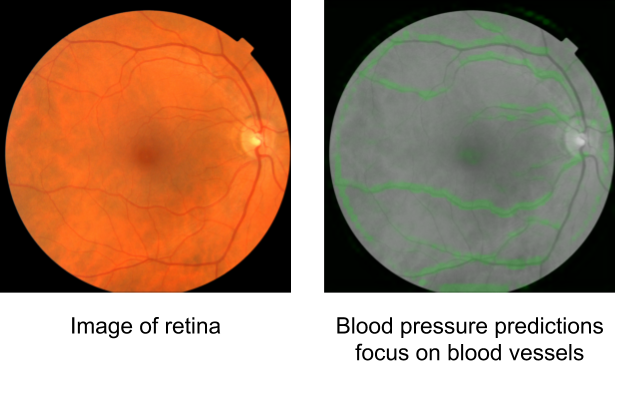
Applying machine learning to fundus photography to uncover correlations between ocular blood flow and cardiovascular diseases.

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*Figure 1 The fundus image on the left is a raw image where the image on the right has heatmaps applied to show blood pressure predictions based on a machine learning heatmap.*

**Abstract**

Cardiovascular diseases (CVDs) are the primary cause for death worldwide. According to the World Health Organization, nearly 18 million annual deaths are directly linked to CVDs (WHO 2021). Early detection of CVDs is paramount in the effort to successfully treat patients and reduce the lethal threat of cardiovascular diseases.

One potential tool for early detection of CVDs is the examination of blood flow in the eyes. Annual eye exams typically include photographs of the eye allowing both optometrists and ophthalmologists to detect high blood pressure, high cholesterol, diabetes, and ocular blood flow anomalies well before patients become symptomatic. These key indicators can lead to not only advanced screenings for heart diseases, but preventative care as well. Ocular blood flow (OBF) anomalies and changes in bloods flow should be areas of serious concern for cardiovascular health. Using artificial intelligence (AI) and deep learning (DL) to review optical imagery may lead to better preventative screenings for CVDs. Establishing public datasets with both chest x-rays and optical images would be the best-case scenario for furthering analysis of this complex dataset.

**Keywords**

| artificial intelligence (AI) | cardiovascular disease (CVD)| ocular blood flow (OBF) |retinal imaging | convolutional neural networks (CNNs) |

**Motivation**

Research evidence shows that early diagnosis of CVDs is key to effective and preventative healthcare management. The enormous impact of cardiovascular disease to the healthcare system continues to grow every day. According to the World Health Organization, 33% of annual worldwide deaths are from CVDs and 85% of these deaths are attributed to heart attack and stroke. One of the major challenges facing the management of CVDs is late diagnosis. The late or often missed diagnoses mean there is reduced chance of effective management of the condition and resulting in premature and preventative deaths. This is why CVDs are often referred to as the ‘silent killer.’

There are many challenges which inhibit early diagnoses of CVDs. One of these is limited access to cardiovascular services, especially among rural populations. There are fewer cardiologists and radiologists in rural areas and limited access to cardiovascular health services including x-ray technicians and radiologists. This disparity results in patients not being properly screened and often diagnosed only after symptomatic and in deteriorating health. According to CDC (2017) rural Americans are more likely to die from cardiovascular disease because they have inadequate access to adequate preventative health services. Another challenge is the high cost of cardiovascular services. The average cost of chest X-ray in US is about $400, or ten-fold the cost of ocular imaging at $40. Thus, the difficulty even for many insured Americans to get appropriately and timely CVD care.

Clinical research studies are concerned with developing low cost yet highly effective strategies to ensure early and accurate diagnosis of CVDs. One of these strategies is assessing the related symptomology in ocular blood flow (OBF). There seems to be a strong relationship between high blood pressure, high levels of cholesterol, diabetes, all risk factors for CVD, and age-related macular degeneration (AMD), retinal blockage, cataracts, and other ocular conditions (*Versant Health,* Mayo Clinic, 2019, Heitmar et al., 2011). According to Flammer et al. (2013) the eye and the heart have a close relationship and share a number of characteristics. The eyes have easily accessible vessels and arterioles which provide a window to blood flow in the heart (*Versant Health, 2021*). Observable characteristics in ocular imagery, like narrowing of retinal arteries, arteriovenous nipping, dilation of retinal veins, and other anomalies are important signs of potential CVDs. These functional alterations may not necessarily indicate an immediate prognosis but can indicate future risks. The annual and thorough examination of OBF data provide an important early indicator for CVDs.

This OBF evidence is best supported when substantial data is collected and cross-referenced with data and images of the heart. Collecting and correlating this data is difficult. First, most optometrists and ophthalmologists are siloed in private practice or in clinics outside of routine hospitals. Second, collecting, labeling, storing and correlating credible data is time consuming and expensive. Finally, when these datasets are collected, they are most commonly used within the hospital or healthcare consortium, rather than having private data stripped and the dataset made available for public use.

**Medical imaging tools**

Medical imaging is an absolute necessity in modern healthcare. Retinal imaging, ocular digital photos, CT scans, CAT scans, fluoroscopy, MRI, MRA, PET scans, PET CT, Ultrasounds, Mammography and nuclear bone scans can be as commonplace today as x-rays. Another improvement in medical imaging is the portability of many imaging devices. Medical imaging devices which used to take an entire lab to operate, are now even deployable in the field and battery powered. Medical imaging is also making advances into the 3d and potentially 4d space.

Traditionally, ocular conditions have been diagnosed using tools like retinal imaging, ocular digital photos, and more recently AI tools assist in ocular anomaly detection. Most eye diseases and the related conditions manifest themselves in the retina (Boyd, 2021). Retinal imaging and qualified analysis of these images provide important information for diagnosis and treatment of ocular conditions. There are various retinal imaging platforms used today but the most commonly used methods are 2-D fundus imaging and 3D optical coherence tomography (OCT) (Abramoff et al., 2010). Fundus photography (a low-power microscope attached to a digital camera for taking pictures of entire eye, through the pupil) is particularly useful in ocular disease detection because it is cheap and easily accessible. Fundus photography can be done using either a low cost and portable fundus camera, or even a smartphone. There are fundus lenses and applications available for a variety of smartphones in the $400 range. These new imaging advancements can be used in rural areas where people often cannot afford costly healthcare services (Flammer et al. 2013). Fundus photography is particularly important because it allows easier detection of cardiovascular risks based on changes in vessel properties like venous diameter ratio, narrowing of arterioles, and aneurysm. According to Abramoff et al. (2010) diseases visible in the retina may originate from other parts of the body including the brain or cardiovascular system.

A picture containing text, compact disk

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*Figure 2- Regions of interest. A shows a smartphone fundus image and B shows the same image with heatmap layering applied.*

Cardiac imaging plays an important role in diagnosis of CVDs. According to Stokes and Thompson (2017) a wide range of cardiac imaging techniques are available to investigate suspected cardiac etiology, including atherosclerosis. Chest X-rays can play a role in preliminary assessment to detect heart inflammation or an increase in pulmonary vascular markings which may indicate advanced heart failure (Karargyris et al., 2021). This technique is however is somewhat costly and may not be an option in rural areas. Another diagnostic tool is echocardiography (ECG/EKG) which provides structural and functional information for cardio diagnosis. Stress ECG (usually involving a treadmill and 12-lead ECG) is a safe and accessible technique but comes with low sensitivity in detecting coronary artery anomalies and can produce false-negatives in testing. Stress ECG can however provide effective assessment of patients showing chest pain. Other CVD imaging techniques including CT coronary angiography, Transesophageal echocardiography, and Cardiac MRI. The major challenge with these tests is the high cost and need for large and complex equipment as well as specialized training.

Management of complex datasets in healthcare is a new reality. According to Abramoff et al. (2010), newer imaging techniques are generating significant amounts of data critical to disease specific analysis. The massive and growing image dataset requires highly trained clinicians to properly sort, classify and store. The amount of information provided from the current diagnostic techniques is becoming locally overwhelming for many clinicians to handle which can lead to errors or even missed diagnosis.

While there are numerous public datasets available for forward-facing chest x-rays, the public datasets for the other medical imagery modalities are more difficult to locate and ever harder to accurately correlate with CVDs through chest x-ray iamges. To successfully discuss, diagnose, treat, monitor, document and follow up with plans, requires immediate and thorough access to medical imagery, patient histories, drug interactions and other critical data. Effective treatment planning and preventative medicine require analysis and correlation of these large and complex sets of data.

*Diagram

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*Figure 3 shows eye with branch retinal vein occlusion*

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*Figure 4 shows coronary angiography*

**Implementation**

One of the strategies that can help in collecting, corelating, analyzing and deploying quality data sets is Artificial Intelligence. Artificial Intelligence or AI is the process of training computers or automated systems to “think” like humans; to react to inputs or stimuli in a predictable manner following a given set of rules defining behavior. AI provides data analytics tools that can be applied to classify the digital image datasets (x-rays, MRIs, EKGs, sonograms, digital optical images, etc) and appropriately label and tag these medical images.

The application of deep learning (DL) techniques to AI models use convolutional neural networks (CNNs) within the software algorithms which repeatedly test, train and reexamine the data getting better at uncovering anomalies in the medical images. These CNNs have weighted scales and values calculated for each input in the algorithm. As the model continues to run it also constantly tests, trains, validates, and reexamines the data. Each pass through the algorithm makes the CNN model more and more accurate. Current AI/DL algorithms being used in x-ray imaging are outperforming medical doctors and licensed radiographers by 10-20% in accuracy and in a fraction of the time it takes doctors to examine the same data. (Armitage, 2018)

DL provides convolutional neural networks (CNNs) which mimic the human brain using neurons in the model to analyze and correlate data yielding important and sometimes overlooked data which can provide early prognosis. According to Mendeley (2018) AI has played a critical role in revolutionizing diagnosis of ocular diseases. Recent clinical advances using AI and DL have given unprecedented insight into ocular disease management. Digital imaging has provided millions of morphological datasets which could be analyzed using DL to yield important insight into ocular disease, related conditions, and correlation to other ailments including CVDs. The AI based methods that emerge from DL can quantify and identify certain pathological features and the related characteristics for macular and retinal conditions.

As medical data becomes more complex, newer tools like AI/ML/DL must continue to develop and be used to correlate medical data. Using a very recent study, Ibrahim et al. (2021) showed how DL can be used to accurately classify digital images using chest x-rays. Using recent Covid-19 data and x-rays, researchers demonstrated that deep learning models accurately labeled pneumonia classification of these x-rays in a three-way classification model. This study further confirms the importance of AI in a modern approach to medical diagnosis.

Just recently, Martin-Isla et al. (2020) reviewed advances of machine learning (ML) in diagnosis of cardiac disease. The authors demonstrate how ML plays a critical role in big data analysis through specific algorithms to analyze datasets and yield important information that can assist in early cardiac etiology diagnosis. Through these complex data models, information from past clinical data, image-based datasets, and medical statics data, the artificial neural networks (ANNs) merge complex and differing data sets to output a binary result. The binary result is usually a positive or negative, for inclusion to review by a medical profession. Properly trained models can even tag or arrow specific anomalies for doctors to review. Data drawn from different data banks such European Cardiovascular Magnetic Resonance registry, NEO Study, SPECT, and others are demonstrating the need for this new emergence of AI technology and medicine to the future of early CVD detection.

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*Chart 1 compares efficiency of Artificial Intelligence systems versus radiologist & physicians*

**Discussion**

Summaries of international clinical studies document direct correlation in OBF and CVDs. “…changes observed in the retinal vasculature, such as the degree of retinal arteriolar narrowing, reflect vascular disease in peripheral, cerebral, and coronary blood vessels and may therefore be a marker of CVD risk.” (Cheung, et al, 2020) The research conducted by Cheung, et al, created convolutional neural networks (CNNs) to view data from numerous studies including: Singapore Chinese eye study (SCES), Singapore Indian eye study (SINDI), Singapore Malay eye study (SiMES), Hong Kong children eye study (HKCES), Australian heart eye study (AHES), Retinal imaging in chest pain study (RICP study), Retinal imaging in renal disease study (IRED study), Cardiovascular disease screening using retinal vascular imaging study (CVD screening study), Singapore Epidemiology of Eye Diseases Study (SEED), Kangbuk Samsung health study (KSH study) and the Austin health study to name a few. The researchers developed an Artificial Intelligence model using a deep learning system (DLS) which calculated CVD factors using ocular imaging. The researchers concluded that retinal caliber measurements are not only correlated with CVD risk, these anomalies often are associated with CVD events.

Changes in OBF can statistically predict cardiovascular events. Research in ‘The eye and the heart’ (Flammer, et al, 2013) contend that the vasculature of the eye and heart share multiple common characteristics and demonstrate interplay in the OBF and CVDs. Noticeable anomalies on OBF not only lead to early diagnosis of diabetic retinopathy, venous dysregulation, arteriole nipping, intraretinal hemorrhages, and hypertension but also indicate increased CVDs risk. The continued and routine eye exams provide an important baseline of ocular imagery. The combination of low cost, low intrusion, and ease of reading ocular imagery compared to high cost, invasive and more difficult process to examine and interpret complex angiography, makes AI-assisted ocular imagery a compulsory tool in detection and prevention of CVD.

The most effective way to combat CVDs is prevention. Annual eye exams can indeed detect anomalies in blood flow, hypertension, diabetes and a myriad of conditions often replicated in blood flow around the heart. The post-diagnosis treatment for CVDs fall into three categories: lifestyle changes, medications and medical procedures. Lifestyle changes include quitting smoking, reduced alcohol consumption, reduced salt consumption, reduced sugar consumption, reduced fat consumption, adding more vegetables to one’s diet, getting at least 30 minutes of exercise per day, and getting more routine health screenings. Medications treatment options can include diabetes medications, blood pressure medications, blood thinning agents, statins to lower cholesterol, beta blockers to treat heart disease, and a variety of medications (including aspirin) to prevent blood clots. Medical procedures and surgical options include coronary angioplasty and stent implantation, thrombolytic therapy, coronary artery bypass graft surgery, pacemaker implantation, defibrillator implant surgery, heart valve replacement, and finally a full heart transplant.

**Take Home**

Recent testing verifiably demonstrates a direct relationship between anomalies in ocular blood flow to cardiovascular diseases. Using artificial intelligence (including machine learning and deep learning tools) to review optical imagery can provide helpful and early insight to blood flow in and around the heart. Remote and rural areas can use this cheaper and more readily available process to screen for diabetes, high blood pressure, cardiovascular diseases, hypertension, tuberculosis and even possible cancers.

The clear association between ocular blood flow and cardiovascular diseases makes a solid case for the continued application of AI tools for preliminary screenings and disease detection. Poplin et al. (2018) prove that deep learning models can be used to predict cardiovascular diseases from retinal fundus photographs by uncovering and highlighting simple correlations. Significant medical progress comes from the process of making associations or correlations, formulating hypothesis, and designing new experiments to test these hypotheses. These experiments and testing of hypothesis can become cumbersome when dealing with Big Data containing thousands or even millions of medical images. By making these large datasets available to the public, doctors, scientists, clinicians, programmers and technicians can design, develop and deploy credible artificial intelligence models using machine learning artificial neural networks, and deep learning convolutional neural networks.

**Future Work**

Results demonstrate the effectiveness of the application of machine learning techniques to fundus imagery for early detection of cardiovascular diseases. As the algorithms get ratified, preprocessing of images gets more effective and more public data sets become available, these convolutional neural networks will undoubtably surpass current methodologies in both time and accuracy. While the basis for this paper was a binary output of 1-likely to have CVD issues and 0-unlikely to currently have CVD issues, I have done similar research for applying artificial intelligence for diagnosis and classification of diabetic retinopathy (DR). That research uses Inception V3 and VGG19 models for CNN to sort a 5 level classification of diabetic retinopathy. class 0-No DR, class 1- Mild, class 2- Moderate, class 3- Severe, class 4- Proliferate. If DR is caught between stage 1 and 3, the disease can be reversed, if caught in stage 4, the disease can only be arrested rather than cured and no lost vision can be restored.

One of the future applications of this work will be to visit medically remote populations of people using mydriatic eye drops, a 20 D lens and lighted smartphone to tertiarily screen peoples for CVD and DR. Another benefit is the data captured in this way can not only serve as a good preliminary screening but also help to train data sets for the CNNs. Lastly these CNNs might possibly be used as a standalone smartphone application. The future work for next year will include the possibility of deploying TEHI-The Eyes Have It as a smartphone app.

**Declarations**

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