# Heart, Eye, and Artificial Intelligence: A Review

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## Abstract

Heart disease continues to be the leading cause of death in the USA. Deep learning-based artificial intelligence (AI) methods have become increasingly common in studying the various factors involved in cardiovascular disease. The usage of retinal scanning techniques to diagnose retinal diseases, such as diabetic retinopathy, age-related macular degeneration, glaucoma and others, using fundus photographs and optical coherence tomography angiography (OCTA) has been extensively documented. Researchers are now looking to combine the power of AI with the non-invasive ease of retinal scanning to examine the workings of the heart and predict changes in the macrovasculature based on microvascular features and function. In this review, we summarize the current state of the field in using retinal imaging to diagnose cardiovascular issues and other diseases.

Keywords: Retinal imaging; Cardiovascular disease; Deep learning

## Introduction: The Retinal Window Into the Heart

Heart disease is the primary cause of death in the USA [1, 2]. Cardiovascular health is invariably dependent on the condition of vascular pipelines that are subject to internal and external stressors, such as genetic factors, improper regulation of lipids and glucose, irregular blood pressure, and hypoxia [3]. Certain cardiovascular conditions have been found to be correlated with specific characteristics of retinal structures and microvasculature. Thus, the retinal microvasculature provides a non-invasive window into the pathological development of systemic vascular diseases. For instance, hypertensive patients exhibit specific retinopathies such as arterial narrowing, papilledema, and arteriovenous nicking [3]. Systemic hypertension can lead to glaucoma, cataracts and age-related macular degeneration, while systemic hypotension can result in glaucomatous optic neuropathies. Retinal atherosclerosis is strongly correlated

with coronary artery disease in regards to the spread of disease and the magnitude of severity, suggesting that microvasculature and macrovasculature are affected in an intertwined manner [4]. The purpose of this review is to focus on the field of cardiovascular diagnostics based on retinal imaging, with an emphasis on the emerging role of deep learning in retinal imaging.

## Current Role of Retinal Scanning in Eye Diseases

### Diabetic retinopathy

According to the National Eye Institute, diabetic retinopathy is a major cause of blindness for adults in the USA [5]. It is suggested that irregular glucose levels damage small blood vessels in the retina and narrow retinal arterioles, causing swelling and ischemia of the eye tissue that leads to blindness. There is a growing understanding that retinal dysfunction in diabetic retinopathy is the result of a complex crosstalk between glial cells, neurons and the retinal microvasculature over a period of time [6]. Since the disease is largely asymptomatic in its earlier non-proliferative stages, diabetic patients require regular screening by retinal fundus exams to monitor and prevent disease progression.

### Retinal imaging

Optical coherence tomography angiography (OCTA) is a non-invasive imaging technique for the visualization of retinal vascular networks that provides accurate information on blood flow and depth and volume of ocular structures and their tendency to scatter or reflect light, all of which help in diagnosing the correct clinical stage of the disease and tracking the severity of disease progression [7, 8]. Fluorescence lifetime imaging ophthalmoscopy (FLIO) is a novel imaging modality that measures retinal fluorophores by their decay lifetime, providing a more comprehensive picture of retinal structure and integrity compared to fundus autofluorescence (FAF), which primarily visualizes lipofuscin [9]. FLIO is used to investigate a variety of ophthalmic conditions including diabetic retinopathy, macular holes, retinal artery occlusion, age-related macular degeneration, central serous chorioretinopathy, macular telangiectasia type 2, Stargardt disease, and even Alzheimer's. Adaptive optics scanning laser ophthalmoscopy (AO SLO) has been used with fluorescein angiography to visualize micro-

scopic details of the retinal vasculature, which has led to its use in studying retinal vasculopathies such as diabetic retinopathy, retinal vein occlusion (RVO) and sickle cell retinopathy [9]. To assist in detection of early microvascular symptoms of diabetic retinopathy, algorithms are now being developed to automate detection of findings such as microaneurysms and cotton wool spots amidst visual artifacts in different types of imaging conditions [10, 11].

## Deep learning diagnostics

In 2018, the Food and Drug Administration (FDA) approved a new artificial intelligence (AI)-based diagnostic system, IDx-DR, to diagnose diabetic retinopathy based on fundus photos and macular OCT after a study evaluating its diagnostic performance showed a specificity of 90.7% (95% confidence interval (CI), 88.3-92.7%) and a sensitivity of 87.2% (95% CI, 81.8-91.2%) [12]. The system diagnosed more than mild diabetic retinopathy and diabetic macular edema in diabetic patients not previously known to have either condition. Notably, the system was used in all primary care locations, demonstrating its ease of use and proving itself to be a powerful tool in identifying patients, who should receive additional referral to an eye care provider. Moreover, combining deep learning algorithms with physician readers has been shown to increase the accuracy and confidence in diagnosing diabetic retinopathy [13].

Another machine learning system combines digital microaneurysm detection from retinal fundus photos with proteomics analysis from tear fluid samples to diagnose diabetic retinopathy with a specificity of 0.78 and a sensitivity of 0.93 [14]. Tear fluid analysis is not routinely used in current clinical practice, but this study demonstrates a potential use for it as another non-invasive method of disease detection. Ultimately, these studies suggest that incorporating clinical biomarkers and physician readers with AI-based deep learning algorithms of retinal imaging could improve the overall accuracy and capability of diagnosing diabetic retinopathy.

Machine learning is also progressing to diagnose other ophthalmologic conditions. Retinopathy in premature infants is an important cause for childhood blindness globally, and scientists are now developing algorithms with deep neural networks to detect tortuosity and dilation of retinal vessels in order to automate diagnosis from retinal photos [15]. Additionally, an AI-based technique revealed that the significantly lower macular vessel density in glaucoma patients was linearly correlated to the ganglion cell-inner plexiform layer thickness (GCIPLT), suggesting the development of potential biomarkers to detect the progression of vision loss in glaucoma [16]. Furthermore, AI methods have been developed to detect age-related macular degeneration, cataracts, and keratoconus, among others [17, 18]. Aside from detection of diseases, deep learning has also been tested to assess OCTA image quality by accurately differentiating between sufficient and insufficient OCTA images based on criteria of motion artifact score, centered vs. decentered fovea, visibility of small capillaries, and segmentation accuracy score [19]. Thus, deep learning in reti-

nal imaging is proving its potential not only in disease diagnosis, but in quality control purposes as well.

## Heart, Eye and AI

### Machine learning in cardiology

The role of AI and deep learning in cardiovascular applications is not new. Deep learning has been used in a number of cardiac imaging techniques, including intravascular OCT, echocardiography, cardiac magnetic resonance, computed tomography, and single-photon emission computed tomography [20]. In 2019, researchers developed a deep learning algorithm to predict mortality in hospitals after percutaneous coronary intervention based on age and ejection fraction, achieving up to 0.927 discrimination performance with the AdaBoost model [21]. A similar study used machine learning algorithms to predict diagnosis and disease complexity of over 10,000 patients with adult congenital heart disease or pulmonary hypertension; the algorithms reached an accuracy of 91.1% for diagnosis and 97.0% for disease complexity [22].

### Retinal imaging, heart disease, and deep learning

The use of deep learning combined with retinal imaging in the diagnosis of cardiovascular conditions is a relatively new area of research (Table 1 [23-31]). In 2007, researchers from Australia, Singapore, and the USA showed that retinopathies obtained from fundus photographs were associated with the presence of any degree of coronary artery calcification (CAC) score > 0, measured by cardiac computed tomography scanning (odds ratio (OR): 1.22; 95% CI: 1.04 - 1.43) in a multi-ethnic population without clinical heart disease, after adjustment for multiple variables [23]. The same group of researchers also showed that narrower retinal arterioles obtained from fundus images were associated with concentric remodeling of the left ventricle as seen in cardiac magnetic resonance imaging (MRI) (OR: 2.06; 95% CI: 1.57 - 2.70) in a study with 4,593 individuals without any clinical cardiac disease [24]. Retinopathy was also correlated with left ventricular (LV) remodeling (OR: 1.31; 95% CI: 1.08 - 1.61), particularly in individuals with diabetes, hypertension or coronary calcification. The researchers inferred that microvascular disease, including retinopathies, can be reflective of subclinical macrovascular disease and share similar pathophysiological processes.

Another study tested the hypothesis that worsening hypertension was associated with capillary blood flow reduction and retinal microvessel remodeling, which was assessed by combining laser Doppler flowmetry with laser scanning tomography. The findings demonstrated that retinal capillary flow, and thus perfusion, was lower in patients with more advanced arterial stiffness (pulse wave velocity > 10 m/s) [25]. Cardiac microvascular disease can also be evaluated by assessing retinal arteriolar narrowing as detected by fundus photography. In patients without coronary artery calcification, narrower retinal

**Table 1.** Studies Using Retinal Imaging to Predict Cardiovascular Disease Characteristics

| Study | Country | Number | Population | Deep learning involvement | Retinal metric(s) | CV outcome | Results |
|---|---|---|---|---|---|---|---|
| Cheung et al, 2007 [24] | USA | 4,593 | Men and women aged 45 - 84 years without history of clinical CV disease | None | Retinal vascular caliber, retinopathy | Left ventricular concentric remodeling | Narrower retinal arteriolar caliber (OR: 2.06) and retinopathy (OR: 1.31) associated with increased odds of concentric remodeling |
| Wong et al, 2008 [23] | USA | 6,814 | Men and women aged 45 - 84 years without history of clinical CV disease | None | Retinopathy, retinal arteriovenous nicking, retinal arteriolar caliber, retinal venular caliber | CAC | Presence of retinopathy was associated with presence of any CAC (OR: 1.22, 95% CI: 1.04 - 1.43); retinal arteriovenous nicking weakly associated with higher CAC scores; no significant associations of retinal arteriolar or venular caliber with CAC scores. |
| Kromer et al, 2018 [29] | Germany | 106 | Males who experienced MI before age 50 and age-matched healthy males | None | Central retinal vessel caliber, AVR | MI | No significant differences in central retinal arterial/venous equivalent or AVR between MI group and control group. |
| Poplin et al, 2018 [28] | UK, USA, and other countries in EyePACS database | 297,360 | Patients from UK Biobank and EyePACS database | Used model to predict CV risk factors from retinal fundus images | Retinal fundus images | CV risk factors, major adverse cardiovascular events (MACEs) within 5 years | Model significantly predicted certain CV risk factors within given margin (P < 0.0001): age within 5 years at 78% accuracy; SBP within 15 mm Hg at 72% accuracy; DBP within 10 mm Hg at 79% accuracy; BMI within 5 at 80% accuracy. Model achieved AUC 0.70 (95% CI: 0.648 - 0.740) of predicting 5-year MACE from retinal fundus images alone compared to AUC 0.72 for European SCORE risk calculator. |
| Li et al, 2019 [27] | China | 162 | Patients with ICA stenosis | None | Subfoveal choroidal thickness, choroidal vascular index | ICA stenosis | Subfoveal choroidal thickness (P < 0.05) and choroidal vascular index (P = 0.001) lower in severe ICA stenosis group. |
| Chang et al, 2020 [31] | Korea | 38,824 | Participants who completed exams at HPC-SNUH between 2005 - 2016 and received retinal fundus exam | Used model to predict atherosclerosis and risk of CV death relative to FRS | Retinal fundus images | Presence of atherosclerosis (DL-FAS), risk of CVD mortality | Model predicted atherosclerosis with accuracy of 58.3% and demonstrated significant association between DL-FAS and CVD mortality. |
| Dabrowska et al, 2020 [25] | Poland | 120 | 88 patients with essential hypertension and 32 healthy participants matched in age and gender | None | Retinal capillary flow | Arterial stiffness (measured by pulse wave velocity) | Lower retinal capillary flow in patients with pulse wave velocity (PWV) > 10m/s compared to those with PWV ≤ 10 m/s (P = 0.02). |

**Table 1.** Studies Using Retinal Imaging to Predict Cardiovascular Disease Characteristics - *(continued)*

| Study | Country | Number | Population | Deep learning involvement | Retinal metric(s) | CV outcome | Results |
|-------|---------|--------|------------|---------------------------|-------------------|------------|---------|
| Druckenbrod et al, 2020 [26] | USA | 143 | US veterans aged 29 - 91 | None | Subfoveal choroidal thickness | CV disease risk factors | Diabetes associated with thinner choroid (P = 0.001). Hypertension (P = 0.006) and hyperlipidemia (P = 0.05) associated with thicker choroid. |
| Zhang et al, 2020 [30] | China | 625 | Participants aged 24 - 83 years | Used model to predict CV risk factors from retinal fundus images | Retinal fundus images | Hypertension, hyperglycemia, dyslipidemia, and other CV risk factors | Model predicted hypertension, hyperglycemia, and dyslipidemia with accuracies of 68.8%, 78.7%, and 66.7%, respectively. |

MI: myocardial infarction; ICA: internal carotid artery; SBP: systolic blood pressure; DBP: diastolic blood pressure; BMI: body mass index; AUC: area under the ROC curve; CV: cardiovascular; CVD: cardiovascular disease; DL-FAS: deep learning-funduscopic atherosclerosis score; FRS: Framingham risk score; OR: odds ratio; CI: confidence interval; CAC: coronary artery calcification; AVR: arterial-venous ratio.

arterioles were associated with lower hyperemic myocardial blood flow and perfusion reserve, which reflect microcirculation in the absence of stenosis [32].

Subfoveal choroidal thickness (SFCT) has been studied as a correlate to common cardiovascular disease (CVD) risk factors; multivariate analysis showed that diabetes was associated with thinner choroid (P = 0.001), whereas hypertension (P = 0.006) and hyperlipidemia (P = 0.05) were associated with thicker choroid [26]. In a separate study, SFCT was found to be significantly thicker in participants with hypercholesterolemia compared to those without (P = 0.041) [33]. However, in patients with severe internal carotid artery stenosis, SFCT was significantly lower. Those with severe stenosis also had a lower choroidal vascularity index (CVI), illustrating that CVI may be an indicator of stenotic changes in the internal carotid artery [27].

Serum amyloid A (SAA) protein deposition can lead to cardiac amyloidosis, although the incidence is very rare. The Beaver Dam Eye Study used retinal imaging to assess if there was a relationship between retinal vascular caliber and different inflammatory markers including SAA. SAA levels were higher in patients who had smaller arteriolar diameters after adjustment for other characteristics [34]. Stettler et al expanded on the Beaver Dam Eye Study and focused on SAA and retinal microvascular parameters in hypertensive patients with and without type 2 diabetes. They found that SAA was significantly higher in diabetic patients compared to nondiabetics (3.15 mg/L vs. 2.65 mg/L; P = 0.03), and that diabetic patients had shorter retinal arteriolar vessels than nondiabetics (446.9 ± 103.7 vs. 466.4 ± 126.8 pixels; P = 0.03) [35]. Overall, more research is still needed to elucidate the association between retinal findings and cardiac amyloid.

In 2018, Google researchers trained a deep learning system based on AI to predict cardiovascular risk factors such as age, ethnicity, gender and smoking status in addition to systolic and diastolic blood pressure from retinal fundus images [28]. Researchers trained the system on images obtained from 284,335 patients of various ethnicities across two datasets, the UK Biobank and the EyePACS, and predicted results on 13,025 patients. The AI system then combined the predicted information from all the risk factors to forecast the onset of major adverse cardiovascular events (MACEs) within 5 years. Using retinal fundus images alone, the model achieved an area under the ROC curve (AUC) of 0.70 (95% CI: 0.648 - 0.740) for predicting 5-year MACE values, which was comparable to an AUC of 0.72 (95% CI: 0.67 - 0.76) obtained from the European SCORE risk calculator. These results advocate for the use of machine learning to predict cardiovascular risk directly from retinal fundus images.

The ages of the participants from the above studies ranged from 40 to 85 years. Researchers are still exploring whether it is age or the characteristics of specific vascular disease that drives the learnability potential of the images. In a 2018 study, scientists compared features of the retinal microvasculature using OCT in a group of men, who experienced myocardial infarction before 50 years of age and found no significant differences in the arterial-venous ratio (AVR) or retinal vessel caliber when compared to an age-matched control group [29]. While the study was powered to 99% to detect the slightest

differences between the two groups, no women were included in either group, suggesting that gender-specific hormonal influences could play a distinguishing role in the development of heart disease in men and women. Further analyses are being performed to examine risk stratification by gender for acute coronary syndromes [36].

In China, deep learning was utilized in a study of 625 subjects to predict hypertension, hyperglycemia, dyslipidemia, and other cardiovascular risk factors based on retinal fundus images. The model achieved an accuracy of 78.7% in detecting hyperglycemia, 68.8% in detecting hypertension, and 66.7% in detecting dyslipidemia. Additionally, other risk factors such as age, drinking status, smoking status, salty taste, and body mass index (BMI) were also predicted with accuracies > 70%. These results support the application of deep learning to retinal fundus images in the identification of individuals at risk for CVD [30].

Furthermore, researchers validated a deep model using retinal fundus images not only to predict the presence of atherosclerosis, but to determine if the atherosclerosis score was correlated with cardiovascular death relative to the Framingham risk score. A total of 6,597 participants with retinal fundus exams and carotid artery sonography were used to develop the deep model for prediction of atherosclerosis, and 32,227 subjects with only retinal fundus exams were used to validate whether the atherosclerosis score could predict future cardiovascular death. The model demonstrated an accuracy of 0.583 for predicting atherosclerosis, with a sensitivity of 0.891, but low specificity of 0.404. In terms of cardiovascular mortality, those with higher deep-learning funduscopic atherosclerosis scores (0.33 - 0.67 and 0.67- 1.00) had significantly higher risk of CVD mortality (hazard ratio (HR): 8.83; 95% CI: 1.41 - 6.15; and HR: 8.83; 95% CI: 3.16 - 24.7, respectively) than those with the lowest scores. Deep learning of retinal fundus images can be used to predict atherosclerosis, which can supplement current risk stratification scores for cardiovascular mortality [31]. Atherosclerosis contributes to the development of RVO, and hyperlipidemia was found to be much higher in those with RVO than in those without [37]. Matei et al evaluated statins for preventive efficacy in patients who were at high risk for developing RVO and for therapeutic efficacy in patients who had developed RVO. Unfortunately, neither a preventive nor therapeutic benefit was seen in patients who took statins compared to those who did not, although it was noted that the study was underpowered (n = 172 eyes) to detect a protective effect [38].

## Other Applications of Retinal Microvasculature Analysis

### Stroke

Extensive research has demonstrated that there is a strong correlation between retinal vascular changes and clinical stroke [39]. Baseline retinopathy is associated with incidental stroke, and retinal venular widening is associated with an increased risk of stroke and stroke mortality. Furthermore, retinal vascular changes may differ based on various stroke subtypes and could help to discern clinical stroke from other causes of focal neurologic deficits. Interestingly, despite the strong correlation of retinal vascular changes with stroke, the addition of retinal imaging has only been shown to improve stroke risk stratification by about 10% from already established risk factors [39].

### Alzheimer's disease

Analysis of retinal microvasculature continues to expand as research finds that it reflects the state of health elsewhere in the body. In patients with Alzheimer's disease, vessel density, perfusion density and GCIPLT in the central macula of the retina were found to be significantly reduced compared to both healthy controls and patients with mild cognitive impairment [40]. Another study found that Alzheimer's patients with β-amyloid deposits in the brain as observed by positron emission tomography (PET) studies had texture differences in retinal microvasculature compared to control subjects without these deposits [41]. In Alzheimer's patients, the retinal arterioles had bigger diameters near the optic nerve head while retinal venules showed an increased mean tortuosity. The amyloid deposits in the retina affecting the scattering of light in the hyperspectral retinal images are a potential biomarker for the disease.

### Multiple sclerosis (MS)

Demyelinating lesions can lead to degeneration of optic nerve axons, which present as atrophied peripapillary retinal nerve fiber layer and ganglion cell-inner plexiform complex on OCT. OCT in MS patients can also show macular microcystoid changes that correlate to disease severity [42]. While use of OCT in MS has expanded considerably, additional research is needed to validate OCT as a biomarker in the diagnosis and progression of MS and as an indicator of response to therapy [43].

### Chronic kidney disease (CKD)

The kidney and the eye share many structural and physiological similarities suggesting that an analysis of the eye may yield valuable information about renal function. Choroidal thinning was found to be directly correlated with a lower estimated glomerular filtration rate (eGFR) and higher proteinuria, but little is known about the exact mechanisms behind this association [44]. More studies are needed to explore the relationship between retinal imaging and CKD outcomes.

### Photoacoustic imaging

Non-invasive and high resolution photoacoustic imaging has recently been adapted to optical applications to improve disease detection and potential treatment [45]. Scientists are

now developing enhanced technologies to combine machine learning with quantitative photoacoustic imaging to measure parameters such as local blood oxygenation in real time [46]. Future studies are focusing on refining the programs to work on volumes of whole tissues at higher resolutions.

### Biological image processing

Researchers at Google are now investigating the application of deep learning into extracting data from cellular images [47]. Scientists have built a software to detect morphology and localization of subcellular and nuclear organelles from fluorescence microscopy photos and to combine this information into a three-dimensional (3D) image [48]. This automated processing could dramatically improve the speed, efficiency, and objectivity of biological imaging analysis.

## Conclusions

With aging populations across the globe, the use of AI and deep learning systems are starting to drive automated diagnoses in clinical ophthalmology [49]. While machines can be trained to discern and learn visual patterns of diseased and healthy microvessels, researchers are seeking ways to characterize the exact series of mechanisms by which machines learn how to detect and assess the severity of disease [50]. The expanded use of deep learning naturally prompts additional questions, such as accountability of diagnoses on the part of humans or machines in the case of software errors, as well as optimization of the technology under clinical constraints [50]. As scientists continue to develop increasingly intuitive algorithms with quick learning capabilities, the possibility of a clinical diagnostic robot that can scan retinas to examine the inner workings of the heart could be a reality in the near future.

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## Conflict of Interest

The authors declare that they do not have conflict of interest.

## Author Contributions

All authors participated in the review. They were involved in writing and revising the article prior to submission.

## Data Availability

The authors declare that data supporting the findings of this study are available within the article.

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