Université de Bourgogne
UFR des Sciences de Santé
Circonscription Médecine

ANNEE 2017

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ÉTUDE DE COHORTE PROSPECTIVE ÉVALUANT LES PARAMÈTRES VASCULAIRES RÉTINIENS EN ANGIOGRAPHIE-OCT AU SEIN D'UNE POPULATION DE PATIENTS HOSPITALISÉS POUR SYNDROME CORONARIEN AIGU.

THESE

Présentée

à l'UFR des Sciences de Santé de Dijon
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et soutenue publiquement le 23/05/2017

pour obtenir le grade de Docteur en Médecine

Par M.AZEMAR Arthur

Né(e) le 30/03/1987

A Narbonne (Aude-11)

Université de Bourgogne
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AVERTISSEMENT

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SERMENT D'HIPPOCRATE

"Au moment d'être admis(e) à exercer la médecine, je promets et je jure d'être fidèle aux lois de l'honneur et de la probité.

Mon premier souci sera de rétablir, de préserver ou de promouvoir la santé dans tous ses éléments, physiques et mentaux, individuels et sociaux.

Je respecterai toutes les personnes, leur autonomie et leur volonté, sans aucune discrimination selon leur état ou leurs convictions.

J'interviendrai pour les protéger si elles sont affaiblies, vulnérables ou menacées dans leur intégrité ou leur dignité.

Même sous la contrainte, je ne ferai pas usage de mes connaissances contre les lois de l'humanité.

J'informerai les patients des décisions envisagées, de leurs raisons et de leurs conséquences.

Je ne tromperai jamais leur confiance et n'exploiterai pas le pouvoir hérité des circonstances pour forcer les consciences.

Je donnerai mes soins à l'indigent et à quiconque me les demandera.

Je ne me laisserai pas influencer par la soif du gain ou la recherche de la gloire.

Admis(e) dans l'intimité des personnes, je tairai les secrets qui me seront confiés. Reçu(e) à l'intérieur des maisons, je respecterai les secrets des foyers et ma conduite ne servira pas à corrompre les mœurs.

Je ferai tout pour soulager les souffrances. Je ne prolongerai pas abusivement les agonies. Je ne provoquerai jamais la mort délibérément.

Je préserverai l'indépendance nécessaire à l'accomplissement de ma mission. Je n'entreprendrai rien qui dépasse mes compétences. Je les entretiendrai et les perfectionnerai pour assurer au mieux les services qui me seront demandés.

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Que les hommes et mes confrères m'accordent leur estime si je suis fidèle à mes promesses ; que je sois déshonoré(e) et méprisé(e) si j'y manque."

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Listes des abréviations

OCT-A : Angiographie OCT

ZAC : Zone avasculaire centrale

SCA : Syndrome coronarien aigu

STEMI : Syndrome coronarien aigu avec sus décalage du segment ST

NSTEMI : Syndrome coronarien aigu sans sus décalage du segment ST

RIC0 : Registre des infarctus de Côte d'Or

IEC : Inhibiteurs de l'enzyme de conversion

ARA2 : Antagonistes des récepteurs de l'angiotensine 2

HBA1c : Hémoglobine glyquée

FEVG : Fraction d'éjection ventriculaire gauche

DVB : Densité vasculaire basse

DVH : Densité vasculaire haute

FC : Fréquence cardiaque

TAS : Tension artérielle systolique

TAD : Tension artérielle diastolique

1-Introduction

Microcirculation anomalies play a determinant role in processes leading to the development of ischemic coronary heart disease. Retinal microvascularization, which is easy to assess using non-invasive imaging examinations, seems to have the same physiological and anatomical characteristics as cerebral and coronary microvascularization [1]. In addition, the development of semi-automatic imaging analysis software provides a precise and reproducible quantitative description of the retinal microvascular network using fundus photographs (vascular caliber, vascular tortuosity and notably the fractal dimension). A certain number of studies involving large population cohorts have attempted to understand what factors contributed to the development of retinal microangiopathy and its link with the onset of cardiovascular events [2].

For example, the recent study of S. Seidelmann published in Circulation in 2016, included 10,470 men and women with no history of cardiovascular disease or heart failure in whom a quantitative analysis of retinal vascular parameters was done [3]. After a mean follow-up of 16 years, the authors reported 1,779 coronary events, 548 ischemic strokes, 1,395 episodes of heart failure, and 2793 deaths. Retinal arteriole narrowing and retinal vein widening were associated with an increased long-term risk of death and ischemic stroke in both sexes and coronary heart disease in women. Moreover, the authors showed that the caliber of retinal arteries and veins made it possible to reclassify 21% of women initially classified as minimum cardiovascular risk (<5%) as moderate cardiovascular risk (>5%) [3].

The meta-analysis of McGeechan included 22,159 participants without coronary heart disease with a follow-up from 5 to 14 years. It showed that the changes in retinal vessel caliber were independently associated with an increased risk of major cardiovascular events but only in women [4][5].

From a pathophysiological point of view, N Cheung et al. showed a significant association between retinal arteriole narrowing and concentric ventricular remodeling independently of classical cardiovascular risk factors in a population without cardiovascular history[6]. In addition, N Cheung et al. found a similar association between retinal arteriole caliber and aortic stiffness. These different studies suggest that the retinal vascularization may

reflectsystemic microvascular modifications [7].

Given the above, retinal vascularization could constitute an inexpensive, non-invasive and quickly-determined biomarker that provides information beyond current recommendations to predict the risk of cardiovascular events.

The evaluation of retinal microvascularization was recently marked by the emergence of a new imaging technique: Optical Coherence Tomography - Angiography (OCT-A) [8]. This quick, non-invasive technique for the acquisition and analysis of vascular flow makes it possible to visualize the retinal capillary plexus and to measure retinal vascular density and the area of the foveal avascular zone. Unlike fluorescein angiography, which was until now the only examination to allow the visualization of retinal vessels and to assess the quality of blood-retinal barrier, OCT-A does not require the injection of a contrast agent. This new approach, which is based on a hemodynamic analysis of blood flow, detects the movement of erythrocytes [9]. The comparison between the OCT signal from moving cells and that from static tissue generates a contrast making it possible to model retinal vascularization thanks to a decorrelation algorithm. OCT-A thus allows a three-dimensional anatomical and functional analysis of retinal microvascularization. In addition, this technique allows a quantitative evaluation of vascular parameters, such as retinal vascular density, which were until now impossible to measure non-invasively.

To date few studies have measured retinal vascular density and the area of the foveal avascular zone using OCT-A and these have been conducted only in healthy subjects (creation of reference data according to age) and in diabetic patients [10][11].

As far as we know, no studies have investigated retinal microvascularization by measuring retinal vascular density and the area of the foveal avascular zone in a population of patients presenting with acute coronary syndrome.

In a population of patients hospitalized for acute coronary syndrome, the principal aim of our study was to determine the parameters associated with altered retinal microvascularization. The secondary objectives of this study were to:

a. Determine the feasibility and the quality of analysis using OCT-A,
b. Analyze and characterize perifoveal retinal vascular density, and the area of the foveal avascular zone.

2-Methods

2.1 Design and population of the study

Our study was a pilot prospective transversal single-center study conducted at the cardiology intensive care unit of Dijon University Hospital from 01/10/2016 to 31/12/2016.

Patients hospitalized for acute coronary syndrome (ACS), with or without ST-segment elevation, who underwent an examination of the retina using OCT-A on the second day of their hospitalization were included.

The non-inclusion criteria were: an ophthalmological history with retinal involvement (diabetic retinopathy, vascular and degenerative diseases of the macula), patients under 18 years of age, those under guardianship, those without national health insurance and those who refused to take part.

Patients were provided with clear accurate and appropriate information on the nature of the examination that was to be done and signed a consent form.

During the ophthalmological consultation and OCT-A, patients' heart rhythm and hemodynamic status were monitored by a cardiologist.

2.2 Data collection

All of the data for the included patients were extracted from medical records and observation sheets of the 'Observatoire des Infarctus de Côte d'Or (RICO).

Since its creation on the 1st January 2001, RICO has collected all of the data relative to patients hospitalized for myocardial infarction in the six cardiology intensive care units of the Côte d'Or, a part of Burgundy: Dijon University Hospital, the Clinic of Fontaine-Les-Dijon and the hospitals of Beaune, Semur en Auxois, Montbard and Chatillon sur Seine. Each patient provided written informed consent before inclusion in the RICO registry.

The collected cardiovascular risk factors were: age, sex, arterial hypertension, diabetes, obesity (body mass index greater than 30kg/m^2), treated hypercholesterolemia or un total cholesterol >2.5 g/l, family history of coronary heart disease (CHD) (premature CHD in at

least one first-degree relative aged 55 years for men or 65 years for women) current smoking. The following were also collected: cardiovascular history (history of ischemic CHD, carotid atheroma and peripheral artery disease), a history of chronic kidney failure, les treatment with beta-blockers and angiotensin converting enzyme inhibitors (ACE)/ angiotensin receptor 2 antagonists (ARA2), systolic and diastolic arterial pressure, the heart rate, glycemia, glycated hemoglobin (HbA1c), full lipid profile, NT-pro-BNP, peak troponin, creatinine and creatinine clearance (MDRD method). Treatments with beta-blockers and ACE/ARA2 expressed as a percentage of the maximal dose were recorded on the second day of the hospitalization and at discharge from hospital. Arterial pressure and heart rate were recorded on admission, on the first and second day of hospitalization and at discharge from hospital whereas biological parameters (apart from peak troponin) were only measured at admission.

From the above data, the cardiovascular risk scores defined by the American Heart Association (AHA risk score) and by the European Society of Cardiology for a moderate risk population (Score risk) were calculated. The AHA risk score included age, sex, the ethnic origin, the history of arterial hypertension and diabetes, active smoking, the systolic and diastolic arterial pressure, levels of total cholesterol and HDL cholesterol [12]. The Score risk included age, sex, active smoking, systolic arterial pressure and the total cholesterol level [13].

The left ventricular ejection fraction (LVEF) was measured in the 24 hours following admission, by an experienced operator, according to Simpson's biplane method of disks [14].

The anatomic Syntax score, a risk stratification score for coronary lesions (length, bifurcation, diffuse disease, calcifications, thrombus, total occlusion) was determined for all of the patients who underwent coronarography to establish the initial SYNTAX score and the residual SYNTAX score after revascularization [15].

We also calculated the Grace score at admission to evaluate the ischemic risk for each patient and his/her prognosis by calculating the probability of in-hospital and 6-month mortality [16].

2.3 Measurement of perifoveal retinal vascular density and area of the foveal avascular zone by OCT-A

Perifoveal retinal vascular density and the area of the foveal avascular zone were measured at the level of the superficial capillary plexus of the retina by OCT-A using automatic quantitative analysis software: Carl Zeiss Meditec AG, Cirrus HD-OCT software Angioplex v10.0.

Vascular density was measured in each sector (superior, inferior, temporal and nasal) of superficial capillary plexus of the retina. It corresponded to the percentage of the zone occupied by the lumen of retinal vessels in the studied sector. Perifoveal retinal vascular density was the mean of the vascular densities of each sector of the retina.

The OCT-A images obtained during the ophthalmological examination were selected according to the following procedure: given the good correlation between the vascular characteristics of both eyes, a single eye was retained for the analysis: the image of the right eye for the first patient and the image of the left eye for the second patient, if images were of equivalent quality, and so on for the following patients. If the patient had only one eye, the image of the remaining eye was used. If one of the two images was impossible to interpret, the image of the other eye was used. Only images with a signal strength > 7/10 were retained.

2-4 Groups of patients

In our population, in the absence of any reference or standard concerning perifoveal retinal vascular density, it was analyzed in tertiles. The first tertile corresponded to the lowest retinal vascular densities and the third tertile corresponded to the highest retinal vascular densities.

Patients with a retinal vascular density in the first tertile were included in the « low vascular density » group and those with a retinal vascular density in the second and third tertiles were included in the « high vascular density» group.

2-5 Statistical analysis

Dichotomic variables were expressed as n (%) and continuous variables as medians

(interquartile range) as the distribution of these variables were not normally distributed according to the Kolmogorov-Smirnoff test. For comparisons of categorical data, a chi2 test or Fischer's exact test was used, and for comparisons of continuous data a Mann-Whitney test was used. The threshold for significance was set at 5%.

A multivariate analysis (backwards elimination) was done to predict low vascular density from significantly predictive variables in univariate analysis, with an inclusion threshold of 5%.

SPPS version 22(IBM Inc, USA) was used for the analyses.

3-Results

3-1 Population

Among the 309 patients hospitalized for acute coronary syndrome in the cardiology intensive care unit between 01/10/2016 and 31/12/2016, 211 patients had their retinas examined by OCT-A on the 2nd day of hospitalization.

Compared with the 98 patients not included in the EYE-MI study (mainly because the OCT-A apparatus was not available, hemodynamic instability or early transfer to another hospital after the ACS), the 211 patients who underwent the OCT angiography were significantly younger (64+/-13 vs 74+/-13, p<0.001), had a lower GRACE score (135+/-38 vs 164+/-34, p<0.001), were more often men (77% vs 63%, p=0.004), were less often diabetic (23 vs 36%, p=0.019) and less often hypertensive (55 vs 70%, p=0.009).

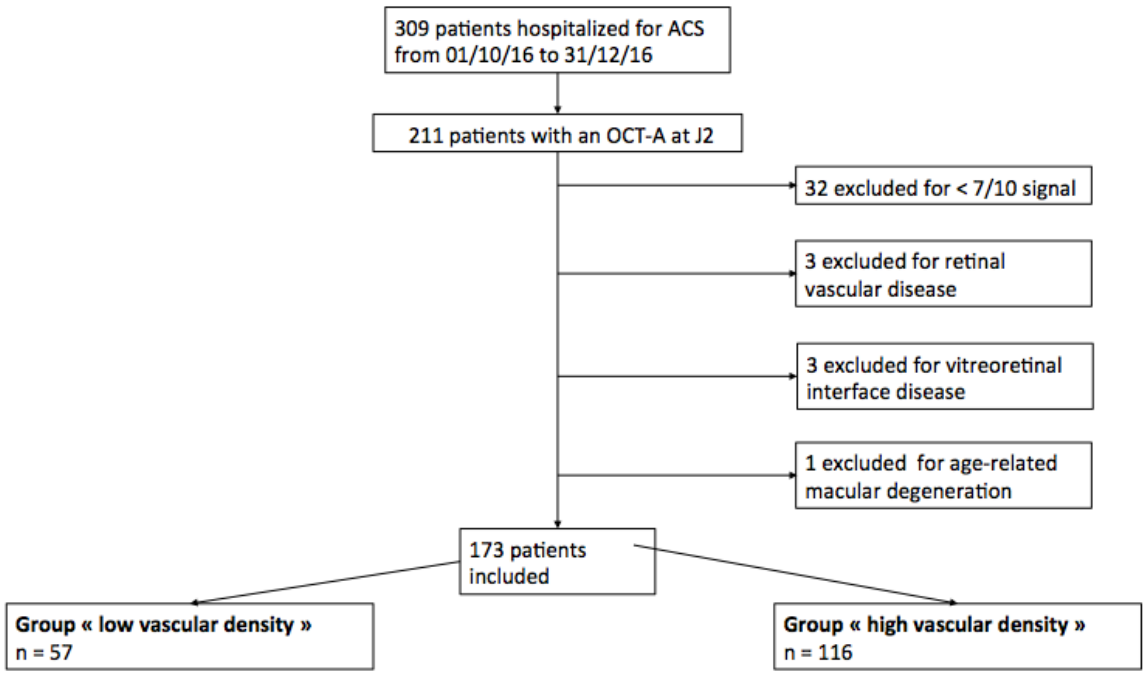
Thirty-two patients were excluded because of poor quality signals (<7/10); three patients were excluded because of the presence of retinal vascular disease; (Occlusion of the central vein of the retina and occlusion of the central artery of the retina), three patients were excluded for a disease of the vitreoretinal interface and one patient because of severe age-related macular degeneration (Figure 1). Indeed, these ophthalmological diseases prevent high-quality OCT segmentation and thus make reliable vascular analysis impossible.

Compared with the 32 patients excluded from the EYE-MI study, the 173 patients analyzed were significantly younger (62+/-13 vs 72+/-12, p<0.001) and had a lower GRACE score (130+/-36 vs 156+/-42, p<0.001). The remaining baseline characteristics were comparable.

Thus OCT-A analysis on at least one eye was done in 82% of the initially eligible patients.

Among the 173 analyses, the mean vascular density was 19,8% and patients were assigned to one of two groups: 57 patients in the « low vascular density » group (LVD) (1st tertile); and 116 patients in the « high vascular density» group (HVD) (2nd and 3rd tertiles) (Figure 1).

Figure1: Flow Chart.



3-2 Characteristics of patients

The median age of the population analyzed was 62 years and the study population included 79% of men.

Table 1 presents the cardiovascular characteristics at inclusion of the overall population and of the two 2 groups.

Patients of the « LVD » group were significantly older than patients of the « HVD » group (70.62 years (63.46-78.36)) vs 59.44 years (49.58-66.43), p<0.001).

Moreover, patients in the « LVD » group presented a significantly greater percentage of arterial hypertension, diabetes and of chronic kidney failure than did patients in the « HVD » group: 65% vs 45% (p=0.013); 37% vs 16% (p=0.002), and 9% vs 2% (p=0.040) (Table 1) respectively.

The AHA and European Society of Cardiology risk scores were significantly higher in patients in the « LVD » group than in patients in the « HVD » group: 26.20 (16.40-35.40) vs 9.35 (6.05-18.95) (p<0.001) and 4.00 (2.00-5.00) vs 2.00 (1.00-4.00) (p<0.001) (Table 1), respectively.

Table 1: Cardiovascular risk factors and of vascular risk scores of the overall population and in the two groups according to the retinal vascular density measured by OCT-A on the 2nd day after an acute coronary syndrome.

n (%), median (interquartile range)	Overall study population n=173	Low vascular density group: 1st tertile (n=57)	High vascular density group: 2nd and 3rd tertiles (n=116)	P LVD vs HVD
CARDIOVASCULAR RISK FACTORS				
Age, years	**62.16 (51.82-70.07)**	**70.62 (63.46-78.36)**	**59.44 (49.58-66.43)**	**<0.001**
Sex female, n (%)	36 (21)	11 (19)	25 (22)	0.73
Arterial hypertension, n (%)	**89 (51)**	**37 (65)**	**52 (45)**	**0.013**
Diabetes, n (%)	**39 (23)**	**21 (37)**	**18 (16)**	**0.002**
Active smoking, n (%)	**72 (42)**	**16 (28)**	**56 (48)**	**0.011**
BMI, m^2/kg	27 (24-30)	27 (25-30)	26 (24-30)	0.71
Hypercholesterolemia, n (%)	75 (43)	23 (40)	52 (45)	0.58
Family history of CHD, n (%)	59 (34)	17 (29)	42 (36)	0.40
AHA risk score	**13.60 (7.60-26.50)**	**26.20 (16.40-35.40)**	**9.35 (6.05-18.95)**	**<0.001**
Score risk	**2.00 (1.00-4.00)**	**4.00 (2.00-5.00)**	**2.00 (1.00-4.00)**	**<0.001**
OTHER HISTORY				
History of ischemic coronary heart disease, n (%)	40 (23)	14 (25)	26 (22)	0.75
History of carotid atheroma, n (%)	7 (4)	4 (7)	3 (3)	0.22
History of peripheral artery disease, n (%)	9 (5)	6 (11)	3 (3)	0.061
History of chronic kidney failure, n (%)	**7 (4)**	**5 (9)**	**2 (2)**	**0.040**

Concerning data for the acute phase of the coronary syndrome, systolic arterial pressure at admission and at discharge were significantly higher in the « LVD » group than in the « HVD » group (151 (130-171) vs 133 (115-165), p=0.004; 125.00 (110.00-139.00) vs 116.50 (107.00-132.00) p=0.030, respectively) (Table 2) even though there were no significant differences in terms of antihypertensive treatments (beta-blockers and IEC/ARA2) between the two groups (Table 4).

Moreover, on admission, patients in the « LVD » group had significantly lower creatinine clearance levels (82.44 ml/min/m^2 (64.40-97.54) vs 90.95 (75.39-106.53), p=0.011), significantly higher NT-pro-BNP levels (824 pg/ml (259-3421) vs 200 (82-706), p<0.001) and significantly higher glycemia (6.66 mmol/l (5.61-9.32) vs 6.22 (5.12-7.49), p=0.020) than

did patients in the « HVD » group (Table 3).

Finally, on admission, patients in the « LVD » group presented a significantly lower left ventricular ejection fraction than did patients in the « HVD » group (50% (40-60) vs 55% (50-60), p=0.010). The admission Grace score and Syntax score were significantly higher in the « LVD » group than in the « HVD » group (146 (125-170) vs 123 (97-143), p<0.001 and 11.8 (7.0-19.0) vs 8.0 (3.0-14.5), p=0.015 respectively) (Table 2).

The area of the foveal avascular zone was significantly greater in the « LVD » group than in the « HVD » group (0.32 mm^2(0.25-0.41) vs 0.25 mm^2(0.18-0.34), p=0.001).

Mean perifoveal retinal vascular density was 16.7% in the « LVD » group and 20.7% in the « HVD » group (p<0.001) (Table 5 and Figure 2). (Table 5).

Table 2: Clinical characteristics of the overall population and in the two groups according to retinal vascular density measured by OCT-A on the 2nd day after an acute coronary syndrome.

n (%), median (interquartile range)	**Total (n=173)**	**Low vascular density group: 1st tertile (n=57)**	**High vascular density group: 2nd and 3rd tertiles (n=116)**	**P LVD vs HVD**
ACS				0.79
STEMI, n (%)	60 (35)	19 (33)	41 (35)	
NSTEMI, n (%)	113. (65)	38 (67)	75 (65)	
GRACE Score	**128 (102-153)**	**146 (125-170)**	**123 (97-143)**	**<0.001**
GRACE Score >140, n (%)	**66. (38)**	**32 (56)**	**34 (29)**	**0.001**
LVEF on admission, %	**55 (45-60)**	**50 (40-60)**	**55 (50-60)**	**0.010**
LVEF on admission <45%, n (%)	**26. (15)**	**17 (30)**	**9 (8)**	**<0.001**
HR on admission, bpm	**71 (64-83)**	**76 (66-90)**	**70 (63-81)**	**0.019**
SAP on admission, mmHg	**140 (119-167)**	**151 (130-171)**	**133 (115-165)**	**0.004**
DAP on admission, mmHg	81 (70-92)	82 (75-89)	80 (68-92)	0.39
HR at D1, bpm	70.00 (61.00-79.00)	69.00 (63.00-78.00)	70.50 (60.00-79.00)	0.65
SAT at D1, mmHg	121.00 (108.00-132.00)	123.00 (111.00-140.00)	120.00 (108.00-129.00)	0.061
DAP at D1, mmHg	71.00 (63.00-80.00)	70.00 (63.00-82.00)	71.00 (61.50-79.00)	0.88
HR at D2, bpm	70.00 (60.00-78.00)	70.00 (62.00-79.00)	69.50 (59.00-78.00)	0.29
SAP at D2, mmHg	118.00 (108.00-130.00)	121.00 (112.00-134.00)	117.00 (107.00-128.50)	0.10
DAP at D2, mmHg	71.00 (62.00-80.00)	73.00 (63.00-78.00)	70.50 (62.00-81.50)	0.71
HR at discharge, bpm	66.00 (61.00-73.00)	67.00 (61.00-74.00)	66.00 (60.00-73.00)	0.53
SAP at discharge, mmHg	**118.00 (108.00-134.00)**	**125.00 (110.00-139.00)**	**116.50 (107.00-132.00)**	**0.030**
DAP at discharge, mmHg	72.00 (64.00-80.00)	74.00 (67.00-82.00)	71.00 (61.50-79.50)	0.18
Syntax Score	**9.5 (4.5-15.5)**	**11.8 (7.0-19.0)**	**8.0 (3.0-14.5)**	**0.015**
Syntax Score >4, n (%)	**74 (43)**	**30 (94)**	**44 (71)**	**0.015**

Table 3: Biological characteristics of the overall population and in the two groups according to retinal vascular density measured by OCT-A on the 2nd day after an acute coronary syndrome.

n (%), median (interquartile range)	Total (n=173)	Low vascular density group: 1st tertile (n=57)	High vascular density group: 2nd and 3rd tertiles (n=116)	P LVD vs HVD
Peak troponin>100ULN	74	29 (52)	45 (39)	0.11
Creatinine (micromol/l)	**78 (68-92)**	**81 (72-104)**	**76 (64-88)**	**0.030**
Creatinine clearance (MDRD)	**87.92 (72.42-103.82)**	**82.44 (64.40-97.54)**	**90.95 (75.39-106.53)**	**0.011**
Creatinine clearance <60 ml/min/m2 , n (%)	**21. (12)**	**11 (19)**	**10 (9)**	**0.043**
Hb1Ac >6.5 %, n (%)	26. (15)	12 (23)	14 (13)	0.14
NT-pro BNP, pg/ml	**334 (100-1223)**	**824 (259-3421)**	**200 (82-706)**	**<0.001**
LDL cholesterol, mmol/l	**3.09 (2.23-3.98)**	**3.00 (2.00-3.45)**	**3.19 (2.45-4.00)**	**0.042**
HDL cholesterol, mmol/l	1.15 ± 0.31	1.15 ± 0.29	1.15 ± 0.33	0.54
Glycemia on admission, mmol/l	**6.41 (5.23-8.13)**	**6.66 (5.61-9.32)**	**6.22 (5.12-7.49)**	**0.020**

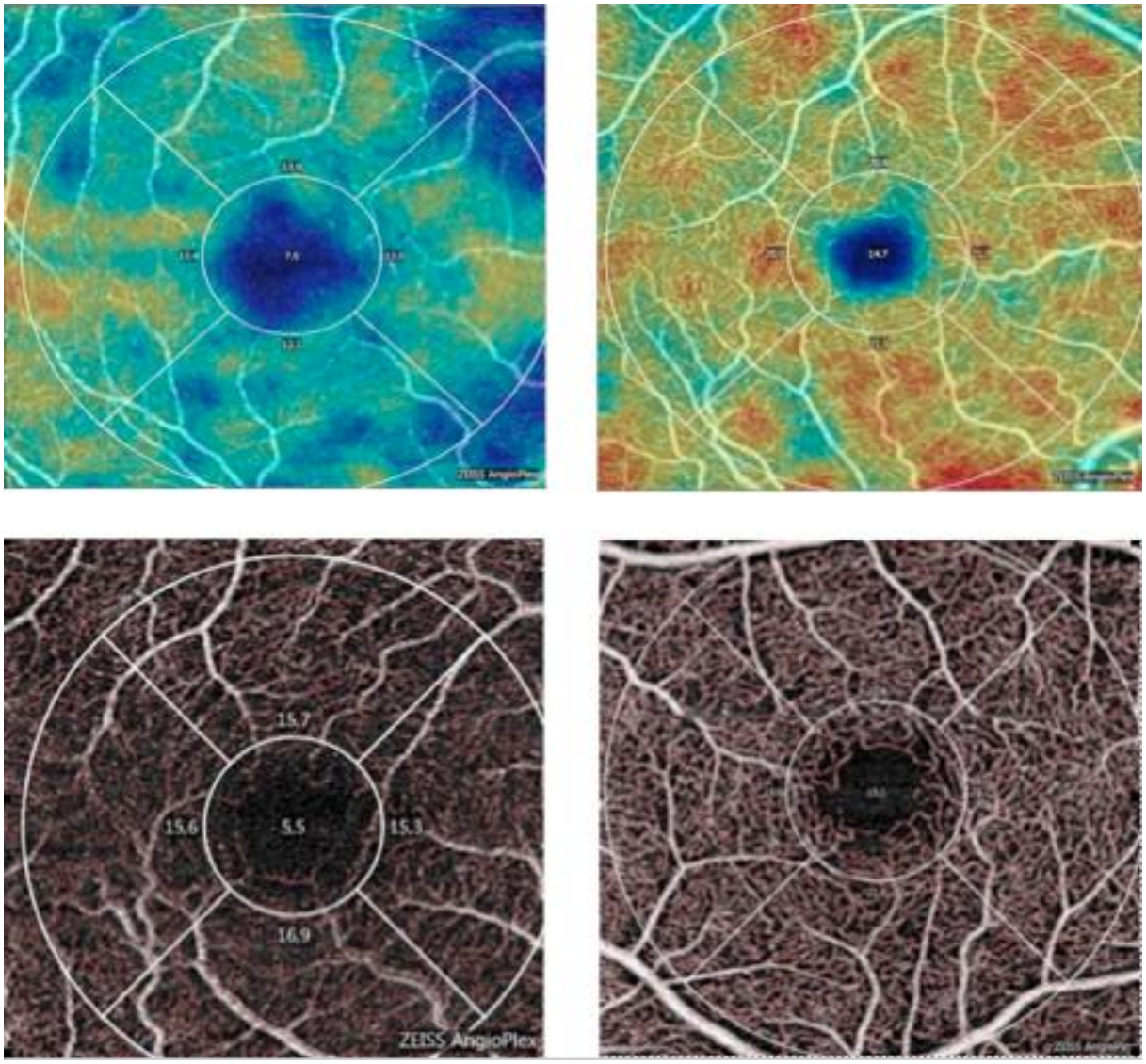
Table 4: Treatments administered in overall population and in the two groups according to the retinal vascular density measured by OCT-A on the 2nd day after an acute coronary syndrome.

n (%), median (interquartile range)	Total (n=173)	Low vascular density group: 1st tertile (n=57)	High vascular density group: 2nd and 3rd tertiles (n=116)	P LVD vs HVD
% of the theoretical maximal dose of beta-blockers at D2	25 (13-50)	25 (13-50)	25 (0-38)	0.83
% of the theoretical maximal dose of beta-blockers at discharge	25 (13-50)	25 (13-50)	25 (13-50)	0.55
% of the theoretical maximal dose of ACE-I or ARA2 at D2	20 (13-40)	20 (13-40)	20 (13-25)	0.75
% of the theoretical maximal dose of ACE-I or ARA2 at discharge	20 (13-40)	20 (13-40)	20 (13-40)	0.24

Table 5: Ophthalmological characteristics measured by OCT-A of the overall population and in the two groups on the 2nd day after an acute coronary syndrome.

n (%), median (interquartile range)	**Total (n=173)**	**Low vascular density group: 1st tertile (n=57)**	**High vascular density group: 2nd and 3rd tertiles (n=116)**	**P LVD vs HVD**
Area of the foveal avascular zone (mm²)	0.26 (0.18-0.35)	**0.32 (0.25-0.41)**	**0.25 (0.18-0.34)**	**0.001**
Retinal vascular density, (%)				
Temporal quadrant, (%)	**19.8 (18.0-21.0)**	**17.4 (15.4-18.4)**	**20.7 (19.8-21.4)**	**<0.001**
Nasal quadrant, (%)	**19.9 (17.8-21.2)**	**17.0 (15.0-18.0)**	**20.8 (19.8-21.7)**	**<0.001**
Superior quadrant, (%)	**19.5 (17.5-20.9)**	**15.7 (14.8-17.7)**	**20.4 (19.5-21.5)**	**<0.001**
Inferior quadrant, (%)	**19.9 (18.0-21.4)**	**16.8 (14.7-18.0)**	**20.7 (19.7-21.9)**	**<0.001**
Perifoveal zone (mean of 4 quadrants), (%)	**19,8 (17,8-21,1)**	**16,7 (15,0-18,0)**	**20,7 (19,7-21,6)**	**<0.001**

Figure 2: Images obtained by OCT-A:



Patient number 210, « LVD » group

Patient number 10, « HVD » group

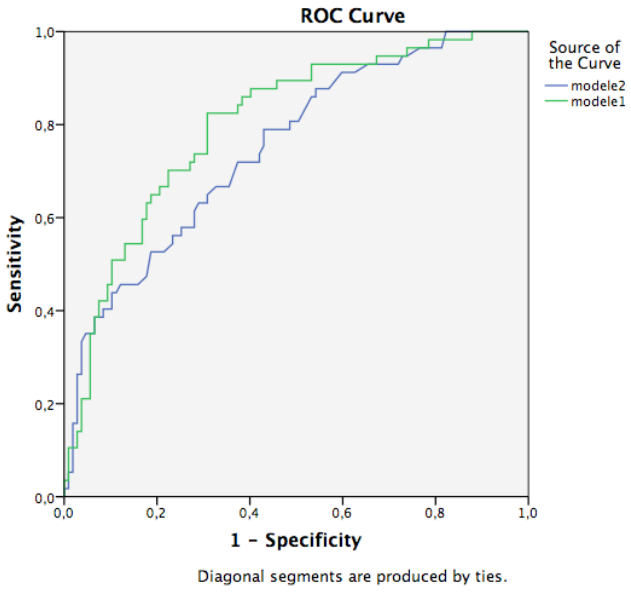
3-3 Multivariate analysis and Spearman correlation

The factors significantly associated with low vascular density (and not collinearity) in univariate analysis were included in the multivariate analysis. Two models were created:

Model 1 included the AHA score, creatinine clearance, LVEF and the Syntax score, while model 2 included the Score risk, creatinine clearance, LVEF and the Syntax score.

The predictive performance of model 1 (AUC 0.80 (0.67-0.83), p<0.001,-2 log likelihood 168, Cox and Sneel R^2 0.22, Nagelkerke R^2 0.31, Hosmer and Lemeshow 7.45 to 8 ddl, p 0.489) was superior to that of model 2 (AUC 0.75(0.67-0.83), p<0.001,-2 log likelihood 181, Cox and Sneel R^2 0.19, Nagelkerke R^2 0.26, Hosmer and Lemeshow 4.8 to 8 ddl, p 0.78). Model 1 was thus retained for the definitive analyses (Figure 3).

Figure 3: Predictive performance of multivariate models 1 and 2.



In multivariate analysis, two factors were significantly associated with the lowest tertile of retinal vascular density measured by OCT-A:

- the left ventricular ejection fraction at admission with an OR (95%CI) of 0.95(0.92-0.98) per percentage point of LVEF (p=0.002).

- the AHA risk score with an OR (95%CI) of 1.07(1.04-1.10) by point of AHA score (p<0.001).

This association between the AHA risk score and retinal vascular density in this population was confirmed by the strong Spearman correlation (R=-0.54, p<0.001) (Figure 4).

The other parameter measured by OCT-A, the diameter of the foveal avascular zone of the retina, also showed a correlation with the cardiovascular risk of patients and notably the AHA score, but the correlation was less marked than that for retinal vascular density (R=0.24, p=0.002), (Figure 5).

Figure 4: Diagram showing the correlation between perifoveal retinal vascular density and the AHA risk score

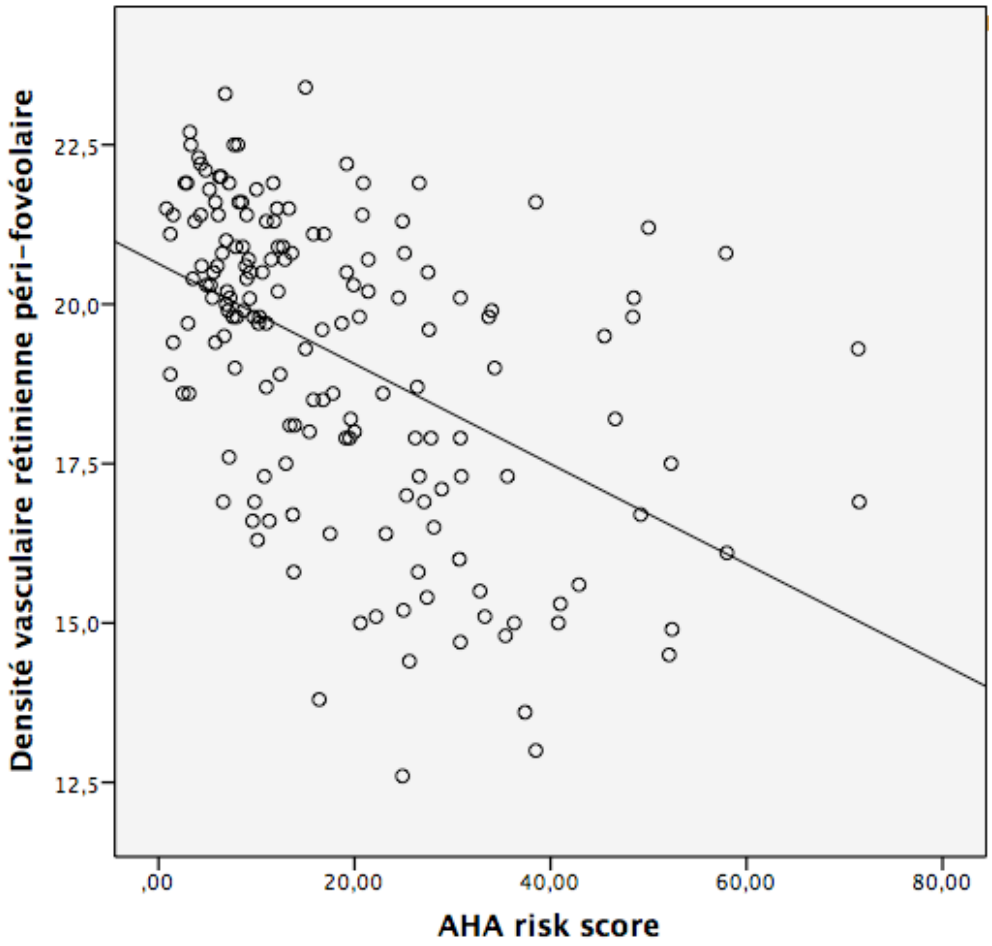
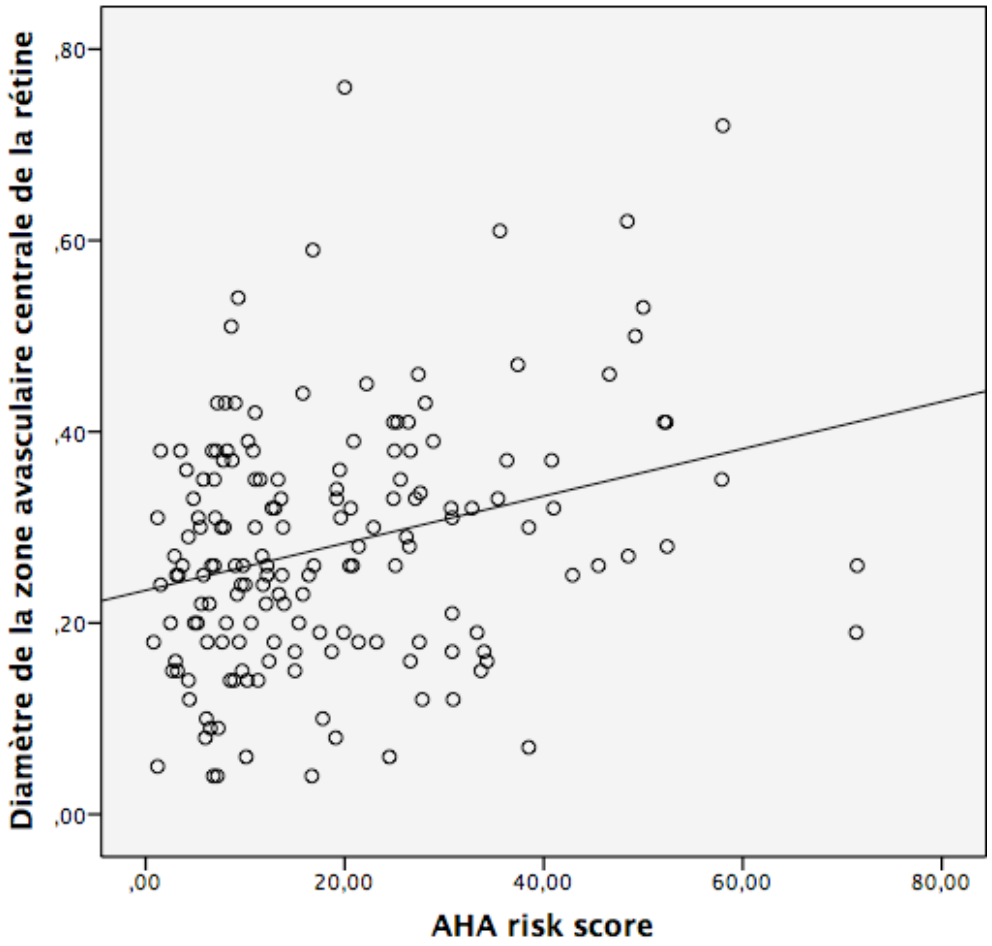


Figure 5: Diagram showing the correlation between the diameter of the foveal avascular zone of the retina and the AHA risk score



4- Discussion

The principal results of our work are:

1) that the analysis of perifoveal retinal vascular density by OCT-A is feasible in patients hospitalized for ACS, and that more than 82% of examinations were suitable for analysis .

2) that there was a relationship between retinal microvascularization and systemic vascular risk, as underlined by the associations between low retinal vascular density and high AHA and European Society of Cardiology risk scores. Moreover, our study also showed in patients with the lowest retinal vascular density, indirect evidence of systemic vascular disease with a higher percentage of patients with arterial hypertension or chronic kidney failure, and a higher SYNTAX score.

Our results also showed that the left ventricular ejection fraction was strongly and independently associated with retinal vascular density measured by OCT-A.

4.1 Feasibility of the OCT-A in coronary patients

Acquiring high-quality signals for the analysis of retinal microvascularization is a problem that cannot be neglected. However, computerized photographic techniques have improved the performance and the speed of acquisition of such examinations, thus avoiding fatigue in patients. In the study by Seidelmann, for example, images from conventional retinal angiography were interpretable in 86% of patients [3]. With 82% of interpretable examinations, our study is in keeping with recent data from the literature. Likewise, in the study by S. Hwang in 24 patients (12 non-diabetic and 12 diabetic) and published in 2016 in the JAMA Ophthalmology, the authors reported only 14% of examinations that could not be interpreted because of poor signal quality [17]. Nonetheless, it must be underlined that studies published to date had small numbers of patients, (30 to 100), and as a result the feasibility needed to be confirmed in larger series. In addition, among the non-interpretable examinations, the majority (84%) were not linked to ophthalmic anomalies that limited the signal (such as myopia, cataract…) but to movement of the patient during the examination and/or of saccades of the eye, which interfered despite an acquisition time of less than 30

seconds per eye.

4.2 Analysis and characteristics of perifoveal retinal vascular density

In our study, mean perifoveal retinal vascular density was 16.7% in the « LVD » group and 20.7% in the « HVD » group ($p<0.001$). Comparison with other studies in the literature is difficult for two reasons: 1/ this technique is recent and published studies included very small numbers of patients, whose cardiovascular characteristics were rarely described, and 2/ the quantification softwares, although limited in number, have never been compared.

In the article by R. Abreu published in 2016, which included 18 healthy subjects (36 eyes) with a different quantitative analysis software « Optovue », the mean vascular density was 17.21 ± 3.09% at the superficial capillary plexus of the retina. In this article, the authors underlined that there were no standards for the measurement of retinal vascular density using OCT-A [18].

In our study, Carl Zeiss Meditec AG, Cirrus HD-OCT software v10.0 was used, this new technology permits a sweep rate of 68,000 analyses per second in zones of 3 × 3mm reflecting erythrocyte flow [19]. Erythrocyte flow by OCT-A in our study was homogeneous in the 4 quadrants of the retina. This result is also in agreement with the literature. For example, the study by G. Coscas in 70 healthy subjects (135 eyes) revealed comparable densities in the four segments. However, there was a progressive decline in overall and/or segmental density with age: in the three control groups [20-29 years, 40-59 years, > 60 years), there was a decline of 10% between the group < 30 years and the group aged more than 60 years [20]. In this study, the density was greater in women than in men but only in those older than 60 years [20]. Our study found no statistically significant difference between the two groups of retinal vascular density for sex, but there were too few patients for a sub-group analysis of younger patients and those older than 60 years. Nonetheless, although the association between retinal vessel caliber and cardiovascular risk is clearly established in women, retinal vascular density measured by OCT-A seems to be less strongly related to sex. This point, however, needs to be investigated by incorporating into models the diameters of retinal vessels measured in semi-automatic fundus image analysis (available soon).

4.3 Analysis and characteristics of the foveal avascular zone

The foveal avascular zone, the anatomic structure in the center of the fovea, is the area with the highest density of cone photoreceptors and has no capillary vascularization.

This zone and the surrounding perifoveal capillary network are altered in certain ischemic vascular diseases, such as diabetes.

In our study, the median area of the foveal avascular zone was 0.26 mm^2: 0.32 mm^2 in the « LVD » group and 0.25 mm^2 in the « HVD » group, and thus significantly greater in the « LVD » group (p=0.001). Moreover, the diameter of the foveal avascular zone correlated with cardiovascular risk, and notably the AHA score. This correlation, however, was less marked than that for retinal vascular density.

L. Wu et al. investigated the area of the foveal avascular zone using fluorescein angiography and showed that it increased significantly with age [21]. In the same way, A. Lafe used OCT-A to show that the area of the foveal avascular zone increased by 0.0014 mm^2 per year in a healthy population (0.63% increase per year)[22].

The study by T. de Carlo in 39 diabetic patients without retinopathy and in 28 healthy subjects showed that the foveal avascular zone of the retina was significantly larger in diabetic patients (0.348mm^2) than in healthy subjects (0.288mm^2) (p=0.04)[11]. More recently, the study by Cennamo G, and Col showed in 52 eyes (31 diabetic and 27 controls) that measuring the vascular zone by OCT gave the same results as conventional angiography [23]. Our results for the area of the foveal avascular zone are in agreement with data from the literature as patients in the LVD group were significantly older and more likely to be diabetic. Nevertheless, although there have been numerous studies on the relationship between the foveal avascular zone and the evolution of diabetic retinopathy, no data are available on the relationship between the foveal avascular zone and cardiovascular risk.

4.4 Relationship between retinal microvascularization and systemic vascular status

Traditional and non-traditional risk factors play a major role in the development of epicardial lesions and in non-endothelium-dependent microvascular lesions that induce a deterioration in coronary reserve. However, it is difficult to analyze myocardial microcirculation and in

particular at the acute phase of the infarction when four mechanisms coexist: 1/ the preexisting coronary microvascular dysfunction; 2/ the specific anomalies related to the ischemia; 3/ the anomalies related to reperfusion ; and 4/ distal emboli [24].

In our study, the cardiovascular risk score defined by the American Heart Association was significantly and independently associated with retinal vascular density measured by OCT-A. The AHA risk score was established in 2013 as a way to predict the risk of cardiovascular events at 10 years. This score includes age, sex, the history of arterial hypertension and diabetes, active smoking, the systolic and diastolic arterial pressure, and total cholesterol and HDL cholesterol levels [12]. This score is independent of acute infarction and thus confirms that altered retinal microcirculation assessed by measuring retinal vascular density is clearly associated with traditional risk factors. Even though no analysis of retinal microcirculation by OCT-angiography has ever been done in a population of patients with acute coronary syndrome, our results are in keeping with data in the literature. Indeed, the work of Coscas et al. showed that retinal vascular density measured by OCT-A significantly diminished with age in a healthy population., The ophthalmological study, however, included specific populations, such as patients with diabetes or hypertension, but did not address patients' overall risk [20]. The work of G. Dimitrova and T. Hwang showed that diabetic patients, with or without retinopathy, presented significantly lower retinal vascular density measured by OCT-A that did non-diabetic patients [17]. The study by Akay et al in patients with hypertension showed a relationship between macular thickness measured by OCT and systolic or diastolic arterial pressure [25]. Retinal anomalies, as an indicator of microvascular anomalies, are very powerful predictors of cardiovascular events. For example, the recent meta-analysis by J Ding showed that among 10,229 participants without hypertension, diabetes or cardiovascular disease, 2599 developed arterial hypertension between 3 and 10 years after inclusion. The authors showed that arteriole narrowing and/or venule widening in the retina were significantly associated with the risk of developing arterial hypertension [26].

Moreover, our segmental analysis showed that the microvascular anomalies were homogeneous over the four quadrants, which contrasts with the coronary macrovascular anomalies evaluated by the SYNTAX score.

Moreover, in our study, patients in the low vascular density group were more likely to present

a history of kidney failure and lower creatinine clearance on admission, which also suggests that retinal microcirculation anomalies reflect systemic microcirculation anomalies.

4.5 Analysis of the impact of the left ventricular ejection fraction

In our study, the left ventricular ejection fraction on admission was significantly and independently associated with retinal vascular density measured by OCT angiography. Similarly, the proportion of patients with a left ventricular ejection fraction below 45% was greater in the LVD group than in the HVD group. To our knowledge, no studies have investigated retinal vascularization by measuring vascular density by OCT-A in patients with a low left ventricular ejection fraction. However, the study by Altinkaynak et al showed that sub-foveal choroid thickness measured by OCT was significantly lower in patients with heart failure with a low left ventricular ejection fraction. According to the authors, the pathophysiological mechanism explaining this link was that the decreased choroid thickness was a phenomenon of peripheral vasoconstriction in choroid vessels in response to low cardiac output. Choroid vascularization thus seems to be associated with the left ventricular ejection fraction [27]. Moreover, the study by Almeida Freitas et al. conducted a Doppler US study of the ophthalmic artery and showed lower diastolic velocities and higher resistance indexes in patients with a lower left ventricular ejection fraction. In addition, the mean ocular perfusion pressure was significantly lower in patients with a low left ventricular ejection fraction [28]. Retinal blood vessel tissue has no sympathetic innervation and is not influenced by the hormones present in the bloodstream. Retinal blood flow is auto-regulated and maintained at a constant level by local mechanisms involving the interaction of a myogenic component (principally modulated by the vascular endothelium) and a metabolic component (in part related to the activity of glial cells) [29]. In our study, the decreased retinal vascular density in patients with a low left ventricular ejection fraction could be explained by the impairment of local auto-regulation mechanisms that control retinal blood flow in these patients. Retinal blood flow is directly proportional to mean ocular perfusion pressure and inversely proportional to mean ocular resistance. The origin of the impaired retinal blood flow is therefore either a decrease in mean ocular perfusion pressure or an increase in mean ocular

resistance. In the follow-up of this study, we intend to measure mean ocular perfusion pressure so as to elucidate the pathophysiological mechanisms underlying the association between impaired LVEF and low retinal vascular density measured by OCT-A.

4.6 Perspectives

Lu Wang conducted an MRI study in 224 patients without cardiovascular disease and showed that retinal arteriole narrowing was significantly associated with low myocardial blood flow and low myocardial perfusion reserve. In the same way, other studies would now be interesting to compare data for retinal vascular density in healthy populations with the results of MRI studies of myocardial perfusion [30]. Finally, although it has been clearly established in CHD patients that myocardial microvascular impairment is a prognostic factor which is independent of both age and the GRACE score at admission, the interest of studies of retinal microvascularization by OCT-A needs to be evaluated in a larger series of patients post ACS and in particular in the longer term. In addition, since a low retinal artery and vein caliber was shown to correlate with a poor cardiovascular prognosis in the general population, other larger studies are necessary to determine whether retinal vascular density measured by OCT-A is a prognostic factor in the general population. Indeed, in our study, retinal vascular density measured by OCT-A was strongly associated with cardiovascular risk, and could thus in due course become a non-invasive and quick marker to screen for cardiovascular risk in primary prevention.

5-Conclusion

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CONCLUSIONS

La densité vasculaire rétinienne péri-fovéolaire mesurée par angiographie-OCT est associée avec le profil de risque cardiovasculaire et l'altération de la fraction d'éjection ventriculaire gauche à l'admission chez les patients hospitalisés pour syndrome coronarien aigu. Ces résultats préliminaires doivent être confirmés sur une plus large série mais la densité vasculaire rétinienne semble être un marqueur intéressant de l'atteinte microvasculaire dont la valeur pronostique est bien établie.

Le Président du jury,

21.04.2017

Pr. Y. COTTIN

Vu et permis d'imprimer
Dijon, le 26 Avril 2017
Le Doyen

Pr. F. HUET

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RESUME

TITRE DE LA THÈSE : Etude de cohorte prospective évaluant les paramètres vasculaires rétiniens en Angiographie-OCT au sein d'une population de patients hospitalisés pour syndrome coronarien aigu.

AUTEUR : M AZEMAR Arthur

INTRODUCTION : Les anomalies microcirculatoires ont montré un rôle déterminant dans le processus de développement de la cardiopathie ischémique. Le rétrécissement artériolaire rétinien a été corrélé à un risque accru d'événements cardiovasculaires et pourrait servir de biomarqueur peu coûteux et reproductible. Récemment, de nouvelles approches d'imagerie (Angiographie OCT) ont été proposées pour évaluer la densité des vaisseaux sanguins de la rétine (basée sur l'évaluation du débit sanguin) sans injection intraveineuse de produits de contraste.

METHODES : Notre étude de cohorte prospective incluait tous les patients admis pour un syndrome coronarien aigu (SCA) dans notre Centre hospitalier Universitaire de Dijon entre le 1er octobre et le 31 décembre 2016. L'examen de la rétine par Angiographie-OCT était réalisé pour chaque patient au deuxième jour d'hospitalisation après le SCA. La densité vasculaire rétinienne et la surface de la zone avasculaire centrale étaient mesurées avec le logiciel d'analyse quantitative automatique Angioplex. La population était divisée en tertiles selon les données de l'Angiographie-OCT et des analyses univariées et multivariées étaient effectuées. Les patients atteints de maladies rétiniennes n'étaient pas analysés.

RÉSULTATS : Sur un total de 212 patients, 173 étaient retenus pour l'analyse. La population analysée avait un âge médian de 62 ans et comprenait 79% d'hommes. Les patients du groupe densité vasculaire rétinienne basse (premier tertile) étaient plus âgés que ceux du groupe densité vasculaire rétinienne haute (deuxième et troisième tertile) et avaient plus souvent une hypertension artérielle systémique, un diabète et un antécédent d'insuffisance rénale chronique. De plus, le score de risque de l'AHA et le SCORE risque étaient significativement plus élevés chez ces patients. En ce qui concerne les paramètres hémodynamiques à l'admission, les patients du groupe densité vasculaire rétinienne basse avaient des scores SYNTAX et GRACE plus élevés, une FEVG plus basse et une fréquence cardiaque et une pression artérielle supérieures malgré des taux de prescription et des doses de bêtabloquants et d'inhibiteurs du système rénine angiotensine aldostérone similaires. Dans l'analyse multivariée, seul le score de risque AHA (OR (IC 95%): 1,07 (1,04-1,10), p <0,001) et la FEVG (OR (IC à 95%): 0,95 (0,92-0,98), p = 0,002) étaient significativement associés au tertile le plus bas de densité vasculaire rétinienne mesuré en OCT-A. La forte association entre le score de risque AHA et la densité vasculaire rétinienne était confirmée par un coefficient de corrélation significatif de Spearman (R = - 0,54, p <0,001).

CONCLUSION : La densité vasculaire rétinienne mesurée par angiographie-OCT est associée avec le profil de risque cardiovasculaire et l'altération de la fraction d'éjection ventriculaire gauche à l'admission chez les patients hospitalisés pour syndrome coronarien aigu. Ces résultats préliminaires doivent être confirmés sur une plus large série mais la densité vasculaire rétinienne semble être un marqueur intéressant de l'atteinte globale microvasculaire dont la valeur pronostique est bien établie.

MOTS CLES : syndrome coronarien aigu ; angiographie OCT ; densité vasculaire rétinienne ; fraction d'éjection ventriculaire gauche ; AHA risk score