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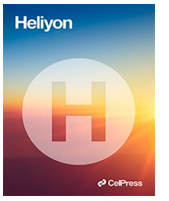

Research article

The impact of serum BNP on retinal perfusion assessed by an AI-based denoising optical coherence tomography angiography in CHD patients

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ABSTRACT

Background: To investigate the correlation between retinal vessel density (VD) parameters with serum B-type natriuretic peptide (BNP) in patients with coronary heart disease (CHD) using novel optical coherence tomography angiography (OCTA) denoising images based on artificial intelligence (AI).
Methods: OCTA images of the optic nerve and macular area were obtained using a Canon-HS100 OCT device in 176 patients with CHD. Baseline information and blood test results were recorded.
Results: Retinal VD parameters of the macular and optic nerves on OCTA were significantly decreased in patients with CHD after denoising. Retinal VD of the superficial capillary plexus (SCP), deep capillary plexus (DCP) and radial peripapillary capillary (RPC) was strongly correlated with serum BNP levels in patients with CHD. Significant differences were noted in retinal thickness and retinal VD (SCP, DCP and RPC) between the increased BNP and normal BNP groups in patients with CHD.
Conclusion: Deep learning denoising can remove background noise and smooth rough vessel surfaces. SCP,DCP and RPC may be potential clinical markers of cardiac function in patients with CHD. Denoising shows great potential for improving the sensitivity of OCTA images as a biomarker for CHD progression.

1. Introduction

Coronary heart disease (CHD) is a cardiovascular disease caused by a variety of factors that can manifest as heart failure, which seriously threatens people's lives and health. Coronary angiography (CAG) is the gold standard for diagnosis in clinical practice. This heavy burden leads to poor health and disabilities; therefore, early diagnosis and prevention of CHD are of great significance in improving the prognosis of such patients. The degree of coronary narrowing on angiography alone is insufficient to evaluate the progression of CHD.

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Various biomarkers have been used in clinical practice to monitor CHD progression [1]. B-type natriuretic peptide (BNP) is the most recognized clinical prognostic predictor of heart failure (HF) and assessment of the severity of ventricular dysfunction [1–3]. BNP is synthesized in the heart ventricles, and increase during ventricular dysfunction. Higher BNP was an independent risk factor of new-onset HF [4,5].

The retina is regarded as a window to the heart and can be noninvasively visualized. Recent research has focused on the correlation between retinal vasculature and cardiovascular diseases; it is thought that the retinal vasculature is often exposed to the same intrinsic and environmental influences on the heart vasculature [6]. The retina provides a window for detecting changes in the microvasculature associated with CHD progression and development. Cumulative studies have attempted to explore the relationship between retinal microvascular abnormalities and markers of cardiovascular risk [7–11]. As previously reported, structural changes in the retinal microvasculature, such as arteriolar narrowing, venular dilation, and vessel tortuosity, have been associated with the prognosis of coronary circulation [12]. While the interaction between serum BNP levels and retinal vasculature in patients with CHD remains unclear.

Retinal blood flow is auto-regulated and independent of perfusion pressure within a certain range. Vascular endothelial cells and neural and glial cells are the main regulators. The retina is supplied by both the retinal and choroid arteries. The inner layers of the retina are supplied by capillaries from the central retinal artery, whereas the outer layers of the retina take up oxygen and nutrients from the choroid. Retinal capillaries are organized in an interconnected two-layer network. The superficial capillary plexus (SCP) is located in the nerve fiber and ganglion cell layers, and the deep capillary plexus (DCP) is formed by two vascular layers present in the inner nuclear and outer plexiform layers.

Currently, Optical coherence tomography angiography (OCTA), based on the variable backscattering of light from the vascular and neurosensory tissue in the retina, provides high-resolution images of blood flow in the retina and choroid without invasive operations. OCTA quantitative parameters have become important biomarkers for systemic vascular diseases, and the VD in retina and choroid has contributed greatly to the early detection of cardiovascular diseases.

OCTA artifacts caused by motion and retinal projection easily degrade image quality, which prevents accurate interpretation and quantitative analysis of OCTA images. Therefore, methods to improve the quality of OCTA images are important. Deep learning has been reported to enhance the quality of OCTA images from a single-shot image using artificial intelligence (AI) technology, which can automatically analyze data and greatly improve image quality. After deep learning training, HS 100 (Canon, Tokyo, Japan) developed an algorithm for denoising images and generated a multiple image averaging (MIA) image from a single-scan image without acquiring multiple images. This deep learning technique may be a viable alternative to the MIA technique.

In this study, we report a novel deep-learning-based algorithm for denoising OCTA imaging. We aimed to evaluate the impact of serum BNP on macular and optic nerve VD parameters by OCTA-HS100 in CHD patients, to elucidate whether denoising could provide a promising improvement in image quality and reliable quantitative data, and further facilitate clinical practice with OCTA images as a

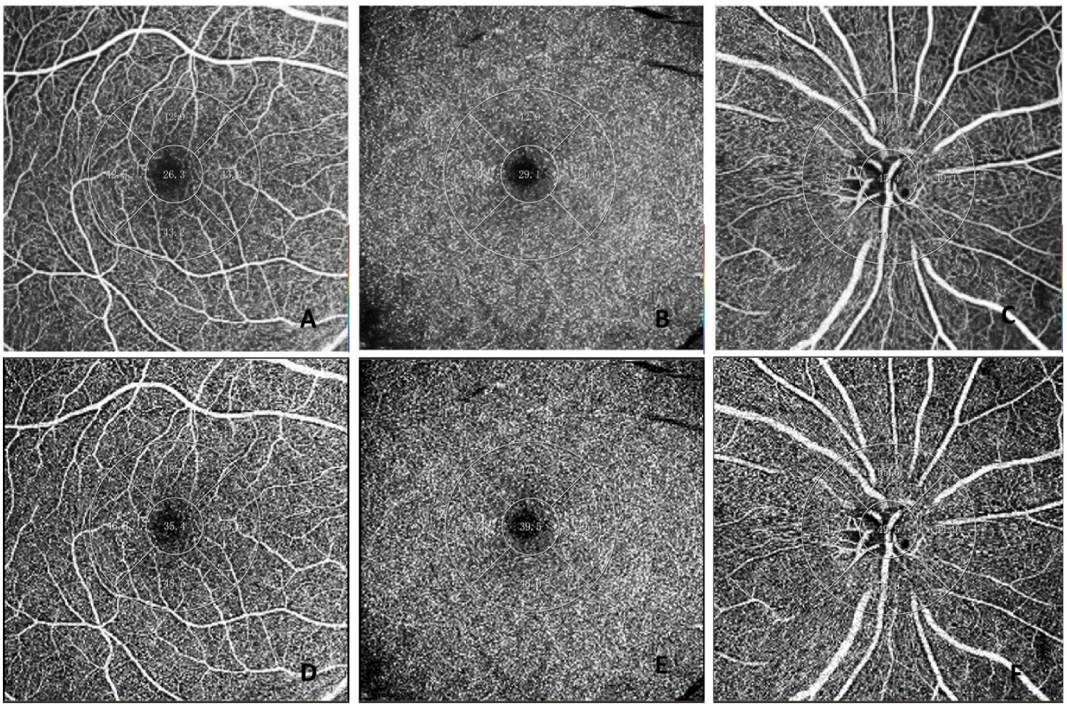

Fig. 1. Impact of deep learning denoising on the quality of optical coherence tomography angiography (OCTA) images. (A–C), OCTA images of Original retinal VD of SCP, DCP and RPC obtained using a 6 × 6 mm^2 scan pattern. (D–F) Denoised OCTA images of SCP, DCP and RPC.

clinical prognostic marker in CHD progression.

2. Materials and methods

2.1. Participants

A total of 176 patients with CHD diagnosed by CAG in our hospital between January 2021 and October 2021 were enrolled and retrospectively analyzed. All patients underwent a comprehensive ophthalmic examination, including measurement of best-corrected visual acuity, slit-lamp biomicroscopy, axial length measurement, color fundus photography, and OCTA. Fasting blood samples, including serum glucose, HbA1c, and BNP, were taken on the same day in the morning after 12 h of fasting. Significant cardiovascular risk factors, such as age, sex, body mass index (BMI), blood pressure (BP), history of hypertension and diabetes mellitus (DM), and smoking, were documented. Written informed consent was obtained from each participant before performing any study procedures or examinations. BP was measured in a sitting position on the right arm using standard mercury sphygmomanometers. Smoking is defined as smoking one or more cigarettes a day for a year or more. A cutoff point >100 ng/L was used for the definition of 'increased BNP' or subclinical HF.

2.2. Optical coherence tomography angiography imaging

Each patient was scanned using a spectral-domain OCTA instrument (OCT HS-100; Canon Inc., Tokyo, Japan). The OCT HS-100 has a scanning rate of 70,000 A-scans/s and a central wavelength of 855 nm, which enables a 3 μm axial resolution in tissue and a lateral resolution at the retinal surface of 15 μm. The retinal VD was obtained and analyzed using commercial default automated segmentation boundaries. The modes of the optic disc (6×6 mm^2) and macula (6×6 mm^2) of the OCTA scans were employed. There was an annulus of concentric circles with diameters of 1 and 3 mm, with the inner circle defined as the fovea and the ring between the two circles defined as the parafovea. Retinal VD of SCP, DCP and peripapillary capillary (RPC) were analyzed. Retinal thickness maps in accordance with the standard Early Treatment Diabetic Retinopathy Study (ETDRS) subfield were automatically created, consisting of three concentric circular areas (1 mm, 3 mm, and 6 mm separately) with nine independent sectors for analysis. A denoising image was obtained by applying a denoised function. The original OCTA images of retinal VD of SCP, DCP and RPC and denoised images of SCP, DCP and RPC were shown in Fig. 1 (A-F). The data were analyzed using commercial default automated segmentation boundaries. All the OCTA scans were performed by an experienced examiner. Poor quality images (signal strength <6) were excluded from the quantitative analysis.

2.3. Statistical analysis

SPSS Statistics (Version 24.0; IBM Inc., Chicago, IL, USA) was used for all statistical analyses. Continuous parametric variables are presented as mean ± standard deviation. Student's t-test was used to assess the differences in retinal VD and retinal thickness parameters between the increased BNP group and the normal group in patients with CHD. Pearson's correlation coefficient was used to analyze the correlation between retinal VD, retinal thickness, and BNP after denoising. Statistical significance was set at $P < 0.05$.

3. Results

A total of 176 patients with CHD were included in this study. The baseline data are summarized in Table 1. Patients were grouped

Table 1
Baseline characteristics of study sample.

	BNP >100 (n = 60)	BNP ≤100 (n = 116)	p
Age (years)	66.97 ± 10.38	64.74 ± 7.87	0.114[a]
Range	28 to 82	38 to 86	
Gender			
Men, n,%	41(68.33 %)	82(70.69 %)	0.747[b]
BMI(kg/m^2)	25.51 ± 3.05	25.20 ± 3.70	0.574[a]
Smoking, n (%)	20(33.33 %)	37(31.90 %)	0.847[b]
HBP, n (%)	37(75.5 %)	55(79.7 %)	0.073[b]
DM, n (%)	11(22.45 %)	19(24.36 %)	0.744[b]
SBP, mmHg	138.37 ± 20.72	141.29 ± 16.86	0.315[a]
DBP, mmHg	76.67 ± 11.90	79.63 ± 11.02	0.102[a]
MBP, mmHg	97.56 ± 12.58	100.18 ± 10.79	0.151[a]
FBG	5.80 ± 1.88	5.82 ± 2.29	0.936[a]
HbAc	6.32 ± 0.96	6.37 ± 1.18	0.785[a]
Axial length	23.40 ± 1.48	23.23 ± 1.56	0.478[a]
BNP	345.2 ± 357.37	47.17 ± 22.57	<0.001[a]

[a] *t*-test.
[b] Chi-square test.

into increased BNP (n = 60) and normal BNP groups (n = 116) according to BNP level (cutoff point >100 ng/L). The average BNP was 345.2 ± 357.37 ng/L and 47.17 ± 22.57 ng/L respectively. The average age was 66.97 ± 10.38 years old for increased BNP group and 64.74y±7.8 years old for normal BNP group. There was no statistical difference in BP, BMI, age, hypertension, DM and smoking between the increased BNP and normal BNP groups. As for the laboratory tests, no significant differences were noted in the blood glucose and HbA1c levels between the two groups.

Retinal VD parameters of the macular (SCP and DCP) and optic nerves (RPC) were calculated automatically with and without denoising based on AI technology in all patients (n = 176). Background noise of the retinal VD was removed and vessel surface was smoothed after denoising (Fig. 1). The fovea SCP, DCP and RPC VD were significantly decreased after denoising (Table 2) ($p < 0.001$, <0.001 and < 0.001 respectively).

3.1. Analysis of retinal thickness of denoising algorithm

In our study, the central retinal thickness was thinner in the increased BNP group (266.07 ± 25.94 μm) than in the normal BNP group (273.58 ± 20.83 μm) ($p = 0.039$). The retinal thicknesses in all ETDRS sectors were significantly lower in the increased BNP group (Table 3). However, no significant correlation was noted between BNP levels and retinal thickness in patients with CHD (Table 4).

3.2. Analysis of retinal VD of denoising algorithm

In our cohort, the retinal vasculature showed a significant decrease in the macular VD (SCP and DCP) in the increased BNP group compared with the normal BNP group in patients with CHD ($p < 0.001$ in all sectors)(Table 5). In the optic nerve VD, no statistical difference was noted of in the fovea sector of the RPC between the two groups ($p = 0.606$). But significant differences were shown in superior, inferior, nasal, temporal sector of the PRC between the two groups(Table 5). Denoising algorithm not only remove background noise also provide much more significant differences in PRC layers between the two groups (supplementary data Table 1). Pearson's correlation showed a significant correlation between BNP level with retinal VD of SCP and DCP but not with RPC (Table 6).

4. Discussion

In this study, the quantitative parameters describing the microvascular density significantly changed after denoising, suggesting that deep learning denoising could remove background noise and smooth the rough vessel surface. This significantly improved the quality of the original OCTA images.

Plasma BNP secreted by cardiomyocytes is a strong predictor of CHD progrssion. In this study, we investigated the impact of BNP on retinal VD using deep learning-based denoising OCTA in patients with CHD. The results showed that retinal thickness and retinal macular VD (SCP and DCP) were significantly thinner in the increased BNP group than in the normal BNP group after the denoising technique. A negative correlation was noted between retinal VD (SCP and DCP) and the BNP level. Our study established an important relationship between BNP levels and retinal perfusion in patients with CHD using AI-based OCTA images.

Multiple large population-based studies have found significant associations between retinal microvascular changes and incident coronary disease or cardiovascular death [13–15]. Subtle changes in the retinal vasculature may mirror preclinical information useful for predicting clinical cardiovascular events [16]. Retinal perfusion might therefore provide an insight into the hemodynamic state of CHD patients [17–19].

Table 2
Retinal VD of original image and denoised image.

Retinal VD	Original n = 176	Denoised n = 176	
SCP density (%)			
fovea	32.10 ± 6.03	20.95 ± 8.67	<0.001
superior	42.73 ± 5.98	38.16 ± 8.62	<0.001
nasal	44.04 ± 4.95	38.99 ± 7.65	<0.001
inferior	43.68 ± 5.63	38.47 ± 8.67	<0.001
Temporal	43.50 ± 5.46	38.80 ± 8.19	<0.001
DCP density (%)			
fovea	29.67 ± 9.82	17.31 ± 8.64	<0.001
superior	40.98 ± 9.11	34.79 ± 10.28	<0.001
nasal	44.14 ± 8.12	37.88 ± 9.16	<0.001
inferior	41.88 ± 8.85	34.83 ± 10.45	<0.001
temporal	43.55 ± 8.49	37.61 ± 8.93	<0.001
RPC density (%)			
fovea	45.44 ± 6.23	41.37 ± 6.98	<0.001
superior	51.90 ± 5.20	41.69 ± 6.34	<0.001
nasal	49.68 ± 5.02	44.70 ± 6.27	<0.001
inferior	52.10 ± 4.33	46.36 ± 5.56	<0.001
temporal	51.10 ± 4.32	44.77 ± 5.73	<0.001

t-test.

Table 3
The retinal thickness in ETDRS sectors.

Retinal thickness	BNP >100 (n = 60) n = 60	BNP ≤100 n = 116	P	95 % CI
Center, μm	266.07 ± 25.94	273.58 ± 20.83	0.039	0.388-14.633
Inner superior, μm	334.95 ± 19.39	344.51 ± 16.56	0.001	4.044-15.073
Inner nasal, μm	337.80 ± 20.27	347.03 ± 16.33	0.001	3.734-15.383
Inner inferior, μm	336.17 ± 16.67	342.22 ± 17.05	0.026	0.739-11.359
Inner temporal, μm	328.18 ± 15.77	332.05 ± 16.99	0.136	−1.339-9.075
Outer superior, μm	297.83 ± 17.93	305.39 ± 13.95	0.002	2.291-12.818
Outer nasal, μm	313.30 ± 17.65	319.88 ± 16.36	0.015	1.304-11.855
Outer inferior, μm	284.48 ± 16.29	288.04 ± 13.08	0.118	−0.912-8.032
Outer temporal, μm	284.12 ± 14.58	289.97 ± 13.06	0.007	1.591-10.124

t-test.

Table 4
Correlation analysis results between retinal thickness and BNP.

Retinal thickness		Center	I–S	I–N	I–I	I-T	O–S	O–N	O–I	O-T
BNP	r	−0.081	−0.092	−0.095	−0.050	−0.034	−0.058	−0.064	−0.015	−0.017
	p	0.248	0.225	0.211	0.511	0.651	0.443	0.399	0.843	0.824

Table 5
The retinal VD in SCP, DCP and RPC after denoising algorithm.

Retinal VD	BNP >100 (n = 60) n = 60	BNP ≤100 n = 116	P	95 % CI
SCP				
fovea	14.253 ± 8.28	24.413 ± 6.61	<0.001	7.89-12.43
superior	32.400 ± 11.41	41.131 ± 4.47	<0.001	6.35-11.11
nasal	33.768 ± 9.87	41.695 ± 4.18	<0.001	5.27-10.58
inferior	33.580 ± 10.87	41.003 ± 5.90	<0.001	4.42-10.42
Temporal	33.402 ± 11.05	41.741 ± 3.93	<0.001	5.40-11.28
DCP				
fovea	11.425 ± 8.49	20.347 ± 7.02	<0.001	6.55-11.29
superior	27.895 ± 13.35	38.354 ± 5.63	<0.001	6.87-14.05
nasal	32.003 ± 12.49	40.924 ± 4.50	<0.001	5.60-12.25
inferior	29.785 ± 13.07	37.439 ± 7.63	<0.001	4.01–11.30
temporal	32.132 ± 12.24	40.438 ± 4.42	<0.001	5.02–11.59
RPC				
fovea	41.472 ± 6.74	41.315 ± 7.12	0.606	−2.35-2.04
superior	44.427 ± 7.60	47.107 ± 5.40	<0.001	0.494-4.87
nasal	43.197 ± 7.71	45.470 ± 5.24	0.001	0.703-4.476
inferior	44.913 ± 6.93	47.105 ± 4.55	0.002	0.224-4.160
temporal	43.063 ± 7.15	45.647 ± 4.63	0.003	0.559-4.607

t-test.

BNP is a polypeptide secreted by ventricular myocytes in response to wall stress induced by pressure overload. BNP (>100 pg/mL) is an acknowledged clinical predictor of HF level and its prognosis. Retinopathy has been reported as an independent predictor of HF [20,21]. Witt et al. noted a correlation between retinal artery abnormalities and the risk of death from ischemic heart disease and stroke [22]. Altinkaynak et al. studied subfoveal choroidal thickness using enhanced depth imaging optical coherence tomography and described a correlation between choroidal blood circulation and the degree of heart failure [23]. Moreover, a significant correlation was shown between the reduced retinal flow density and the systolic left ventricular ejection fraction [24].

The current study showed that retinal perfusion was significantly decreased in patients with CHD with serum BNP levels of >100 pg/mL. The possible mechanism underlying the relationship between BNP levels and retinal perfusion is as follows: BNP level is higher in patients or animals undergoing cardiac stress and is strongly associated to left ventricular pressure and dysfunction [25–28]. Ventricular dysfunction may lead to a decreased cardiac output and causes a reduction in the blood supply to the retina VD. Moreover, BNP was shown to induce natriuresis and vasodilatation [29].BNP is elevated in accordance with endothelial dysfunction and arterial stiffness in patients with cardiovascular diseases [30]. The retinal blood vessels might compromise like other peripheral vascular with the elevated BNP level. Thus, retinal VD parameters detected by OCTA showed a negative relationship with BNP level in CHD patients.

A significant decrease in retinal thickness was found in patients with increased BNP compared to the control group, which supported the anatomical changes associated with decreased retinal VD in patients with increased BNP. However, retinal thickness was not correlated with the BNP level in CHD patients. And some studies on CHD found that changes in retinal VD were typically characterized in the SCP rather than the DCP in patients with CHD [12,16]. In our study, SCP and DCP were both significantly correlated with the BNP level.

Table 6
Correlation analysis results between retinal VD and BNP level.

VD	SCP															
		DCP										RPC				
		Fovea	super	nasal	infer	tempor	Fovea	super	nasal	infer	tempor	Fovea	super	nasal	infer	tempor
BNP	r	−0.398**	−0.363**	−0.381**	−0.325**	−0.401**	−0.349**	−0.373**	−0.370**	−0.281**	−0.389**	0.029	−0.0900.202	−0.063	−0.091	−0.118
	p	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	0.725		0.405	0.229	0.118

*$p < 0.05$, **$p < 0.01$.

The present study has several limitations. First, this cross-sectional study lacked the CHD duration of each patients and long-term follow-up data. Second, we did not assess the heart using echocardiographic detection in all patients. Whether OCTA or retinal vasculature could add incremental predictive value beyond traditional cardiac characteristics in a practical manner has yet to be confirmed. However, the current results have shown the influence of BNP levels on retinal microvasculature and retinal perfusion in patients with CHD.

5. Conclusions

The retinal vasculature provides a non-invasive window for detecting the development and progression of CHD. Our results indicate that retinal VD (SCP and DCP) was significantly decreased in patients with CHD with increased serum BNP levels. Thus, retinal vasculature may be a surrogate for detecting microvascular damage and assisting in the assessment of CHD progression.

6. Ethics approval and consent to participate

The research was approved by the Institutional Review Board of Huashan Hospital affiliated to Fudan University (No. KY2016-274) and performed following the tenets of the Declaration of Helsinki. The subjects in the study signed written informed consent before undergoing the examination.

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Availability of data and materials

The datasets used and analyzed during the current study are available from the corresponding author upon reasonable request.

CRediT authorship contribution statement

Jin wang: Writing – review & editing, Conceptualization. **Huan Weng:** Writing – original draft, Visualization, Methodology. **Yiwen Qian:** Writing – original draft, Data curation. **Yuceng Wang:** Formal analysis, Data curation. **Luoziyi Wang:** Software, Investigation, Data curation. **Xin Wang:** Investigation, Formal analysis. **Pei Zhang:** Writing – original draft, Validation, Methodology, Investigation, Data curation. **Zhiliang Wang:** Writing – review & editing, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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