Retinal Vein Occlusions. The patients were brought in and given 3 hours of normobaric oxygen via an oxygen concentrator with imaging and vision checked both before and after the therapy.

Results: Eighty-eight percent of our patients in this pilot study saw a decrease in macular thickness after 3-hour oxygen therapy. The mean change in Maximal Macular Thickness was a decrease of 7.1% which was statistically significant when compared to healthy eyes ($p<0.001$). Additionally, 44% of patients saw an increase in visual acuity, the primary measure of vision. Visual acuity showed a statistically significant change when compared to changes in healthy eyes ($p=0.015$). No statistical significance was found in the testing of contrast sensitivity nor intraocular pressure.

Conclusion: Our study showed improvement in central macular thickness and quality of life for individuals using noninvasive normobaric hyperoxia as a treatment for retinal vein occlusions. However, further research is needed to improve the impact of the study and a full randomized control trial should be implemented to further understand the potential impacts of a noninvasive normobaric hyperoxia treatment as a means to alleviate symptoms in retinal vein occlusions. In addition, in the future oxygen supplementation in conjunction with periodic injections of Anti-VEGF could be investigated as a treatment regimen with potential benefits beyond individual therapy.

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Anterior Chamber ..... AC
Best-Corrected Visual Acuity ..... BCVA
Branched Retinal Vein Occlusions ..... BRVO
Central Macular Thickness..... CMT
Central Retinal Vein Occlusions ..... CRVO
Contrast Sensitivity..... CS
Cycles Per Degree ..... cpd
Dihydronicotinamide-adenine dinucleotide phosphate ..... NADPH
Early Treatment Diabetic Retinopathy Study ..... ETDRS
Liters Per Minute ..... LPM
Maximum Macular Thickness..... MMT
Montreal Cognitive Assessment Test ..... MOCA
National Eye Institute- Visual Functioning Questionnaire- 25..... NEI-VFQ 25
Optical Coherence Tomography..... OCT
Panretinal Photocoagulation ..... PRP
Posterior Chambers ..... PC
Retinal Vein Occlusions ..... RVO
Spectral Domain OCT ..... SD-OCT
Time Domain OCT..... TD-OCT
Vascular Endothelial Growth Factor ..... VEGF
Visual Acuity ..... VA

INTRODUCTION

In ~360 BC Aristotle published the first of his books entitled Metaphysics, within which was theorized that vision was the dominant sense for humans due to its ability to allow for distinction and classification of objects (“XXIV.I. Which of the five Senses is most Noble,” n.d.). Over time with the implementation of new technologies such as the automobile, computer, and smartphone, sight has only gained greater importance for functionality within society. As a result, in this study we wanted to look at a novel noninvasive treatment that could provide benefits to both the disease state and quality of life of afflicted patients.

Anatomy of the Human Eye

The human eye is the dominant visuospatial organ in the body for humans, used both for orientation and identification within day to day life. Sitting within the orbit the eye refracts light from the surrounding world through the cornea, lens, and the aqueous humor onto the retina. The image that is formed on the retina is then communicated to the occipital lobe of the brain, thus allowing an individual to categorize and gain information from the image that is created.

The eye is divided into two major divisions the anterior and the posterior segment. The major purpose of the anterior segment is making the necessary adjustments in order to focus light onto the retina for the proper formation of an image. The anterior segment is filled with an extracellular aqueous humor and the major structures are the iris, cornea, lens, and the ciliary bodies. It is further

subdivided into the anterior chamber (AC) and the posterior chambers (PC), marked by the iris. Movement of the iris controls the size of the pupil, thereby allowing varying levels of light into the eye based on environmental levels of light. The majority of the posterior segment of the eye consists of the vitreous body, a space filled with thick extracellular vitreous humor. Other major structures in the posterior segment are the retina, choroid, and optic nerve. The choroid is a dense network of capillaries that operates as the vasculature for the outer layers of the retina providing both nutrients and oxygen (Khurana, Khurana, & Khurana Bhawna, 2015) ("Normal vision | Children's Hospital of Wisconsin," n.d.).

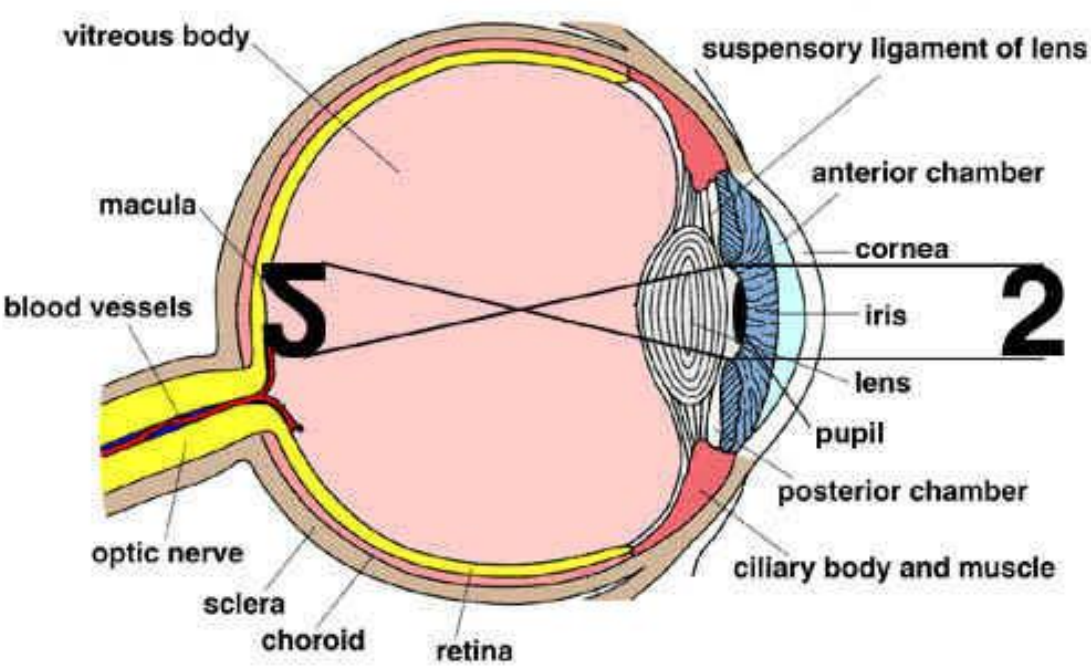


Figure 1: This illustration shows the general anatomy of the eye. The eye is separated into two segments the anterior segment and the posterior segment. The anterior segment consists of structures anterior to the lens, its primary function is the focusing of light onto the posterior segment. The posterior segment is posterior to the lens and has the primary function of image formation. Image adapted from Children's Hospital of Wisconsin, 2019.

Retina

The retina is found posterior to the vitreous body and is a neuronal layer of the eye responsible for light capture and image formation. The retina is divided into ten layers that run in parallel; the inner limiting membrane, nerve fiber layer, ganglion cell layer, inner plexiform layer, inner nuclear layer, outer plexiform layer, outer nuclear layer, outer limiting membrane, photoreceptor layer, retinal pigmented epithelium, and choroid.

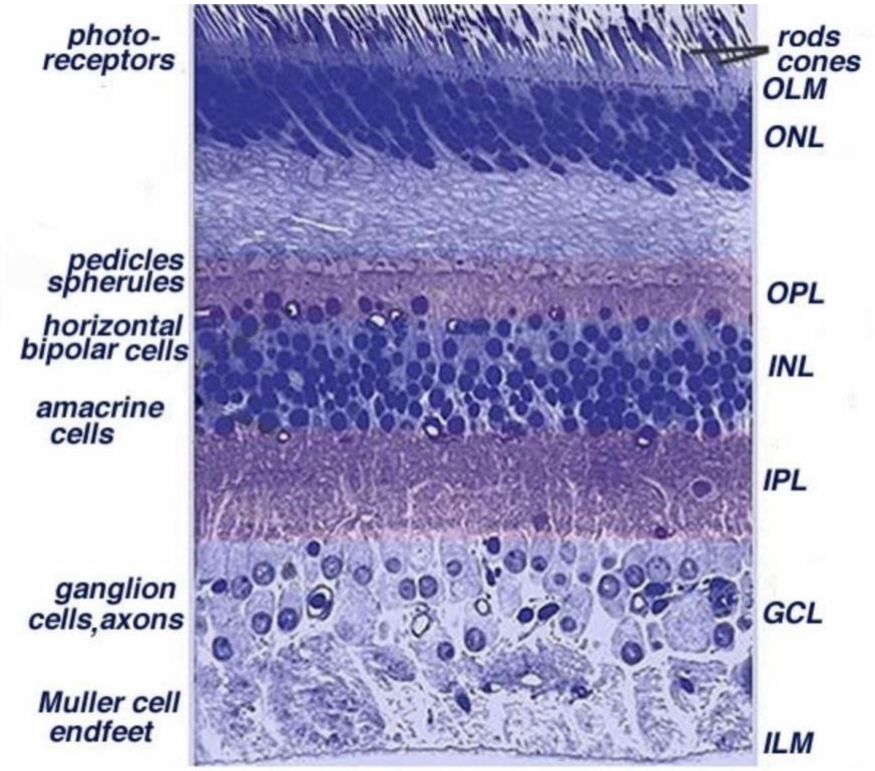


Figure 2: The retina is composed of multiple layers of neuronal tissue depicted by this image. Light hits the layer in the following order; Inner Limiting Membrane (ILM), Ganglion Cell Layer (GCL), Inner Plexiform Layer (IPL), Inner Nuclear Layer (INL), Outer Plexiform Layer (OPL), Outer Nuclear Layer (ONL), Outer Limiting Membrane (OLM), and the photoreceptor layer. Each layer of the retina has cells specialized for their unique functions. Within the Photoreceptor Layer and the ONL can be found rods and cones. Within the OPL and INL horizontal and bipolar cells can be found. Image adapted from Kolb, et. al, 2012.

The retina has six major cell types that each have their own specialization for function; photoreceptors, bipolar cells, horizontal cells, amacrine cells, ganglion cells, and Müllerian glia. Bipolar cells have primary function of communicating information from the photoreceptors to the dendrites of the ganglion cells. Horizontal cells mediate these signals at the photoreceptor level by communicating laterally between photoreceptors, thereby modulating the output of information between photoreceptors and bipolar cells. Similarly, the amacrine cells communicate laterally between the bipolar cells to modulate information at the level of the bipolar cell to ganglion cell. Finally, ganglion cells are responsible for the communication of information to the optic nerve in the final step of light transduction within the eye (Kolb, Fernandez, & Nelson, 1995).

Most important among the cells are the photoreceptors. There are two main types of photoreceptors; rods and cones, responsible for the capture of light and the formation of images. The photoreceptors function through the absorption of light, absorption of light causes a decoupling of vitamin A from rhodopsin, this reaction leads to the conversion of light energy into electrochemical energy. This electrochemical energy is subsequently communicated through the cells of the retina to the optic nerve, where it is carried to the occipital lobe and signal transduced. The two types of photoreceptor cells vary in function and quantity. Rods are the most prevalent type of photoreceptor, outnumbering cones in a 20:1 fashion, and they are responsible for the capture of black and white light. In

contrast cones are responsible for the capture of colored light and are responsible for the sharpness of images.

Within the retina there are two main areas the macula and the periphery. The periphery of the retina is primarily composed of rod photoreceptors, it has the responsibility for the peripheral vision and night vision in humans. Despite being approximately 5 mm in diameter the macula is the most important portion of the eye when it comes to image formation, it is located directly in line with the lens and is the desired focal point for the eye. At the center of the macula is the fovea, a region of the eye composed exclusively of cone cells, which has the highest concentration of photoreceptors and creates the sharpest image for humans (Laouri, Chen, Looman, & Gallagher, 2011).

Retinal Imaging

When it comes to retinal imaging there are two main forms used: a fundus examination and optical coherence tomography (OCT). OCT functions by splitting light from a source into two beams, one called the reference arm and one called the sample arm. Through computer analysis of the interference between the two beams both axial and transverse scanning is achieved, by the reference and sample arm respectively, for the formation of a 3D image output. There are two main types of OCT, Time Domain OCT (TD-OCT) and Spectral Domain OCT (SD-OCT). TD-OCT uses a moving mirror where as a SD-OCT uses a fixed mirror on the reference arm, the fixation of the mirror in SD-OCT allows for higher image

definition and the elimination of mechanical speed limitations that are present with a moving mirror (Popescu et al., 2011). For our study we used an SD-OCT due to the improved time of acquisition and higher image resolution.

A fundus exam requires a physician to use an indirect ophthalmoscope or a slit lamp to shine a light through a patient's dilated pupil in order to visualize the retina. This form of retinal evaluation allows the physician to see the entirety of the retina, both the periphery and the macula, and any symptoms that present on the surface of the retina such as areas of atrophy, microaneurysms, edema, tears,

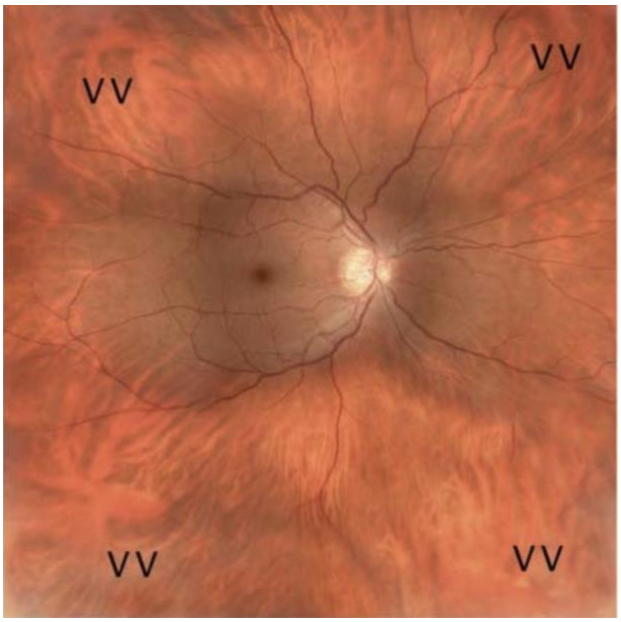


Figure 3 Image of a normal fundus exam adapted from Tabandeh and Goldberg, 2009.

detachments, or traction. A fundus exam is the primary form of retinal evaluation for an ophthalmologist and can elucidate a large amount of information in order to make a differential diagnosis.

Optical Coherence Tomography (OCT) is another form of imaging commonly used for both clinical and research application in ophthalmic practices. OCT allows for noninvasive imaging through computer interpretation of the scattering and reflection of light from a camera in the eye, resulting in a digital cross-sectional image of the retina. While there are various additional features that researchers have found and implemented with OCT the basics of the imaging technology allow us to visualize each layer of the retina and allows us to see the layers deep to the inner retina.

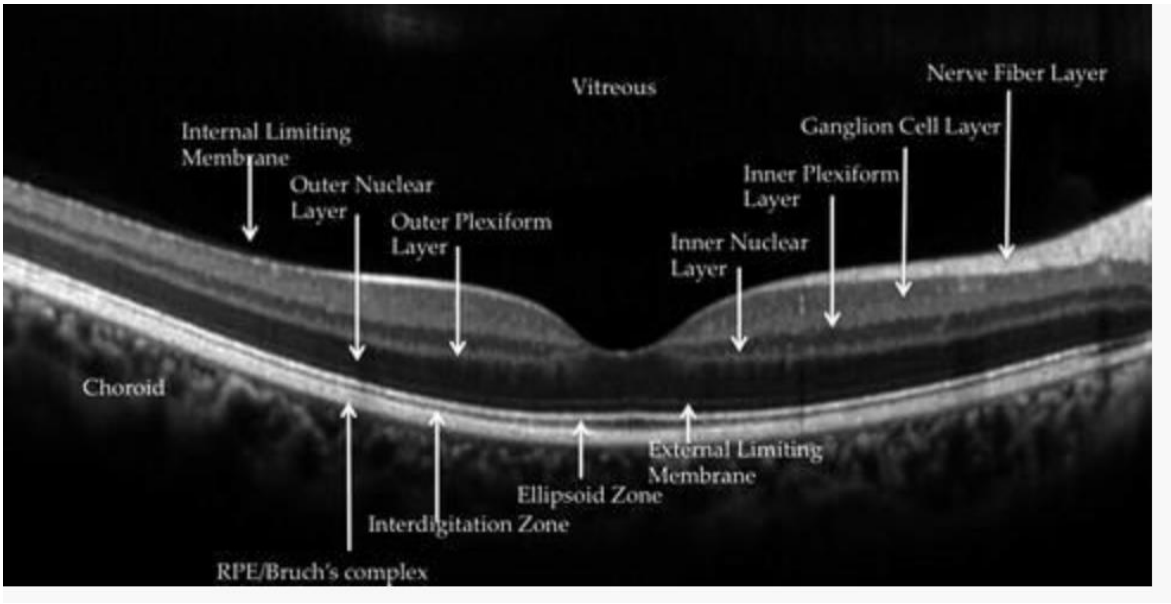


Figure 4 Image produced of a normal image taken of the macula with Optical Coherence Tomography. Image adapted from Sharma and Sergott, 2016.

Pathogenesis of Retinal Vein Occlusions

The retina has two major blood supplies, the retinal vessels and the choroidal vessels, both of which branch from the ophthalmic artery. The retinal arteries primarily supply the inner layers of the retina and these vessels maintain autoregulation. In contrast the choroidal vessels supply the inner layers of the retina and have little autoregulation, leading to a relatively constant flow of blood through the choroid. Both the Choroidal network and the retinal vessels have their own respective veins for drainage. In the case of the retinal vasculature conditions can arise in which the retinal veins get blocked, these conditions are broadly known as Retinal Vein Occlusions and are further subdivided into Central Retinal Vein Occlusions (CRVO), which has a prevalence rate of 0.2%, and Branched Retinal Vein Occlusions (BRVO), with a prevalence rate of 2% (Laouri et al., 2011).

While each condition has unique presentations and their own pathogenesis the risk factors are common and include; Hypertension Atherosclerosis, Diabetes, Primary Open Angle Glaucoma, Macular Edema, or Vitreous Hemorrhage. The primary risk factor for a manifestation of a retinal vein occlusion is hypertension (Bertelsen et al., 2012). Atherosclerosis is often secondary to hypertension and is due to the hardening of the retinal arteries at locations where they are adjacent to retinal veins. As the arteries become more atherosclerotic, they induce a change in the retinal veins leading to the formation of blood clots in the veins, and creating an occlusion (Chong, 2012). Additionally, the atherosclerotic secondary risks to Retinal Vein Occlusions include retinal edema, vitreous hemorrhages, and rare

instances of secondary glaucoma. In instances where retinal edema occurs in the area of the macula, patients experience a drastic decrease in visual acuity (Tabandeh, 2009).

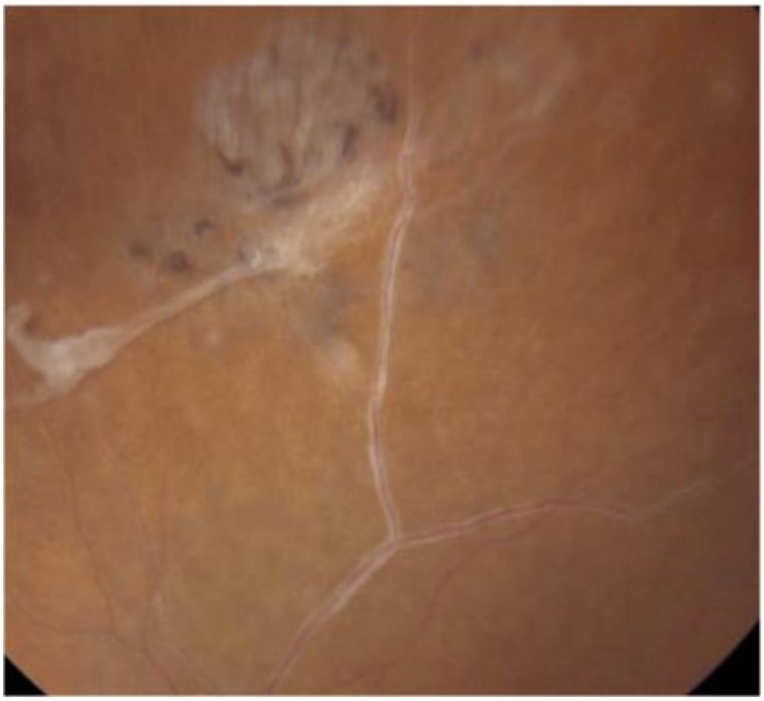


Figure 5 This image shows a branched retinal vein that has developed a sheathing over time, a possible long-term effect if the vein occlusion does not resolve. Image adapted from Tabandeh and Goldberg, 2009.

Diabetes also has a strong correlation to the onset of Retinal Vein Occlusions due to the effects that diabetes has on the vasculature and the higher risk of atherosclerotic plaque formation. In diabetics blood vessels get damaged due to the higher amounts of glucose in the blood, as the constant elevation of glucose levels leads to hyperactivity of the polyol pathway, also known as the sorbitol pathway. In turn the hyperactivity of the polyol pathway leads to a depletion

of endothelial cells Dihydronicotinamide-adenine dinucleotide phosphate (NADPH), and subsequent damage of the endothelial lining of the microvascular network in patients with diabetes (Rask-Madsen & King, 2013) The damage to the microvascular network leads to greater microvasculature permeability, hemostasis and potential endothelial cell apoptosis. As a result, diabetic patients have elevated

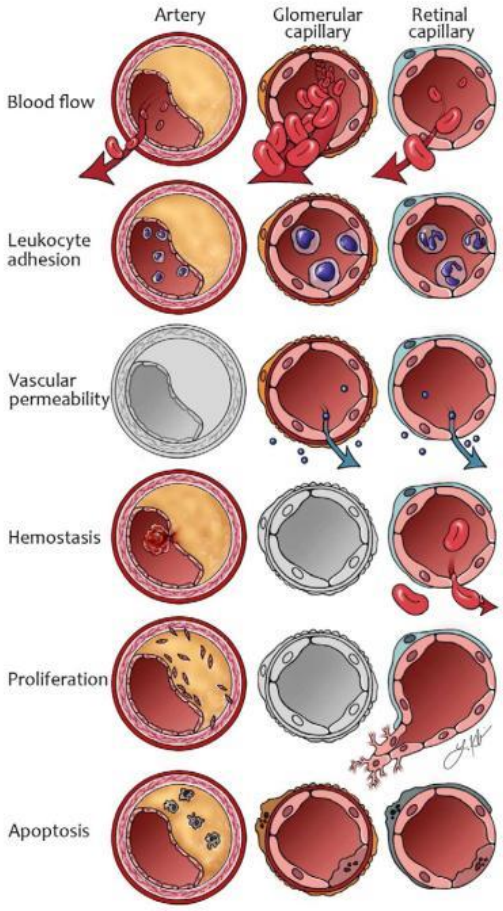


Figure 6 This image demonstrates the effects of diabetes on normal vasculature and on retinal capillaries. In the normal vasculature diabetes leads to a higher risk of plaque formation. The binding of Leukocytes to the plaque leads to a higher risk of thrombus formation. In the retinal capillaries diabetes leads to higher rates of leukocyte binding, which leads to greater leakage of red blood cells and associated proteins. The damage to the blood vessels subsequently can lead to neovascularization and or apoptosis. Image adapted from Rask-Madsen and King, 2013.

risk factors associated with the development of occlusions due to thrombosis and greater risk of edema.

Current Treatment Options

Currently the main healing agents in Retinal Vein Occlusion treatment is time, as both CRVOs and BRVOs eventually resolve themselves as the clot breaks up. However, both conditions lead to the secondary development of ME which can lead to retinal degeneration and a decrease in visual acuity if left untreated and neovascularization if very severe cases. Thus, treatment generally involves managing symptoms to minimize the amount of permanent damage done to the retina until the occlusion passes, which can take months to decades.

The primary treatment for neovascularization is Panretinal Photocoagulation (PRP), an in-office procedure using an argon laser to indirectly decrease the number of new growing blood vessels in the periphery of the retina. The effectiveness of PRP ultimately lies in the destruction of highly metabolically active peripheral outer retinal tissue, decreasing the amount of oxygen consumed by the retina and subsequently decreasing the amount of Vascular Endothelial Growth Factor (VEGF) produced (Stefánsson, 2001). In addition, through the destruction of the outer retinal tissue the inner retinal layer is preserved through relief of hypoxia via oxygen diffusion from the choroid (Linsenmeier & Zhang, 2017). While PRP does not work instantaneously, a course of treatment over several months has shown to decrease the proliferation of new blood vessels in

the retina through the easing of hypoxemia experienced by the inner retinal tissue. Potential complications of PRP include the worsening of macular edema, exudative retinal detachments, decreased visual field, and difficulty seeing at night (Reddy & Husain, 2018).

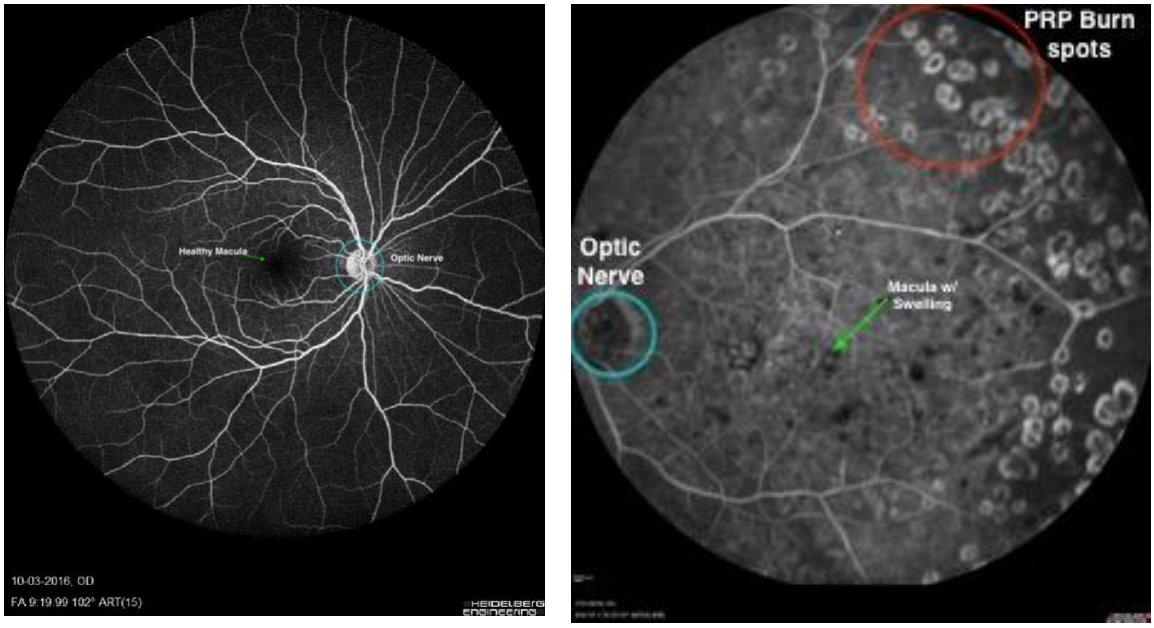


Figure 7 Image of patient with a Central Retinal Vein Occlusion (CRVO) treated with Panretinal Photocoagulation (PRP) over several years. The left image is of the healthy right eye and the right image is of the eye with a diagnosis of CRVO after several years of treatment. Through PRP the outer retinal layer is destroyed allowing for decreased consumption of oxygen and allows oxygen to travel through the scarred tissue to the inner retina more easily. Images adapted from Beth Israel Deaconess Medical Center Records, 2019.

Another form of treatment for macular edema is the intraocular injection of Anti-VEGF drugs, directly delivered into the vitreous to decrease the presence of VEGF. There are currently three main Anti-VEGF drugs used bevacizumab, aflibercept and ranibizumab. Bevacizumab, known as Avastin, is the most commonly used and is a humanized antibody created for the binding of VEGF-A. Aflibercept, known as Eylea, is a recombinant VEGF binding protein that targets VEGF-A though direct binding. Ranibizumab, known as Lucentis, is a fragment of a monoclonal antibody that binds to VEGF-A (Bressler, 2017).

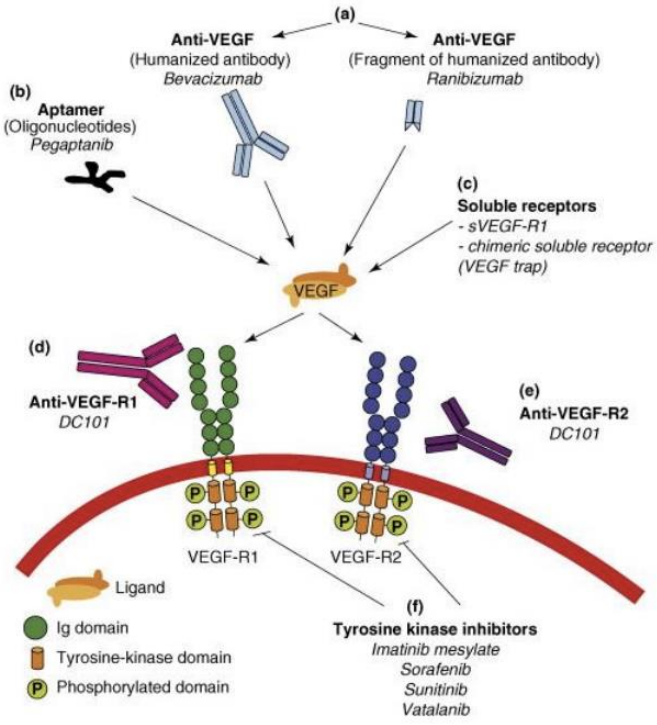


Figure 8 In this figure the VEGF mediated pathway is diagramed. The VEGF pathway is an angiogenic pathway that operates via the molecule VEGF binding to a Tyrosine kinase receptor, leading to the initiation of a cascade pathway. At the top of the image are visual representations of both Avastin and Lucentis. Image adapted from Pandey, 2017.

History of Supplemental Oxygen

In a Retinal Vein Occlusion there is major concern of the tissue adjacent to the occlusion becoming atrophic due to hypoxia. While the actual occlusion often will resolve itself over time there is concern that the prolonged state of macular edema and hypoxia will lead to atrophy of the photoreceptors, leading to long-term loss of vision. In addition, the hypoxic state leads to the production of VEGF, and other mediators, which are the primary cause of the secondary complications of vein occlusions like macular edema (Linsenmeier & Zhang, 2017). Prevention of these secondary complications through oxygenation has the potential to decrease the loss of vision in patients with vein occlusions through the preservation of viable retinal tissue. In animal models it has been seen that in the case of retinal detachments the use of hyperbaric oxygen can lead to improved post repair vision as opposed to operations that were not treated with oxygen (Wang & Linsenmeier, 2007). In the model of retinal detachments, it is believed that the separation of the inner retina from the outer retina leads to atrophy of the photoreceptors and decreased visual outcomes. In addition, a study done by Dr. Quan Dong Nguyen looked at the use of supplemental oxygen for the treatment of macular edema. The study found that long term oxygen therapy led to a statistically significant decrease in central macular thickness, with some of the individuals also having visual acuity improvement of greater than 2 lines (Nguyen et al., 2004). These two studies are the basis of the belief that macular edema and the resultant decrease in visual

acuity has a hypoxic component to the disease, and as a result increased oxygen can have benefits for those suffering from macular edema.

Visual Acuity

Visual Acuity (VA) is the traditional method for the measuring of vision, it is what most people think of when they go to their optometrist or ophthalmologist, involving the reading of several varying letters. The most common form of visual acuity measure is the Snellen chart that is the most used chart in clinical settings. The Snellen chart ranges from 20/400-20/15 vision and is traditionally administered in a dark room projected onto a wall from a lamp or projector. However, limitations of the Snellen chart are the varying number of letters per row and an inconsistent decrease in the letter size decrease from line to line (Shamir, Friedman, Joskowicz, Mimouni, & Blumenthal, 2016). For clinical use and quick assessment of visual acuity the Snellen chart preforms adequately. However, as a

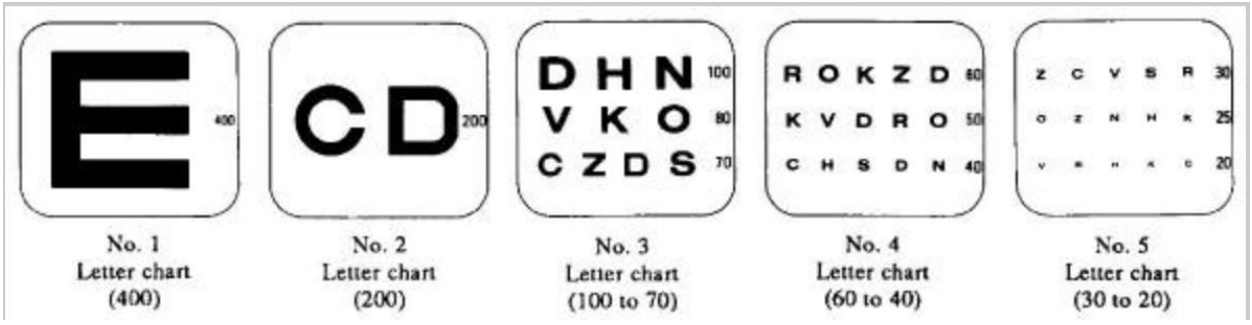


Figure 9 This is a traditional Snellen chart formatted for a slide projector used to measure visual acuity. Of note is that each line represents a different level of visual acuity, calculated by the visual angle for the letters on the respective line. One shortcoming of this chart is the lack of intraline consistency, due to inconsistency in number of letters and size decrease in lettering. Image adapted from Peter Kaiser, 2009.

result of the limitations, there can be a large range of variability that is experienced for an individual patient being repeatedly tested.

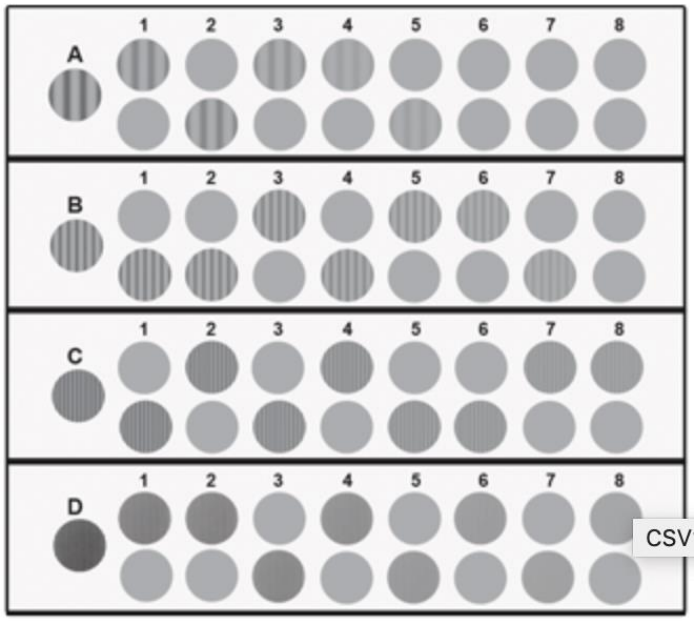
A second chart used for testing visual acuity was developed in response to the limitations of the Snellen chart, giving way to the Early Treatment Diabetic Retinopathy Study (ETDRS). The ETDRS poses distinct advantages to that of the Snellen in that it is not a fixed chart, allowing for ability to measure vision at various distances, and has enhanced sensitivity for individuals with low visual acuity. In addition, the ETDRS chart operates on a logarithmic scale that creates equal decrease in size from row to row of the chart with a consistent number of letters per row, thereby eliminating the shortcomings of the Snellen chart. These changes in the formulation of the ETDRS chart have led to greater test retest reliability for patients and more reliable visual acuity measures for individuals with diseases such as AMD and Diabetic Retinopathy (Silva et al., 2012). A study done by Dr. Peter Kaiser showed that the differences in such disease states can be as many as 10 letter difference in visual acuity for individuals with vision of <20/200, 5 letters for individuals with vision 20/50 to 20/200, and 4 letters for individuals with 20/20 to 20/50 vision (Kaiser, 2009). As a result, there was an inverse relationship between difference between charts and visual acuity, as visual acuity worsened the difference between charts grew greater. While the ETDRS chart does have its benefits there are also shortcomings. In particular it is a larger physical chart to ensure consistency and it requires a minimum space of 13 feet to accurately test vision. These limitations have decreased its clinical applications, however, the

ETDRS chart is a standardized means for research due to its translation between studies and higher level of reliability in data (Silva et al., 2012).

Figure 10 The image above is an adapted image of a standardized Early Treatment Diabetic Retinopathy Study chart. This chart differentiates in from the Snellen chart through a greater level of standardization intralines. Visual acuity is determined based on the number of letters correctly read. These alterations lead to a greater consistency intratest for visual acuity. Image adapted from Kaiser, 2009.

Finally, one last form of visual acuity measure is Contrast Sensitivity (CS). Unlike the ETDRS and the Snellen charts the Contrast Sensitivity chart outputs an acuity measure called the Contrast Sensitivity Function (CSF). The CSF is calculated by measuring contrast thresholds over four different spatial frequencies, expressed in cycles per degree (cpd). Through the graphical measurement of at all four cpds a numeric outcome is achieved which represents an individuals

Contrast Sensitivity Function. The CSF is a measure of how well an individual is able to detect differences in gradation of black and white, which is representative of their ability to visually function in day to day life (National Academy of Sciences).



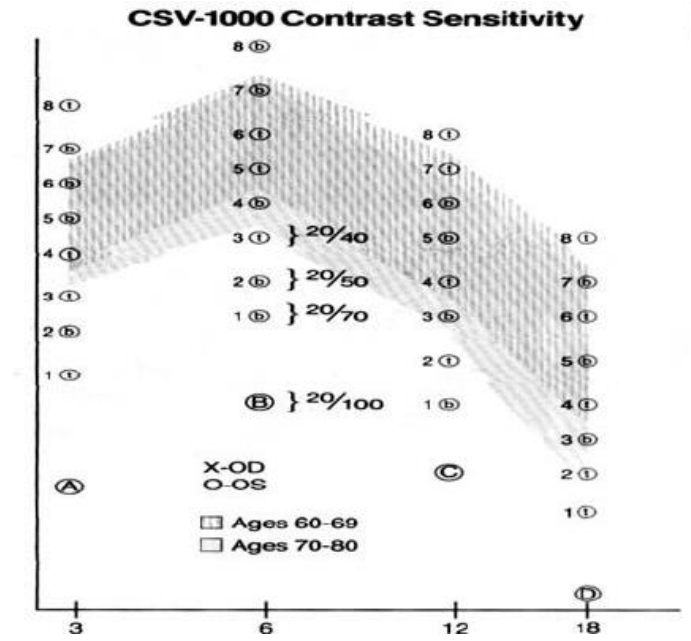


Figure 11 The chart above is the CSV-1000e the same type if contrast sensitivity chart we used in our research. It works by patients correctly identifying which circle contains the vertical lines. Each lettered row represents a different spatial frequency, measured cycles per degree. With Row A, B, C, and D measuring 3, 6, 12, and 18 cpd respectively. The second image is the key and standardized chart used for calculating functional acuity, a measure of an individual's ability to operate within daily life. This image is provided courtesy of Vector Vision the manufacturer of the CSV 1000e, 2018.

Quality of Life

The majority of ophthalmic conditions are not life threatening, however they can have drastic impact on a patient's independence and how they are able to live their life. The measurement of quality of life is data that must be gathered through query and conversation with the patient. The National Eye Institute- Visual Functioning Questionnaire- 25 (NEI-VFQ 25) was created and validated through the National Eye Institute for the purpose of standardization across ophthalmic research in regards to quality of life measures. The NEI-VFQ 25 also is 25 questions that can be taken as a repeated measure to track the changes in quality of life for a patient longitudinally both during and after a treatment regimen. In addition, the NEI-VFQ 25 has developed several subsections that can be given for the purpose of tracking near vision, social functioning, independence and mental state (Orr et al., 2011). The NEI-VFQ is the gold standard in ophthalmology for measuring how an individual's life changes longitudinally over the course of their treatment for ocular conditions. In ophthalmology a group of physicians led by Dr.

Gary Brown have conducted a series of studies that look at the correlation between visual acuity and quality of life, as well as have led independent studies on the effects of quality of life for the treatment of various ocular conditions with Anti-VEGF treatments. In these studies they established that the standards for quality of life should be measured through an NEI-VFQ questionnaire and then subsequently look at the utility of the treatment through a standard gamble analysis and time-tradeoff analysis (Brown, Brown, Stein, Smiddy, & Ophthalmic Utility Research Study Group, 2018).

MOCA Test

The Montreal Cognitive Assessment Test (MOCA) is a standardized rapid assessment of an individual's mental capacity and function. It can be given in a repeated fashion to analyze whether an individual has had any changes in their mental faculties. The test is a short 8 question response sheet that mixes visuospatial, speaking, math and identification exercises. While this test is not a major component of our research we were interested in using it to ensure there were no adverse mental effects beyond the norm for patients who were treated with oxygen therapy. Because the treatment leads to a higher oxygen concentration in the blood, we wanted to ensure proper blood flow to the brain was maintained and that the treatment did not change blood flow drastically to the body as a whole. (Freitas, Simoes, et. al., 2012)

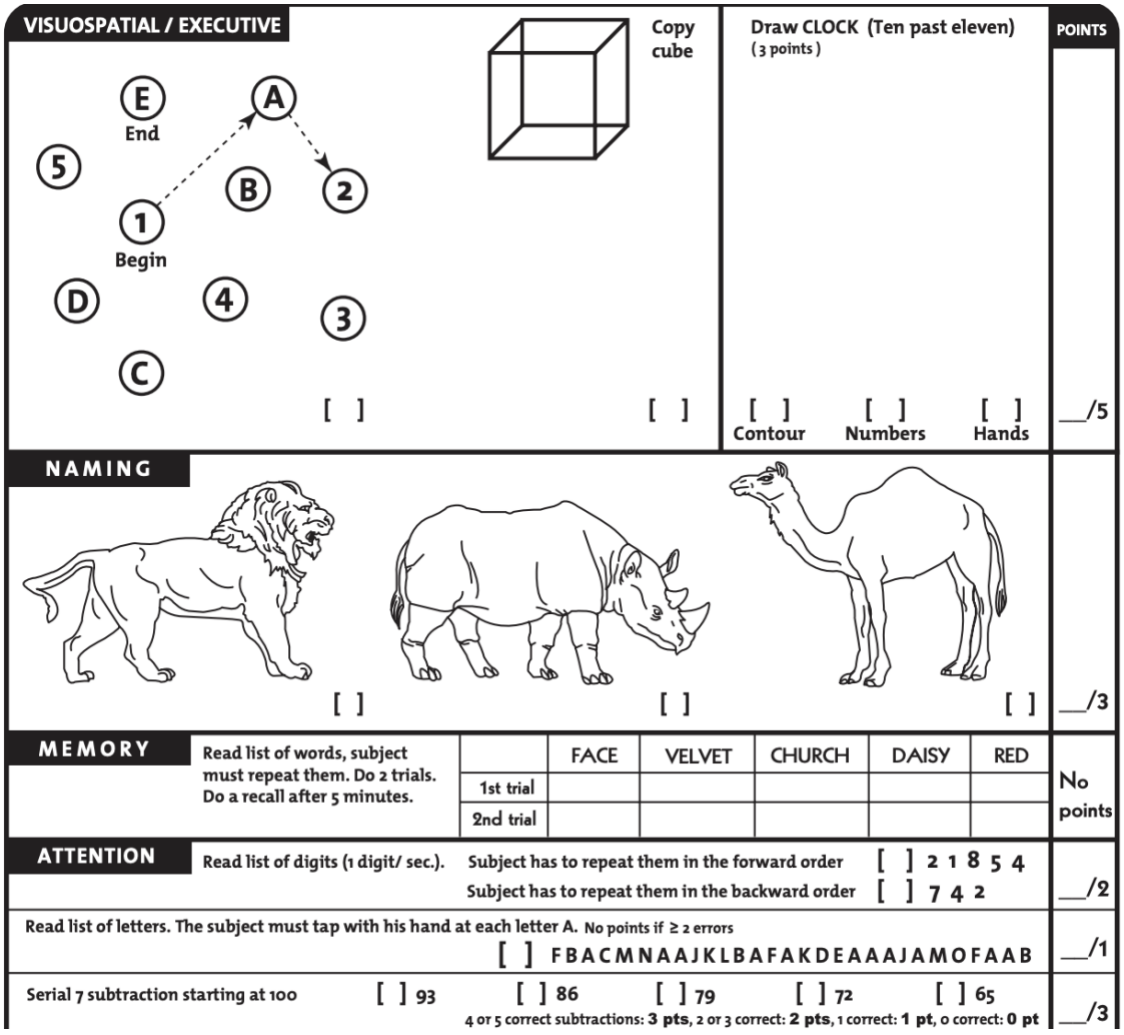


Figure 12. This image contains a portion of the Montreal Cognitive Assessment test. These questions elucidate the various types of knowledge that MOCA tests for including; visuospatial, memory, identification and math. Image captured directly from "MOCA-Test-English.pdf", 2019.

SPECIFIC AIMS

This paper looks at analyzing the potential improvement in quality of life through the implementation of a non-invasive treatment for Retinal Vein Occlusions that traditionally use lifelong intraocular injections as the first line treatment. In this paper we will look at the decision criteria and setup of the study, as well as investigate the preferences and impact on the quality of life of patients who are being treated for ocular conditions with an underlying ischemic basis for the disease. While many studies have validated the effectiveness of intraocular injections, primarily Anti-VEGF, as means of treatment for these conditions, few studies have investigated how such a course of treatment effects the patient and their daily lives.

This study aims to investigate the impact of intraocular injections on the quality of life of our patient cohort and investigate whether a noninvasive treatment that we have found to improve visual measures could also serve to increase quality of life in patients suffering from Retinal Vein Occlusions.

METHODS

This study is a case series of a pre-clinical trial therapy: normobaric hyperoxia therapy to treat retinal vein occlusions. All patients were diagnosed with a Central Retinal Vein Occlusion or a Branched Retinal Vein Occlusion at the Beth Israel Deaconess Medical Center in Boston, MA and had a history of prior treatments, including anti-VEGF injections and pan retinal photocoagulation. Patients with other concurrent retinal disease, significant media opacities, history of lung disease or smoking and recent treatment (< 3 months) were excluded. All patients signed an informed consent form reviewed by BIDMC's Institutional Review Board and this research adhered to all specificities outlined in the Tennents of Helsinki.

Recruitment

Patients were recruited through conversations with their retinal specialist. Recruitment generally occurred at the end of a routine clinical visit, with the principal investigator explaining the risks and potential benefits associated with this study. Participants then signed an informed consent form and followed up for their study visit.

Oxygen Therapy

The oxygen therapy consisted of 3 hours of normobaric oxygen set to 5 liters per minute. Each patient was given oxygen from either an oxygen tank set to

5 liters per minute (LPM) or an Everflo Oxygen Concentrator set to 5 LPM. The oxygen concentrators take in normal room air and decrease the amount of nitrogen by implementation of a molecular sieve, creating an air mixture that is higher in oxygen (Phillips Respironics, USA). Patients then sit in an examination chair with the machine on and an oxygen mask is placed over their face. Prior to initiation of therapy patients were instructed to inhale and exhale normally throughout the course of the therapy. Most commonly patients used the time to talk with loved ones, read, or sleep. Upon initiation of treatment the time was marked on the patients chart to ensure consistency in the delivery of 3 hours of oxygen.

Oxygen Trial Independence

In a previous study we found that each trial can be treated independently based on analysis by Paired Welch T-tests of our study population. We found that in Retinal Vein Occlusions (RVO) there was no significant difference between the effectiveness of each trial administered, with a p-value of .11. In addition, there was no significant difference between end of trial Maximal Macular Thickness between trials, with a p-value of .41. As a result, in our research for this study we treated each oxygen trial as an independent data point, and only analyzed data within a 5 hour time frame.

Imaging

In order to ensure both consistency and accuracy we developed a protocol for the imaging of patients receiving normobaric oxygen therapy. All images were taken on the same Heidelberg Spectralis OCT machine to ensure consistency. We modeled this protocol on those used in previous diabetic retinopathy and Age-related Macular Degeneration trials. A series of images were taken both prior and post 3-hour normobaric oxygen therapy. In order to ensure we imaged the same location each time a reference image was set within the Heidelberg program. Included in the images were a high-quality fast raster, seven-line macular scan, star scan, vertical scan and horizontal scan. Data from the fast raster was subsequently reviewed and corrected to ensure validity of measurements. From the images Central Macular Thickness (CMT) was recorded and the Maximum Macular Thickness (MMT) within the eye was located and data was recorded. CMT was acquired due to its correlation to visual acuity, while MMT was acquired due to swelling also occurring in the periphery. Through both pre and post-therapy imaging we were able to create a change map demonstrating the increase or decrease in macular thickness over the course of the 3 hours.

Visual Measures

In addition to visual imaging we checked both visual acuity with an ETDRS chart and a contrast sensitivity chart. Patients were brought into the same room in Beth Israel Deaconess both before and after oxygen therapy was administered. In

this room patients had vision checked first via the ETDRS vision chart set at a distance of 13 feet, if vision was <20/200 the chart was moved to 5 feet to gauge vision. Patients were then asked to read the letters on the chart to the best of their ability beginning at the 20/200 level and moving progressively down the chart until they missed majority of the letters on a line, being 3 or more letters. As a result, vision was noted in the manner of the best line achieved with the potential of +2, representing 2 letters on the subsequent line, or -2, representing missing two on that line. Vision was checked as best corrected vision first and subsequently checked with pinholes in order to account for any refractive error, or absence of glasses.

We then converted visual acuity measures according to the LogMAR scale in order to standardize the comparison of multiple measurements at once. Visual acuity taken form the ETDRS measurements was converted into loMAR units in order to compare pre-oxygen therapy and post-oxygen therapy. For the conversion of visual acuity we used the following equation:

$$\text{LogMAR} = -\text{Log}(20/\text{Distance of best line read in feet})$$

Table 1. Conversion Between Vision Acuity in Feet and LogMAR Score

Snellen Visual Acuity (Feet)	LogMAR
Light perception (LP)	2.60
Hand motions (HM)	2.30
Count fingers (CF)	1.85
20/200	1.00
20/150	0.88
20/100	0.70
20/80	0.60
20/70	0.54
20/60	0.48
20/50	0.40
20/40	0.30
20/30	0.18
20/25	0.10
20/20	0.00

*Table adapted from review done in Kaiser, 2009.

After ETDRS vision was checked patients were given a tutorial on contrast sensitivity with subsequent vision check via the CSV-1000e set at a distance of 8 feet. First the CSV-1000e was turned on, then patients were asked whether they

were able to distinguish the vertical lines underneath the letter of the first line. If they answered yes then vision for that line was checked by asking the patient each number and if they saw the same pattern in the top circle, bottom circle, or neither. Patients proceeded until they got an answer incorrect or no longer were able to see the vertical lines, at which point the researcher would mark the furthest point the patient reached. If there was concern about a patient guessing or not having reached a similar visual level from row to row then the patient was asked to repeat a row but in reverse. This measure was instituted to decrease the likelihood of chance in the testing process (Kaiser, 2009).

Quality of Life Measures

In order to gain a greater understanding of how our treatment effects patients and their day to day life we chose to implement several measures of quality of life data gathering. During the patient's time in our waiting room we worked with them to administer an electronic version of the NEI-VFQ 25. This electronic version allowed for a streamlining of data collection and buy being guided we ensured patients understood the questions to the best of their ability. (Awdeh et al., 2010)

While a secondary thought we also had some concerns about changes in mental states with a treatment that could affect blood flow to various major organs. As a result, we would like to monitor the mental capacities of patients longitudinally

to continue gathering data as to if there is any correlation between brain activity and increase levels of oxygen in the blood.

In order to accurately calculate the effect of a noninvasive treatment versus the current gold standards of treatment we asked patients to answer a series of questions in order to calculate a utility score for each of the treatment options. The current treatment options of PRP and Anti-VEGF treatments both have in clinic visits with potential associated risks such as infection and pain. In contrast the noninvasive treatment regimen has the potential of in clinic visits with relatively few to no associated risks. In order to calculate a utility score, we chose to use the ophthalmic standard previously used by Dr. Brown and others including the time trade off method and standard gamble method. Both questionnaires were given to patients during their wait time while on oxygen.

Statistical Analysis

Statistical Analysis was preformed through a two-tailed Welch t-test for both best-corrected visual acuity (BCVA) and maximal macular thickness (MMT) in the RVO patients. In addition, an analysis of the quality of life measures was analyzed through a regression model. Statistical analysis was considered to be significant with a p-value less than or equal to 0.05.

RESULTS

After administering 102 normobaric oxygen trials over the course of six months, data was reviewed and classified by disease state, extent of designated disease and visual acuity. From this data we analyzed 21 cases of Retinal Vein Occlusion which presented with minimal ocular opacity, no concurrent retinal diseases, initial maximal macular thickness (MMT) of less than 350 microns, and no intravitreal injections within 3 months prior to oxygen therapy. In addition, 13 of those individuals presented with a healthy eye upon initiation of the normobaric hyperoxia treatment. Our data was split relatively equally between men (57%) and women (43%), with no statistically significant difference. There was a statistical difference between eye of onset, however, this is explained by the smaller sample size of the pilot study and that retinal vein occlusions usually only effect one eye ($x^2=0.03$). In addition, our population was predominantly white (57%), with Hispanics making up the second largest portion of our population (38%). These numbers are not representative of historical demographic data for presentation of retinal vein occlusions, and we hope in a larger study to have a more diverse patient population (Rogers et al., 2010).

Table 2. Demographics of Patient Population for Pilot Study

	Mean	SD	N	%
Total Patients			21	-
Age	73.7	11.4		
Sex				
Male			12	57
Female			9	43
Diagnosis				
BRVO			6	24
CRVO			15	76
Time Since Diagnosis (Months)	49.14	49.02		
Effected Eye				
Right eye (OD)			14	67
Left eye (OS)			7	33
Ethnicity				
White			11	52
Hispanic			8	38
Asain			2	10
Diabetes				
Yes			5	24
No			16	76
Hypertension				
Yes			16	76
No			5	24
Hx of Smoking				
Yes			5	24
No			16	76
Currently Smoking				
Yes			1	5
No			20	95
Prior Anti-VEGF Injections	9.4	7.7		
Time Since Injections	10.5	20.31		
Prior Surgeries	0.6	1.1		
Prior PPV	0	0		
Prior Focal Laser	1.3	1.08		
Prior Panretinal Photocoagulation	4.6	2.7		

*Data obtained from Beth Israel Deaconess Medical Center between July 2018 and May 2019.

Outcomes

For the Maximal Macular Thickness (MMT) we found the point with the most macular swelling via OCT. Based on that point, we calculated the change of the central subfield, measuring 1 millimeter in diameter, surrounding the location of MMT as a percentage change. Our hypothesis was that these changes in the anatomy of the retina would lead to improvement in vision. We found that individuals with retinal vein occlusions on average had a decrease of 7.1% at the point of maximal swelling after 3 hour treatment with normobaric oxygen, this data was statistically significant when compared to both healthy eyes treated (Welch's paired t test, $p<0.001$) and untreated retinal vein occlusions observed over 3 hours (Welch's paired t test , $p<0.001$). In addition, Central Macular Thickness decreased a lesser amount of 4.6%, however, this was still statistically significant when compared to healthy eyes (Welch's paired t test, $p<0.001$). Healthy eyes treated with oxygen therapy for 3 hours had insignificant changes in macular thickness when compared to untreated healthy eyes over the same period of time.

Table 3. Results of Macular Thickness from 3 Hour Hyperoxia Trial

	Mean	95% CI	P Value
Before Therapy			
Central Macular Thickness (μ)	455.80	(407.2, 504.4)	-
Maximal Macular Thickness (μ)	511.2	(467.0, 555.4)	-
After Therapy			
Central Macular Thickness (μ)	434.4	(428.0, 440.8)	-
Maximal Macular Thickness (μ)	475.9	(468.6, 483.2)	-
Anatomical Changes			
Percent Change MMT (%)	-7.1	(-5.34, -8.06)	<0.001
LogMAR Visual Acuity Changes**	0.04	(-0.01,0.09)	0.015

*Data obtained via image analysis with Heidelberg Spectralis Optical Coherence Tomography
**Data obtained via visual testing with ETDRS chart and alreted to LogMAR for standardization
***Data obtained from Beth Israel Deaconess Medical Center between July 2018 and May 2019.

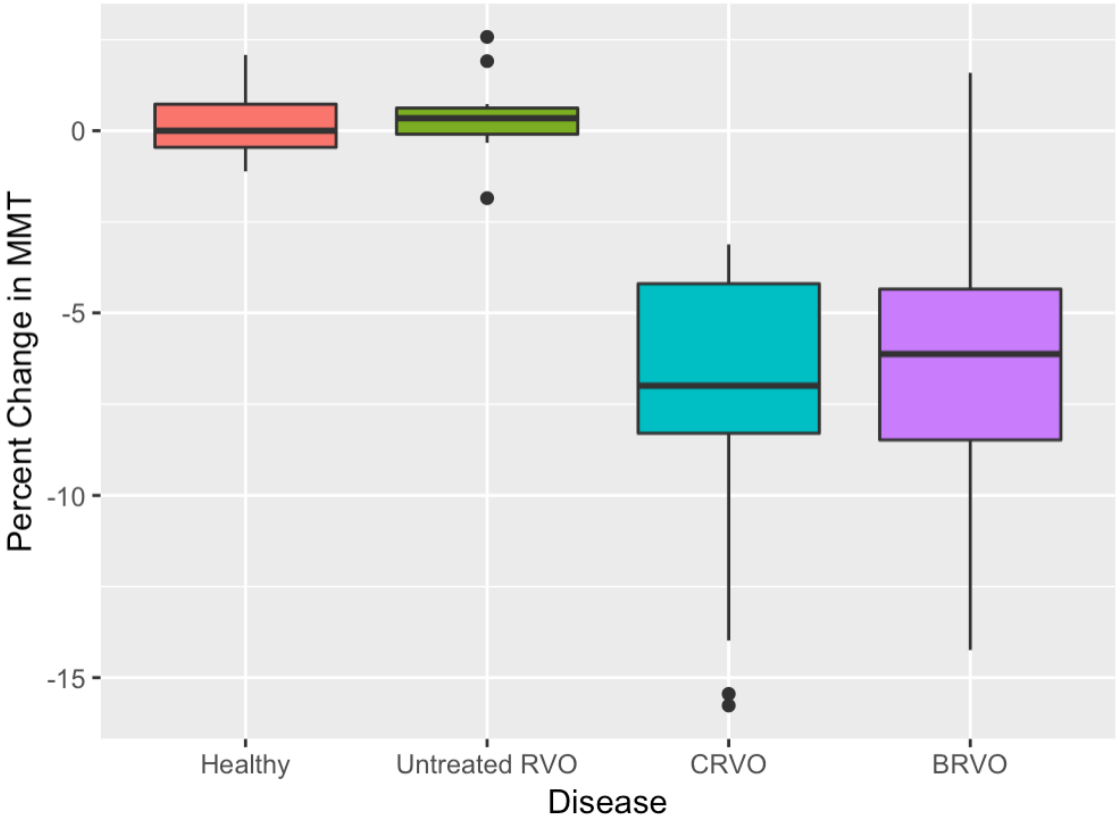


Figure 13: *Change in Maximum Macular Thickening after Normobaric Hyperoxia Treatment by Disease*. A 3-hour session of NBH resulted in decreased MMT (mean 7.1%, t_{34}=9.63 *P*<.001) and CMT (mean 4.6%, t_{37}=6.90, *P*<.001) when compared to untreated eyes with RVO measured over the same time frame or their healthy other eye (t_{36}=-9.60, *P*<.001*;* t_{36}=-6.72, *P*<.001). Twenty-seven out of 28 patients receiving their first session of NBH for RVO saw a significant reduction when compared to controls (Untreated RVO 95% CI -0.50 to 0.77). BRVO and CRVO did not differ significantly if MMT (t_{15}=0.50, *P*=.63) or CMT (t_{16}=2.06, *P* =.057) were used. Data adapted from Beth Israel Deaconess Medical Center, 2019.

Visual Acuity

Visual acuity testing conducted both before and after administration of 3 hour normobaric hyperoxia demonstrated a significant change, as measured by visual improvement of 5 letters or more. Seven (44%) of our patients experienced a statistically significant change in their visual acuity, while one patient (6%) experienced a decrease greater than one letter, represented in figure 14. Based on a Welch paired T test with 14 degrees of freedom we found that there was no significant difference between visual changes in Central Retinal Vein Occlusions and Branched Retinal Vein Occlusions.

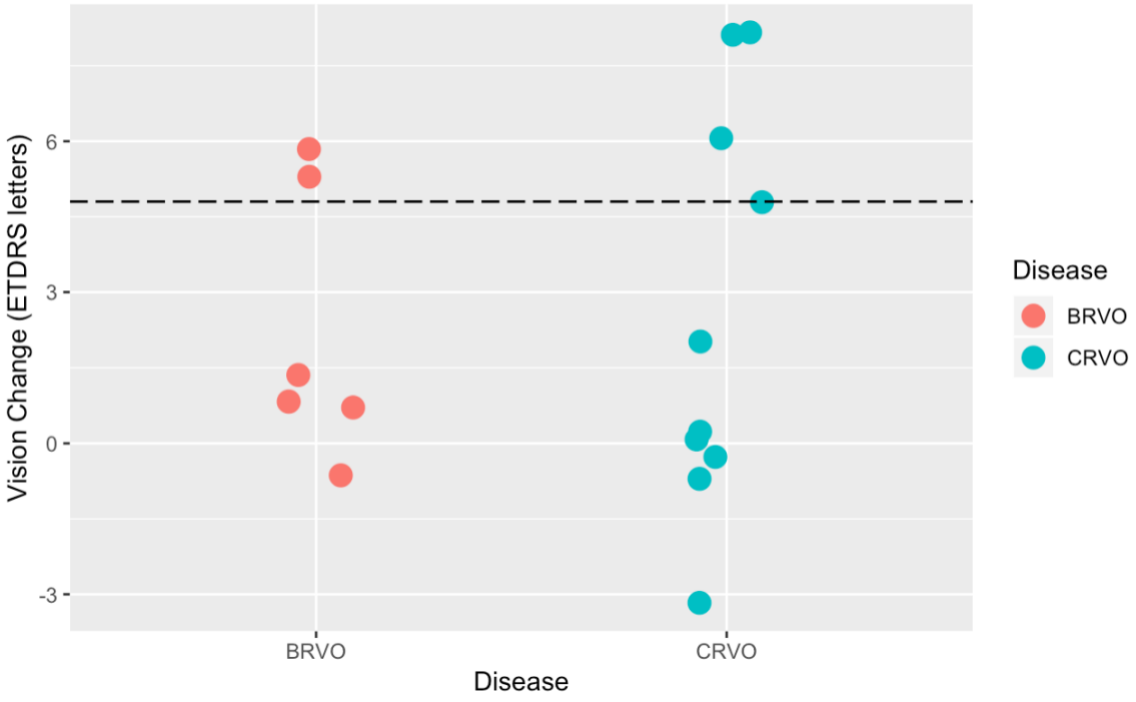


Figure 14: Change in ETDRS Visual Acuity by Disease. Sixteen patients had vision in our inclusion range on presentation, with an average increase of +0.04 LogMAR (2.4 ETDRS letters, t_{15}=2.76, *P*=.015). Of these, 7 (44%) experienced an improvement of at least 5 letters, the commonly held threshold for significance on the ETDRS chart. There was no

difference in improvement by condition (t_{14}=-0.20, P=.84). Data adapted from Beth Israel Deaconess Medical Center, 2019.

Quality of Life Measures

Due to restrictions in our Institutional Review Board for Quality Improvement and changes in the institutional review process we were unable to gather data within our patient population. In future studies we continue to strive to better understand the full implications of using a noninvasive treatment for retinal vein occlusions treatment through measures including; National Eye Institute-Visual Function Questionnaire 25 (NEI-VFQ25), standard gamble method, trade-off method and Montreal Cognitive Assessment (MOCA).

DISCUSSION

Retinal vein occlusions (RVO) are spontaneous occurrences affecting roughly 16 million individuals. The manifestation of retinal vein occlusions is the result of thrombosis due to atherosclerotic plaque formation, and individuals with hypertension and diabetes are at higher risk for developing retinal vein occlusions due to the associated effects on the vasculature. The condition presents both as occlusions in the branched vessels (BRVO) of the retina and the central vessels (CRVO), with greater loss of visual acuity in individuals who have experienced a CRVO. With no available treatment for RVOs, physicians are left to treat the associated symptoms in order to best maintain vision for patients. Treatments include multiple panretinal photocoagulation treatments and monthly intravitreal Anti-VEGF injections.

Of our 21 patients we administered 34 treatments of 3 hour normobaric hyperoxia for treatment of a branched retinal vein occlusion (BRVO) or central retinal vein occlusion (CRVO). Additionally, we administered 22 treatments of 3 hour normobaric hyperoxia to 13 patients whose non-RVO eye was deemed healthy. Of the healthy eyes we found that one eye developed dry age-related macular degeneration and one eye developed proliferative diabetic retinopathy, at which point any subsequent trials were excluded from the healthy pool. Our median patient age was 73.7 years old. Our patient population was 57.15% male and 42.85% female. Ethnically our population was predominantly White, 57.14% with individuals of Hispanic ethnicity comprising of 38.09% and Asian ethnicity

4.76%. The limited ethnic representation in our study is one point of inquiry that could limit the impact of the study, and points to a need for further research in order to increase the implications of our work.

Prior to treatment patients had a mean maximal macular thickness (MMT) of 511.23 microns with a mean central macular thickness (CMT) of 468.58 microns. Post-treatment for 3 hours with normobaric oxygen patients saw a mean decrease in MMT of 35.52 microns and a decrease in CMT of 21.24 microns. As a result, we saw a 7.1% decrease in MMT post-oxygen therapy, when analyzed with a Welch paired T-test with 34 degrees of freedom we found statistical significance with a P-value of less than 0.001. This is suggestive of a strong correlation between decreased macular thickness post treatment with oxygen for 3 hours. In contrast healthy eyes saw a mean decrease of 0.4% in MMT post-oxygen therapy. In addition, 95% of our trials saw a decrease in MMT while 88% of trials saw a decrease in CMT.

In addition, we saw a statistically significant change in visual acuity which increased on average 5.1 letters (test $P<0.05$) for individuals after treatment with oxygen therapy. This is in line with our hypothesis that decreasing the physiological manifestations of retinal vein occlusions, primarily macular swelling, will lead to visual improvement. In future studies we would like to expand upon this data by further adding a quality of life longitudinal measure to better understand how this visual acuity improvement effects patient's daily life.

While we were unable to obtain a full spectrum of quality of life data quality of life data, we believe that future studies will demonstrate positive effects on quality of life due to the decreased burden of patients traveling to the office for intravitreal injections, decreased anxiety of needle placement in close proximity to the eye, and simplicity of the noninvasive treatment option.

Confounding Variables

Because this was a pilot study, the study was limited by the number of participants and limited amount of data. Furthermore, while majority of patients were treated using two standardized Phillips everflo oxygen concentrators, there were instances in which oxygen tanks were used rather than the concentrators due to limited quantity of equipment. While the difference between the concentrator and oxygen tank are relatively insignificant in a full clinical trial all potential sources of variation should be eliminated to decrease potential impact on the results. In addition, while we did see slight increase in visual acuity, we discovered at the end of the trial that for some patients the flow of oxygen dried out the surface of the eye. As a result, in future research lubricating eyedrops prior to visual acuity testing should alleviate any potential impact corneal drying could have posed on our measures of visual acuity (Benítez-Del-Castillo et al., 2017). Finally, all diagnostic decisions were made by a single retinal surgeon, and a larger diversity of opinions with a standardized selection criterion could increase both the population of the study and potentially broaden the impact of the study.

CONCLUSION

In this project we looked at the potential changes in quality of life for patients with retinal vein occlusions when treated with a noninvasive treatment regimen of normobaric oxygen with minimal office visits as opposed to monthly intraocular injections. Our study showed improvement in central macular thickness and quality of life for individuals using noninvasive normobaric hyperoxia as a treatment for retinal vein occlusions. However, further research is needed to improve the impact of the study and a full randomized control trial should be implemented to further understand the potential impacts of a noninvasive normobaric hyperoxia treatment as a means to alleviate symptoms in retinal vein occlusions. From a full randomized control trial larger amounts of data could be obtained, providing a better understanding as to whether our findings have universal implications moving forward. In addition, in the future oxygen supplementation in conjunction with periodic injections of Anti-VEGF could be investigated as a treatment regimen with potential benefits beyond individual therapy.

In conclusion, we have demonstrated that treatment of retinal vein occlusions with short-term oxygen supplementation can be beneficial in decreasing macular swelling and increasing visual acuity. We find that increasing oxygen delivery to the inner retina through oxygen supplementation decreases symptoms of retinal vein occlusion, which suggest that there is an ischemic component to retinal vein occlusions for which oxygen therapy can serve as a viable treatment option. Furthermore, future research is still needed to fully understand the breadth of this study.

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