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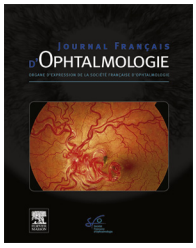

ORIGINAL ARTICLE

Influence of cardiac hemodynamic variables on retinal vessel density measurement on optical coherence tomography angiography in patients with myocardial infarction

Influence des paramètres hémodynamiques systémiques sur la mesure des densités vasculaires rétiniennes en OCT angiographie chez des patients coronariens

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KEYWORDS
Retina, OCT angiography, Myocardial infarction,

Summary
Introduction. — Quantitative measurements of retinal microvasculature by optical coherence tomography angiography (OCT-A) have been used to assess cardiovascular risk profile. However, to date, there are no studies focusing on OCT-A imaging in the setting of the altered hemodynamic status found in high-risk cardiovascular patients.

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Cardiovascular disease

Methods. — To determine the potential association between retinal vascular density on OCT-A and a comprehensive battery of hemodynamic variables in patients with myocardial infarction (MI) using data from the acute phase and at 3 months follow-up after cardiac rehabilitation. This prospective longitudinal study included patients who presented with MI in the cardiology intensive care unit at Dijon University Hospital. Main outcomes and measurements were retinal vessel density on OCT-A, hemodynamic status based on left ventricular ejection fraction (LVEF), and indexed cardiac output during the acute phase of myocardial infarction and at 3 months follow-up.

Results. — Overall, 30 patients were included in this pilot study. The median (IQR) age was 64 years (55—71) with 87% men. At admission, the mean (SD) LVEF was 53% (11), and the mean indexed cardiac output was 2.70 (0.83) L/min/m^2. On OCT-A, the mean inner retinal vascular density was 19.09 (2.80) mm^{-1}. No significant association was found between retinal vascular density and hemodynamic variables.

Conclusion. — We found no significant association between retinal vascular density on OCT-A and hemodynamic variables in the acute phase of a myocardial infarction or after 3 months of cardiac rehabilitation. Therefore, OCT-A findings do not seem to be influenced by the hemodynamic changes associated with myocardial infarction.

MOTS CLÉS
Rétine ;
OCT angiographie ;
Infarction infarctus du myocarde ;
Maladie cardiaque athérosclérotique

Résumé

Introduction. — Les caractéristiques quantitatives de la microvascularisation rétinienne en tomographie par cohérence optique angiographie (OCT-A) ont été utilisées pour évaluer le profil de risque cardiovasculaire. Cependant à ce jour, aucune étude ne s'est intéressée à la description microvasculaire en OCT-A dans un contexte d'une altération de l'état hémodynamique chez des patients présentant un risque cardiovasculaire élevé.

Méthodes. — Déterminer l'association potentielle entre la densité vasculaire rétinienne en OCT-A et un ensemble exhaustif de variables hémodynamiques chez des patients atteints d'un infarctus du myocarde en utilisant les données de la phase aiguë et du suivi à 3 mois, après une rééducation cardiaque. Cette étude longitudinale prospective a inclus des patients présentant un infarctus du myocarde dans l'unité de soins intensifs cardiologique du centre hospitalier universitaire de Dijon. Les critères principaux étaient la densité vasculaire rétinienne en OCT-A, la fraction d'éjection ventriculaire gauche (FEVG) et le débit cardiaque indexé à la phase aiguë de l'infarctus du myocarde et lors du suivi à 3 mois.

Résultats. — Au total, 30 patients ont été inclus dans cette étude pilote. L'âge médian (écart interquartile) était de 64 ans (55—71) avec 87 % d'hommes. À l'admission, la FEVG moyenne (écart type) était de 53 % (11) et le débit cardiaque indexé moyen était de 2,70 (0,83) L/min/m^2. De plus, la densité vasculaire rétinienne interne moyenne était de 19,09 (2,80) mm^{-1}. Aucune association significative n'a été trouvée entre la densité vasculaire rétinienne et les variables hémodynamiques.

Conclusion. — Nous n'avons pas trouvé d'association significative entre la densité vasculaire rétinienne en OCT-A et les variables hémodynamiques ni à la phase aiguë de l'infarctus du myocarde ni après 3 mois de réadaptation cardiaque. Par conséquent, les résultats quantitatifs de l'OCT-A ne semblent pas être influencés par les variations hémodynamiques chez des patients ayant présenté un infarctus du myocarde.

Introduction

Ischemic cardiovascular disease (CVD) is one of the leading causes of mortality and morbidity worldwide [1]. The clinical presentation is either sudden, in the form of an acute coronary syndrome (ACS), or a low-grade process that evolves over several years. It is therefore crucial to detect at-risk patients as early as possible in order to improve follow-up and monitoring. The most reliable approach would be to explore the coronary vasculature of patients, but the currently available techniques are very invasive [2,3]. In this context, retinal vascular imaging appears to be an appropriate approach for refining patients' risk stratification. Optical coherence tomography angiography (OCT-A)

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can be a valuable tool to assess a patient's cardiovascular risk profile [4,5]. Indeed, retinal vascular density seems to be a promising biomarker of cardiovascular status [6,7].

However, there are potential concerns regarding the use of imaging of the retinal microvasculature in cases of altered hemodynamic status during acute CVD since we previously found a significant correlation between decreased retinal vessel density on OCT-A and impaired left ventricular ejection fraction (LVEF) on echocardiography [1]. Contrarily to the Doppler imaging technique, OCT-A is not a retinal blood flow-imaging device [8—10]. As a matter of fact, the correlation between quantitative retinal microvascular characteristics on OCT-A and systemic hemodynamic features remain unclear and literature is sparse about the association between systemic blood flow and retinal OCT-A interpretation.

If the retinal vessel density on OCT-A is associated to hemodynamic changes, it seems very unlikely that it could be used as a screening tool for cardiovascular risk factors' assessment. Therefore, this study aimed to determine the potential association between retinal vascular density on OCT-A and a comprehensive range of hemodynamic variables of patients with myocardial infarction (MI) at the acute phase and at 3 months follow-up visit after cardiac rehabilitation.

Research design and methods

We conducted a prospective longitudinal ancillary study of the EYE-MI study, which has already been reported [4]. Briefly, from May 2017 to February 2018, patients presenting with MI in the cardiology intensive care unit in Dijon University Hospital and with a 3-month follow-up after cardiac rehabilitation were included. Patients presenting with non-stable angina pectoris and myocarditis were excluded from the analysis. The protocol was approved by the regional ethics committee on human research and followed the tenets of the Declaration of Helsinki. Participants have given their written informed consent. We followed the STROBE statement according to the EQUATOR guidelines [11].

Cardiac hemodynamic variables

The hemodynamic variables of each patient were assessed upon admission by means of a transthoracic echocardiography (General Electric, VIVID, Boston, MA, USA). The parameters measured were blood pressure, left ventricular ejection fraction (LVEF), the indexed cardiac output measured at the left ventricular output tract, and Doppler measurements of diastolic function (E/A, E/E′). These measurements were repeated on the same device and by the same cardiologist (SP) 3 months after MI and after completion of a cardiac rehabilitation program. Several patients underwent complementary hemodynamic evaluation via the photo-plethysmography device FINAPRES® (Demcon, Enschede, the Netherlands) at admission [12]. FINAPRES® is used for non-invasive analysis of information such as left ventricular ejection volume, myocardial contractility, aortic impedance, and vascular compliance.

Description of retinal microvasculature with OCT-A

The method for the collection of quantitative retinal microvascular data was previously described [1]. In summary, we performed an OCT-A with CIRRUS HD-OCT 5000 and Angioplex v10 software (Carl Zeiss Meditec, Lena, Germany) in order to determine retinal microvascular characteristics at admission and at the 3-month follow-up visit [13]. The OCT-A examination was performed within the first two days after admission under mydriasis obtained with eye drops containing tropicamide 0.5% (Thea, Clermont-Ferrand, France). OCT-A was performed by nurses or technicians. We collected retinal vascular features in the superficial capillary plexus (SCP) and we measured the area of the FAZ (mm^2) in 3×3 mm angiograms. Two types of vascular density were measured: perfusion density (area, unitless), which represents the total area of perfused vasculature per unit area in a region of measurement; and vessel density (length, mm^{-1}), which represents the total length of perfused vasculature per unit area in a region of measurement. All densities were measured automatically in the total and inner sectors of the SCP. The measurements were made on both eyes but one eye only was retained for the analysis according to the following procedure:

- OCT-A of the right eye for participants born in even-numbered years and the left eye for those born in odd-numbered years;
- in single-eye patients, the functional eye was selected;
- when a scan was uninterpretable for one eye, the other one was retained for the analysis.

Only images with a signal strength > 7/10 were retained. The same protocol was applied for the second retinal examination at 3-month follow-up after cardiac rehabilitation and we kept for analysis the same eye. Quantitative studies on retinal microvasculature were shown to be repeatable [14,15].

Statistical analysis

Continuous variables were tested for normality (Shapiro-Wilk test). When continuous variables respected normal distribution, they were expressed in means (standard deviation, SD) and compared with one-way ANOVA for repeated measures. If not, they were expressed in medians (interquartile-ranges, IQR) and compared using Friedman Repeated Measures Analysis of Variance on Ranks. Categorical variables were summarised in numbers and percentages. We randomly selected only one eye for the analysis. They were compared with the Fisher exact test. The Spearman correlation was used to assess the association between hemodynamic status and retinal microvascular parameters. ANOVA one-way analysis was used for repeated measures and subgroup analyses were performed in patients with impaired LVEF (< 50%) at admission [16]. Statistical analysis was performed with SigmaPlot 12.0 and SPSS 22.0 software programs (SPSS Inc., Chicago, DE, USA) and a P value ≤ 0.05 was considered to be statistically significant.

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Table 1 Hemodynamic status and retinal microvascular parameters on optical coherence tomography angiography of patients with acute coronary syndrome, $n = 30$.

	Intensive care unit admission	Three months follow-up	*P* value
Hemodynamic variables			
LVEF (%)	53 (11)	55 (7)	0.130
Aortic blood flow (mL/s)[a]	19.15 (5.40)	21.20 (3.50)	0.001
Indexed cardiac output (L/min/m^2)[a]	2.70 (0.83)	2.60 (0.71)	0.600
Heart rate (bpm)[a]	72 (16)	60 (10)	< 0.001
E/A[a]	0.72 (0.20)	0.71 (0.18)	0.470
E/E′[a]	7 (5.88—8.40)	7.19 (6.02—10.14)	0.470
Systolic blood pressure (mmHg)	117 (107—127)	138 (125—153)	< 0.001
Diastolic blood pressure (mmHg)	73 (10.85)	83 (12.31)	< 0.001
Retinal microvascular parameters			
FAZ (mm^2)	0.22 (0.17—0.26)	0.23 (0.17—0.28)	0.140
Inner vessel density (length, mm^{-1})	19.09 (2.80)	19.51 (1.98)	0.290
Total vessel density (length, mm^{-1})	18.03 (2.73)	18.36 (1.98)	0.400
Inner perfusion density (area, unitless)	0.36 (0.34—0.38)	0.36 (0.34—0.38)	0.850
Total perfusion density (area, unitless)	0.33 (0.04)	0.34 (0.03)	0.390

Continuous variables are presented as mean (SD) or median (IQR) depending on their distribution. bpm: beats per minute; LVEF: left ventricular ejection fraction; FAZ: foveal avascular zone; E/A: early to late transmitral flow velocity; E/E′: early mitral annular velocity.
[a] $n = 23$

Table 2 Hemodynamic status and retinal microvascular parameters on optical coherence tomography angiography of patients with altered left ventricular ejection fraction at admission (< 50%), $n = 13$.

	Intensive care unit admission	Three months follow-up	*P* value
Hemodynamic variables			
LVEF (%)	42 (8)	50 (9)	< 0.001
Aortic blood flow (mL/s)	17.88 (5.25)	21.20 (3.15)	0.130
Indexed cardiac output (L/min/m^2)	2.70 (0.83)	2.60 (0.71)	0.600
Heart rate (bpm)	70 (61—82)	60 (52—67)	0.001
E/A	1.06 (0.88—1.55)	1.46 (1.13—1.58)	0.770
E/E′	8.69 (4.20)	8.44 (2.76)	0.540
Systolic blood pressure (mmHg)	117 (107—127)	138 (125—153)	< 0.001
Diastolic blood pressure (mmHg)	71 (65—84)	84 (72—89)	0.150
Retinal microvascular parameters			
FAZ (mm^2)	0.21 (0.07)	0.22 (0.07)	0.390
Inner vessel density (length, mm^{-1})	18.62 (2.79)	19.64 (1.04)	0.210
Total vessel density (length, mm^{-1})	17.58 (2.70)	18.52 (1.09)	0.250
Inner perfusion density (area, unitless)	0.36 (0.29—0.38)	0.36 (0.35—0.38)	0.770
Total perfusion density (area, unitless)	0.32 (0.05)	0.34 (0.02)	0.180

Continuous variables are presented as mean (SD) or median (IQR) depending on their distribution. bpm: beats per minute; LVEF: left ventricular ejection fraction; FAZ: foveal avascular zone; E/A: early to late transmitral flow velocity; E/E′: early mitral annular velocity.

Results

Overall, 45 patients were included in the prospective pilot study. At the 3-month follow-up visit, 33 patients had the comprehensive ophthalmic and cardiac examination. Finally, retinal vessel density for both consultations was kept for 30 patients (no segmentation abnormality and signal strength > 7/10). Complementary hemodynamic evaluation with the FINAPRES® NOVA system was performed in 23 patients. The median (IQR) age was 64 (55—71) years with 87% men (eTable in the supplement). At admission, the mean (SD) LVEF was 53% (11) and the mean indexed cardiac output was 2.70 (0.83) L/min/m^2 (Table 1). On OCT-A, the mean inner retinal vascular density was 19.09 (2.80) mm^{-1}. At the 3-month follow-up visit, there was no significant difference for LVEF (55% [7], $P = 0.13$) and indexed cardiac output (2.60 [0.71] L/min/m^2, $P = 0.60$) compared with baseline. Moreover, there was no significant change concerning inner retinal vessel density between admission and the 3-month follow-up visit ($P = 0.29$). No significant association was found between the retinal vessel density and hemodynamic variables measured by the FINAPRES®

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Table 3 Correlation between retinal vascular density and hemodynamic variables of patients with acute coronary syndrome at admission and at 3 months follow-up, $n = 30$.

	Retinal vascular density at admission		Retinal vascular density at 3 months follow-up	
	Correlation coefficient (r)	P value	Correlation coefficient (r)	P value
Hemodynamic variables				
LVEF (%)	0.172	0.160	0.051	0.790
Aortic blood flow (mL/s)	0.093	0.460	−0.126	0.520
Indexed cardiac output (L/min/m^2)	0.164	0.180	0.185	0.350
Heart rate (bpm)	0.165	0.190	−0.455	0.017
E/A	0.128	0.300	0.030	0.880
E/E′	0.174	0.160		
Systolic blood pressure (mmHg)	0.102	0.410	0.094	0.630
Diastolic blood pressure (mmHg)	0.259	0.033	0.171	0.380

Correlations presented are Spearman correlation. bpm: beats per minute; LVEF: left ventricular ejection fraction; E/A: early to late transmitral flow velocity; E/E′: early mitral annular velocity.

(data not shown). In the subgroup of patients with impaired LVEF (< 50%, $n = 13$) at admission, there was no significant change in retinal vessel density even though a significant improvement in LVEF was observed at the 3-month follow-up (Table 2). Finally, no significant correlation was found between acute or chronic hemodynamic variables and retinal vessel density (baseline and at 3 months follow-up) (Table 3).

Discussion

In this pilot study, we found no significant association between retinal vessel density and cardiac hemodynamic variables, including cardiac output as estimated by echocardiography or with FINAPRES®.

Few studies focused on the variations in retinal microvasculature on OCT-A with systemic hemodynamic modifications. In contrast to our results, variations of retinal microvascularisation on OCT-A were assessed in healthy subjects, before and after physical exercise [17,18]. These contradictory results could be explained by the difference in the study population. Furthermore, we assessed chronic hemodynamic modifications and not transient evolution after a physical exertion.

Our results suggest that retinal hemodynamic is self-regulated and independent from systemic circulation. In fact, local self-regulation of ocular blood flow makes it possible to maintain a constant supply of oxygen and nutrients despite normal range variations in hemodynamic status. Changes in arteriolar diameter are controlled by vasoactive molecules in the endothelium of retinal capillaries [19]. As a result, the association found in the EYE-MI study between impaired LVEF and decreased retinal vessel density would not be related to a decrease in retinal blood flow by defeating self-regulation processes. The mechanism underlying the relation between retinal vessel density and LVEF is unclear based on the present data. However, impaired coronary microvasculature in patients with reduced retinal vascular density could lead to larger infarct size and thus to lower LVEF, as suggested by the higher troponin peak release in the low retinal vascular density group of the EYE-MI study [4,20]. This hypothesis is consolidated by results in the subgroup with initial altered LVEF. Despite a significant improvement of the LVEF after cardiac revascularisation and rehabilitation, we did not find any significant change in the retinal vascular density on OCT-A. These results might support the thesis that in high cardiovascular risk profile patients, OCT-A could provide an insight of the long-term microvascularisation abnormalities and not hemodynamic modifications. Future studies should be carried out to investigate the association between decreased retinal vessel density and impaired coronary microstructure.

We acknowledge limitations to this study. Firstly, we included only patients with a relatively stable hemodynamic status compatible with ophthalmologic examination, so these results cannot be extrapolated to more severe hemodynamic impairments. Secondly, since this study was a pilot study, only a limited number of participants were included, thus limiting the value of the findings. Thirdly, we were not able to measure vessel density in the deep capillary plexus on OCT-A and on larger samples (such as 6×6 mm or 12×12 mm scans) with the version of the angiography software. This limitation should be addressed in future studies.

Conclusion

We found no significant association between retinal vessel density on OCT-A and hemodynamic variables, suggesting that retinal self-regulation compensates for mild and moderate changes in cardiac output. Moreover, OCT-A measurements were stable between the acute phase of ACS and after 3 months follow-up, which supports the hypothesis of a chronic microvascular process and excludes the role of acute hemodynamic alterations on retinal vascular density

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values. Further work is needed to clarify the chronological association between altered retinal microvascularisation and systemic microvascularisation and to confirm the prognostic value of retinal biomarkers.

Statement of ethics

The research was conducted ethically in accordance with the World Medical Association Declaration of Helsinki.

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Disclosure of interest

The authors declare that they have no competing interest.

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