International Journal of Cardiology 291 (2019) 19–24

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

VEGF-A plasma levels are associated with microvascular obstruction in patients with ST-segment elevation myocardial infarction

Rodrigue Garcia [a,b,1], Claire Bouleti [c,1], Marc Sirol [d], Damien Logeart [e], Catherine Monnot [b], Corinne Ardidie-Robouant [b], Giuseppina Caligiuri [f,2], Jean-Jacques Mercadier [g,2], Stéphane Germain [b,*,2,3]

[a] CHU Poitiers, Service de Cardiologie, 2 rue de la Milétrie, 86021 Poitiers, France
[b] Center for Interdisciplinary Research in Biology (CIRB), College de France, Centre National de la Recherche Scientifique (CNRS), Institut National de la Santé et de la Recherche Médicale (INSERM), Paris Sciences et Lettres (PSL) Research University, 11, place Marcelin Berthelot, Paris F-75005, France
[c] Hôpital Bichat, APHP, Cardiology Department, 46 Rue Henri Huchard, 75877 Paris, Paris Diderot University, DHU Fire, France
[d] Hôpital Ambroise-Paré, 9 Avenue Charles de Gaulle, 92100 Boulogne-Billancourt, INSERM U1018, Team 5 Université Paris Sud-Université Versailles Saint Quentin en Yvelines, CESP (Centre for Epidemiology and Population Health EpReC Team, Renal and Cardiovascular Epidemiology), France
[e] Hopital Lariboisière, HEGP 2 rue Ambroise-Paré, 75010 Paris, France
[f] INSERM U 1148, Paris F-75018, France
[g] Signalisation and Cardiovascular Pathophysiology - UMR-S 1180, Univ. Paris-Sud, INSERM, Université Paris-Saclay, 92296, Châtenay-Malabry, France

ARTICLE INFO

Article history:
Received 5 September 2018
Received in revised form 6 February 2019
Accepted 27 February 2019
Available online 6 March 2019

Keywords:
VEGF-A
Myocardial infarction
Microvascular obstruction
No-reflow phenomenon
Magnetic resonance imaging

ABSTRACT

Background: Microvascular obstruction (MVO) is associated with poor outcome after ST-segment elevation myocardial infarction (STEMI). Vascular endothelial growth factor-A (VEGF-A) is a vascular permeability inducer playing a key role in MVO pathogenesis. We aimed to assess whether VEGF-A levels are associated with MVO, when evaluated by magnetic resonance imaging (MRI) in STEMI patients.
Methods: The multicenter prospective PREGICA study included a CMR substudy with all consecutive patients with a first STEMI who had undergone cardiac MRI at baseline and at 6-month follow-up. Patients with initial TIMI flow >1 were excluded. VEGF-A levels were measured in blood samples drawn at inclusion.
Results: Between 2010 and 2017, 147 patients (mean age 57 ± 10 years; 84% males) were included. MVO was present in 65 (44%) patients. After multivariate analysis, higher troponin peak (OR 1.005; 95% CI 1.001–1.008; $p = 0.007$) and VEGF-A levels (OR 1.003; 95% CI 1.001–1.005; $p = 0.015$) were independently associated with MVO. When considering only patients with successful percutaneous coronary intervention (final TIMI flow 3, $n = 130$), higher troponin peak ($p = 0.004$) and VEGF-A levels ($p = 0.03$) remained independently predictive of MVO. Moreover, MVO was associated with adverse left ventricular (LV) remodeling and VEGF-A levels were significantly and inversely correlated with LV ejection fraction (EF) at 6-month follow-up.
Conclusion: Our results show that VEGF-A levels were independently associated with MVO during STEMI and correlated with mid-term LVEF alteration. VEGF-A could therefore be considered as a biomarker of MVO in STEMI patients and be used to stratify patient prognosis.

© 2019 Published by Elsevier B.V.

1. Introduction

Despite successful opening of the culprit coronary vessel in patients undergoing percutaneous coronary intervention (PCI), re-perfusion of the tributary myocardial tissue remains impaired due to the "no-reflow" phenomenon with microvascular obstruction (MVO) in about 50% of patients after STEMI [1,2]. Among the biologic processes taking place in impaired myocardial reperfusion, the compression of the cardiomyocytes by the local edema due to increased vascular permeability plays an important role: the alteration of tight and adherens junctions leads to vascular leakage with leukocyte infiltration, erythrocyte accumulation in the interstitium and further exacerbation of MVO [3,4].

Recognition of MVO is important because it carries a poor prognosis with a higher occurrence of heart failure and a 1.7 fold increased risk of death [5].The detection of hypo-enhancement zones on first-pass perfusion magnetic resonance imaging (MRI) represents the reference for non-invasive diagnosis [6]. However, MRI is not available in a number of centers and cannot be performed in patients with hemodynamic instability. Availability of a biomarker would dramatically help to broaden the diagnosis of MVO and improve the clinical management of patients with STEMI [7].

* Corresponding author at: Collège de France, 11, place Marcelin Berthelot, Paris F-75005, France.
E-mail address: stephane.germain@college-de-france.fr (S. Germain).
[1] Both these authors contributed equally to this work.
[2] These authors contributed equally to this work.
[3] This author takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

https://doi.org/10.1016/j.ijcard.2019.02.067
0167-5273/© 2019 Published by Elsevier B.V.

Vascular endothelial growth factor-A (VEGF-A), which is actively produced in the damaged myocardium to foster angiogenesis and tissue repair, is a major effector of endothelial junction disruption and vascular leakage through activation of the Src Signaling pathway [8,9]. Plasma VEGF-A levels were recently identified as a possible biomarker of MVO in STEMI patients but given the limited power of the sample size, the results were not statistically significant [10].

The aim of this study was to assess whether plasma VEGF-A levels are associated with MVO diagnosed by MRI in patients with a first STEMI included in the CMR substudy of the PREGICA cohort (https://clinicaltrials.gov/ct2/show/NCT01113268).

2. Methods

2.1. Patients

The PREGICA study (ClinicalTrials.gov identifier: NCT01113268) involved 6 French centers. All consecutive patients between 18 and 80 years old referred for a first STEMI between September 2010 and December 2017 was screened for eligibility. STEMI was defined by the presence of i) electrocardiogram ST-segment elevation or Q-wave in at least 2 contiguous leads; ii) significant rise of troponin ≥3-fold higher than the upper limit reference; iii) >2 myocardial akinetic segments at trans-thoracic echocardiography carried out at day 4 ± 2 after hospital admission, which was the inclusion day. Patients were not included if they had permanent atrial fibrillation, or history of valvular, hypertrophic or dilated cardiomyopathy, cardiac surgery, anthracycline treatment or any contra-indications to MRI (claustrophobia, severe renal failure defined as creatinin levels >1.5 mg/dl, cardiogenic shock or hemodynamic instability, non-retrievable metallic implants). As part of the protocol, cardiac MRI was systematically performed if available at day 4 ± 2 days and at 6-month follow-up. The patients who underwent cardiac MRI constitute the population of the CMR substudy of the PREGICA cohort, as previously reported [11]. Blood samples were drawn at the same time, for VEGF-A measurements. In order to avoid cofounder pathophysiology such as myocardial infarction with non-obstructive coronary arteries, we excluded patients with a pre-PCI TIMI flow ≥2 on their initial coronary angiogram. The study was conducted according to the ethical principles stated in the Declaration of Helsinki and approved by local ethics committees. Written informed consent was obtained from all subjects.

2.2. Cardiac magnetic resonance imaging

Cardiac MRI was performed using a 1.5-T unit at day 4 ± 2 after hospital admission and at 6-month follow-up in all patients of the CMR substudy ($n = 185$). All studies were performed using dedicated cardiac software, phased-array surface receiver coil, and electrocardiogram triggering, as previously described [12]. A standardized MRI protocol was followed in all centers. Cine images were acquired using a breath-hold steady-state free-precession sequence in long-axis and short-axis views. A stack of short-axis slices covering from the atrioventricular ring to the apex was used to derive left ventricular (LV) volumes, and ejection fraction (EF). Ten minutes after intravenous injection of gadolinium-based contrast agent, late gadolinium enhancement (LGE) images were acquired using a breath-hold segmented T1-weighted inversion-recovery gradient-echo sequence in the same long-axis and short-axis views of cine images. Inversion time was individually optimized to null normal myocardium. LGE images were assessed for infarct size and MVO.

All images were anonymized, stored in DICOM format, and centrally analyzed in a core lab at the Ambroise Paré University Hospital, Boulogne Billancourt, France, using vendor independent software (Qmass MR 7.0; Medis, Leiden, the Netherlands) by consensus of 2 experienced operators blinded of clinical data. The mass of infarcted myocardium was quantified on LGE images using the full width at half maximum (FWHM) technique, which uses half the maximal signal within the scar as the threshold. MVO was defined as a subendocardial hypo-enhanced region within the infarcted myocardium. Quantitative MVO size was determined on short axis images by manual tracing on LGE images, and expressed as a percentage of infarct size, as previously described [13].

2.3. Laboratory assays

Peripheral blood samples were drawn at inclusion (day 4 ± 2) for all patients, the same day as cardiac MRI was performed. Aliquots were stored at −80 °C until assayed. On the day of the biomarker analysis, EDTA plasma samples were thawed, centrifuged at 16,000*g* to get rid of cryoaggregates and macroparticules, and the supernatant was used for analysis, diluted 1:4 in saline buffer. Concentrations of VEGF-A were determined using immunodetection bead-based (Luminex®) technology (Bio-Plex Pro Human Cancer2 VEGF-A Set, Bio-Rad reagent), following the manufacturer's instructions (the detailed protocol is described in Supplementary Material 1). C-reactive protein and Troponin T serum levels were measured every 6 h during the first day and once a day during the following 4 days, using standardized methods, in each center participating in the PREGICA study.

2.4. STEMI management

All patients were treated by primary percutaneous coronary intervention (PCI) in accordance with the consensus guidelines [14].Coronary flow in the culprit artery before and after revascularization by PCI was graded according to the TIMI study group classification [15]. All patients underwent a dedicated 2D echocardiography in order to determine the number of akinetic segments at day 4 ± 2. The use of appropriate antithrombotic and heart failure therapy was left to the discretion of the cardiologists in charge.

2.5. Statistical analysis

Categorical variables were expressed as numbers and percentages, continuous variables as mean ± standard deviation or median (25–75° percentiles). Comparisons between groups were performed using chi-square for categorical variables and Student *t*-test or Mann-Whitney test as appropriate for quantitative variables. The analysis of the factors associated with MVO was initially evaluated in univariable analysis. Multivariable logistic regression was used to assess whether VEGF was independently associated with MVO. The variables with $p < 0.10$ in univariable analysis were included in the multivariable model with a backward logistic regression analysis with a threshold of $p = 0.05$. Correlations were assessed using Pearson or Spearman correlation coefficient, as appropriate.

Analyses were performed using SPSS 22 (SPSS, Inc., Chicago, IL, USA). Two-sided *p* values <0.05 were considered statistically significant.

3. Results

3.1. Microvascular obstruction in patients with pre-PCI TIMI flow 0–1

In the PREGICA study, 929 consecutive patients were prospectively included, among whom 185 underwent a cardiac MRI and form the population of the CMR substudy (Fig. 1).

Baseline characteristics of the 147 included patients are illustrated in Table 1. Mean age was 57 ± 10 years and 124 patients were male (84%). The mean time between patient symptoms and PCI was 4.9 ± 4.7 h and the maximal delay between chest pain onset and PCI was 9.6 h. The culprit coronary vessel was the left anterior descending artery in 94 (64%) patients, the right coronary artery in 33 (22%) patients and the circumflex artery in 20 (14%) patients. MVO as assessed by systematic cardiac MRI at day 4 ± 2, was present in 65 (44%) patients. All patients with MVO exhibited a transmural infarction as assessed by contrast enhancement, whereas 73% exhibited this feature in patients without MVO ($p < 0.001$). VEGF-A serum levels were significantly higher in patients with MVO as compared to patients without MVO: 250 ± 211 vs. 191 ± 119 pg/mL; $p = 0.03$. The mean delay to VEGF measurement was 3.8 ± 1.1 days without significant correlation between time to VEGF analysis and VEGF concentration ($R = 0.007$; $p = 0.93$).

T-Troponin peak and C-reactive protein levels at day 4 were significantly higher in patients with MVO as compared to patients without MVO: 141 ± 139 μg/L vs. 86 ± 112 μg/L; $p = 0.009$ and 38 ± 48 mg/L vs. 22 ± 29 mg/L; $p = 0.02$, respectively. Patients with MVO more frequently had a history of hypertension as compared to patients without MVO ($p = 0.03$), while there was no difference between groups regarding the other cardiovascular risk factors.

The following variables with a $p < 0.10$ in univariable analysis were included in the multivariable analysis: hypertension, transmurality of the infarction, troponin, C-reactive protein and VEGF-A levels. According to the results, only 2 independent factors were associated with MVO as assessed by cardiac MRI:

i) higher troponin levels with OR 1.005 with 95% confidence interval (CI) (1.002–1.009) per μg/L increase; $p = 0.003$.
ii) higher VEGF-A serum levels with OR 1.003; 95% CI (1.001–1.005) per pg/ml increase; $p = 0.012$.

The median extent of MVO (expressed as the percent of left ventricular myocardial mass) was 2.16% IQR (0.0–6.5). There was no significant correlation between delay to MRI and extent of MVO ($r = 0.12$; $p = 0.16$). There was a significant positive correlation between MVO and infarct size ($r = 0.60$, $p < 0.001$), as well as between MVO size and VEGF levels ($r = 0.20$, $p = 0.018$) and a negative correlation between MVO size and LVEF ($r = -0.33$; $p < 0.001$).

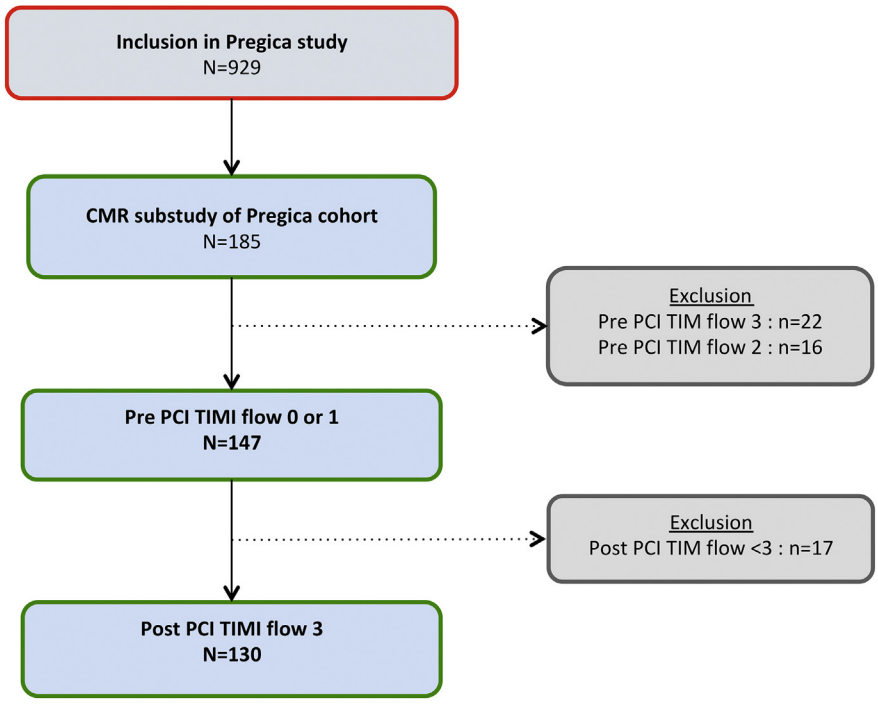

Fig. 1. Flow chart.

No pretreatment was significantly associated with MVO, but patients under statin therapy did exhibit lower VEGF levels as compared with patients free of statin: median VEGF levels 114 (84–196) pg/mL versus 196 (103–291) pg/mL; $p = 0.04$. To analyze whether VEGF levels remained significantly associated with MVO, independently of statin treatment, we performed a second multivariable analysis with the variable "statin therapy" forced in the model. The results were unchanged with this second model and only higher troponin levels and higher VEGF-A serum levels remained significantly associated with MVO (Supplementary Material 2). The combination of VEGF levels and troponin peak led to an area under the curve for MVO diagnosis of 0.68.

Table 1
Characteristics of patients according to the presence or absence of microvascular obstruction.

Variables	All patients ($n = 147$)	No MVO ($n = 82$)	MVO ($n = 65$)	P
Clinical variables				
Age (years)	57.5 ± 10.1	57.1 ± 9.8	58.0 ± 10.6	0.59
Male gender	124 (84)	68 (83)	56 (86)	0.65
Height (cm)	172 ± 8	171 ± 8	172 ± 9	0.94
Weight (kg)	77 ± 14	77 ± 15	76 ± 13	0.57
Body mass index (kg/m^2)	26 ± 4	26.2 ± 4.4	25.8 ± 3.9	0.58
Systolic BP (mm Hg)	138 ± 27	134 ± 28	142 ± 26	0.11
Diastolic BP (mm Hg)	87 ± 19	85 ± 19	89 ± 19	0.25
Heart rate (bpm)	81 ± 19	81 ± 20	80 ± 19	0.93
Active smoking	82 (56)	50 (61)	32 (49)	0.46
Hypertension	42 (28)	17 (21)	25 (39)	0.03
Dyslipidemia	72 (49)	45 (55)	27 (42)	0.14
Diabetes	27 (18)	15 (18)	12 (19)	1
Family history of CAD	40 (27)	23 (30)	17 (27)	0.85
Pretreatment (at admission)				
Beta-blockers	13 (9)	8 (10)	5 (8)	0.47
ACEi or ARBs	17 (12)	7 (9)	10 (15)	0.21
Statin	15 (10)	11 (13)	4 (6)	0.18
Coronary artery angiography				
Time from pain onset (hour)	4.9 ± 4.7	4.8 ± 5.0	5.1 ± 4.3	0.67
LAD as culprit artery	94 (64)	53 (65)	41 (63)	0.86
TIMI flow <3 after angioplasty	17 (12)	9 (11)	8 (13)	0.66
Biological data				
T Troponin peak (μg/L)	74 (16–153)	59 (18–107)	140 (62–234)	0.002
Hemoglobin (g/dL)	13.3 ± 1.5	13.3 ± 1.6	13.2 ± 1.4	0.50
Creatinin (mg/L)	9.9 ± 3.7	9.7 ± 4.4	10.3 ± 2.49	0.40
C reactive protein (mg/L)	12 (5–32)	11 (4–25)	15 (6–45)	0.04
VEGF-A (pg/mL)	217 ± 168	191 ± 119	250 ± 211	0.03

Abbreviations: BP, blood pressure; CAD, coronary artery disease; LAD, left anterior descending.

3.2. Microvascular obstruction in patients with post-PCI TIMI flow 3

Among the 147 patients analyzed at first step, 17 patients (12%) had a final TIMI flow <3 despite PCI, including 1 patient with TIMI flow 0, 6 with TIMI flow 1 and 10 with TIMI flow 2.

VEGF-A levels were statistically higher in the 17 patients with post-PCI TIMI flow <3 as compared to patients with successful PCI, defined as a final TIMI flow of 3: median 235 (83–483) pg/mL and 187 (103–263) pg/mL respectively, $p = 0.03$, as illustrated in Supplementary Material 3. The characteristics of these 17 patients with angiographic NR as compared to patients with good results of PCI are presented in Supplementary Material 4.

To make sure that the higher VEGF-A levels found in patients with MRI-diagnosed MVO were not due to these 17 patients with suboptimal results of PCI, they were excluded and the analysis was performed on the 130 patients with a successful PCI.

Among the 130 patients with final TIMI flow 3, 56 patients (43%) had MVO diagnosed by MRI. The characteristics of these patients are presented according to the presence or absence of MRI-diagnosed MVO in Supplementary Material 5. In line with the previous results, higher VEGF-A levels as well as increased troponin and C-reactive protein levels were found in patients with MVO as compared to patients without MVO. Patients with MVO also more frequently had high blood pressure as compared to patients without MVO. These 4 variables with $p < 0.10$ were consequently included in the multivariable analysis. We found 2 factors to be independently associated with MVO: i) higher troponin levels OR 1.006 95% CI (1.002–1.009); $p = 0.004$ and ii) higher VEGF-A levels OR 1.003 95% CI (1.000–1.006); $p = 0.03$.

Taken together, these results show that higher VEGF-A levels are associated with MVO, diagnosed by coronary angiography (final TIMI

flow < 3) and by MRI only in patients who underwent successful PCI (final TIMI flow = 3).

3.3. Immediate and 6-month follow-up deleterious consequences of MVO

As previously reported, MVO was associated with significantly higher myocardial infarction size and lower LVEF. In the 130 patients with final TIMI flow = 3, the 56 patients with MVO had a mean infarct size, assessed by cardiac MRI at day 4, of 47.3 ± 17.2 g versus 28.9 ± 14.8 g in patients without MVO, $p < 0.0001$. In line with these results, the number of akinetic segments, assessed by echocardiography at inclusion, was significantly higher in patients with MVO as compared to patients without MVO: 5.6 ± 2.0 versus 4.3 ± 2.0 segments respectively; $p = 0.0003$. These 56 patients also exhibited significantly lower LVEF of 43.7 ± 6.5% versus 47.0 ± 7.0% in patients without MVO, $p = 0.007$ (Fig. 2).

Patients were once again evaluated at 6 months follow-up with cardiac MRI for LV remodeling assessment. The data were available for 53 of the 56 patients with MVO and 72 of the 74 patients without MVO at initial MRI examination. These 5 patients were missing because of loss for follow-up in 2 cases and refusal to undergo repeated cardiac MRI for 3 others. At 6-month examination, MVO had disappeared in all patients.

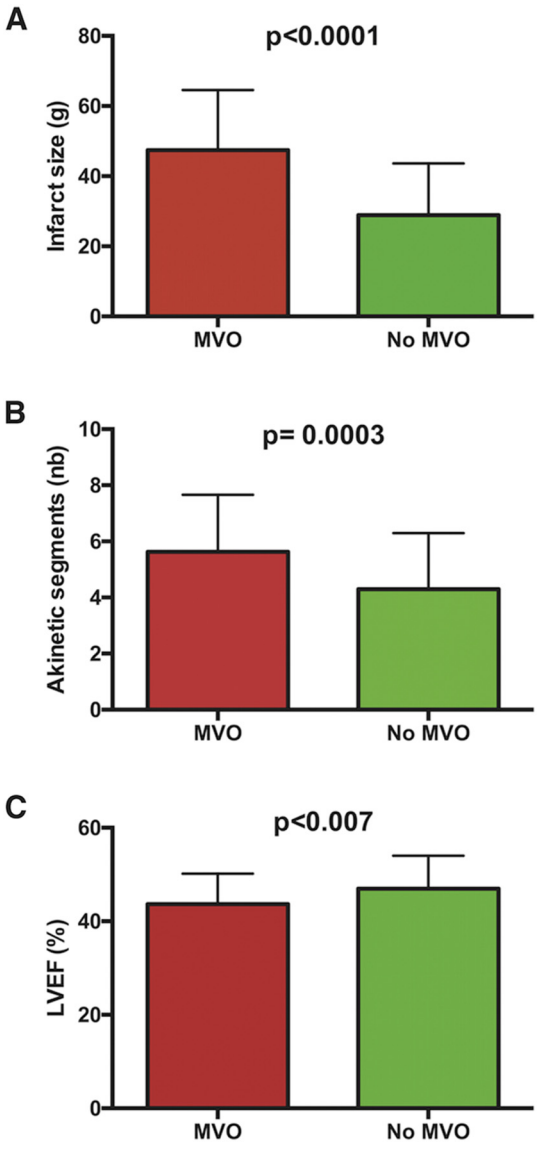

Fig. 2. Myocardial infarction characteristics according to the presence or absence of microvascular obstruction in patients with post-PCI TIMI flow = 3. A. Infarct size; B. number of akinetic segments; C. left ventricular ejection fraction (LVEF).

The presence of MVO diagnosed at admission was associated with adverse LV remodeling. Indeed, while there was no significant difference in indexed LV end-diastolic volumes (LVEDVi) between MVO and non-MVO patients at day 4, (83.8 ± 13.8 versus 89 ± 20 mL/m^2, $p = 0.11$), patients with MVO exhibited significant increased LVEDVi at 6 months follow-up as compared to patients without MVO: 99.7 ± 20.9 versus 89.6 ± 27.7 mL/m^2, $p = 0.03$. Moreover, compared to baseline, mean LVEDVi significantly increased at 6 months for the 53 patients with MVO: 83.8 ± 13.8 mL/m^2 at day 4 versus 99.7 ± 20.9 mL/m^2 at month 6; $p < 0.0001$. On the other hand, patients without MVO had no LV remodeling over time with no significant change in LVEDVi: 89.1 ± 20.5 mL/m^2 at day 4 versus 89.6 ± 27.7 mL/m^2 at month 6, $p = 0.79$. The remodeling index, as defined by the ratio between LVEDV at month 6 and at day 4 was significantly increased in MVO patients as compared to patients without MVO: 1.2 ± 0.2 versus 1.0 ± 0.2, $p < 0.0001$.

In accordance with these results, LVEF as assessed by cardiac MRI at 6 months was significantly impaired in patients with MVO as compared to patients without MVO. Indeed, mean LVEF was 45.7 ± 7.8% in MVO patients as compared to 50.8 ± 9.0%, $p = 0.001$ (Fig. 3). Finally VEGF-A levels were inversely correlated with LVEF, with a non-significant trend at baseline ($p = 0.12$) but statistically significant at 6-month follow-up ($R = -0.21$, $p = 0.017$) (Supplementary Material 6). This correlation remained significant after adjustment for statin therapy, neurohormonal blockade treatments and beta-blockers.

4. Discussion

In the present study, we assessed the association between VEGF-A levels and MVO after a first STEMI. We found that VEGF levels were associated with MVO both in patients with angiographic no-reflow (post-PCI TIMI flow < 3) and in patients with successful PCI (final TIMI flow ≥ 3). Moreover, after successful recanalization, only increased VEGF-A and troponin levels were independently associated with the presence of MVO in multivariable analysis. High VEGF-A level was associated with impaired LVEF at 6 months.

4.1. VEGF is independently associated with MVO

VEGF-A is expressed in response to hypoxia during acute myocardial infarction [8,9,16,17]. Its beneficial pro-angiogenic effect in the ischemic myocardium has been demonstrated [18,19]. VEGF-A was therefore the first candidate for therapeutic trials in ischemic myocardial diseases but with disappointing results in randomized controlled trials [20,21]. Focusing only on the pro-angiogenic role of VEGF-A seems to be a limitation of the multiple functions of this factor. Indeed, VEGF-A also has pro-inflammatory properties and is an important inductor of vascular permeability [22]. Pannitteri et al. showed that VEGF-A has a 2-peak release during MI in humans and, while the second peak may support the pro-angiogenic effects, the first peak is likely to be responsible for vascular leakage [8]. At the acute phase of ischemic injury, VEGF-A increases permeability in infarcted tissues [23–25]. Myocardial edema contributes to vessel collapse, reperfusion arrhythmias and stunning, and may also be involved in adverse ventricular remodeling through changes in myocardial stiffness [20]. All of these mechanisms could be responsible for extended tissue lesions and increased infarct size. Blockade of the VEGF-A pathway in preclinical models of MI has led to decreased infarct size and improved outcome [23]. Cerebral ischemia shares common pathophysiology with MI and promising results have been reported when inhibiting or counteracting VEGF-A pathway after ischemic stroke [26,27]. However, none of these trials were performed in humans. Another study on 50 consecutive MI patients reported that decreased VEGF levels by statin therapy were associated with

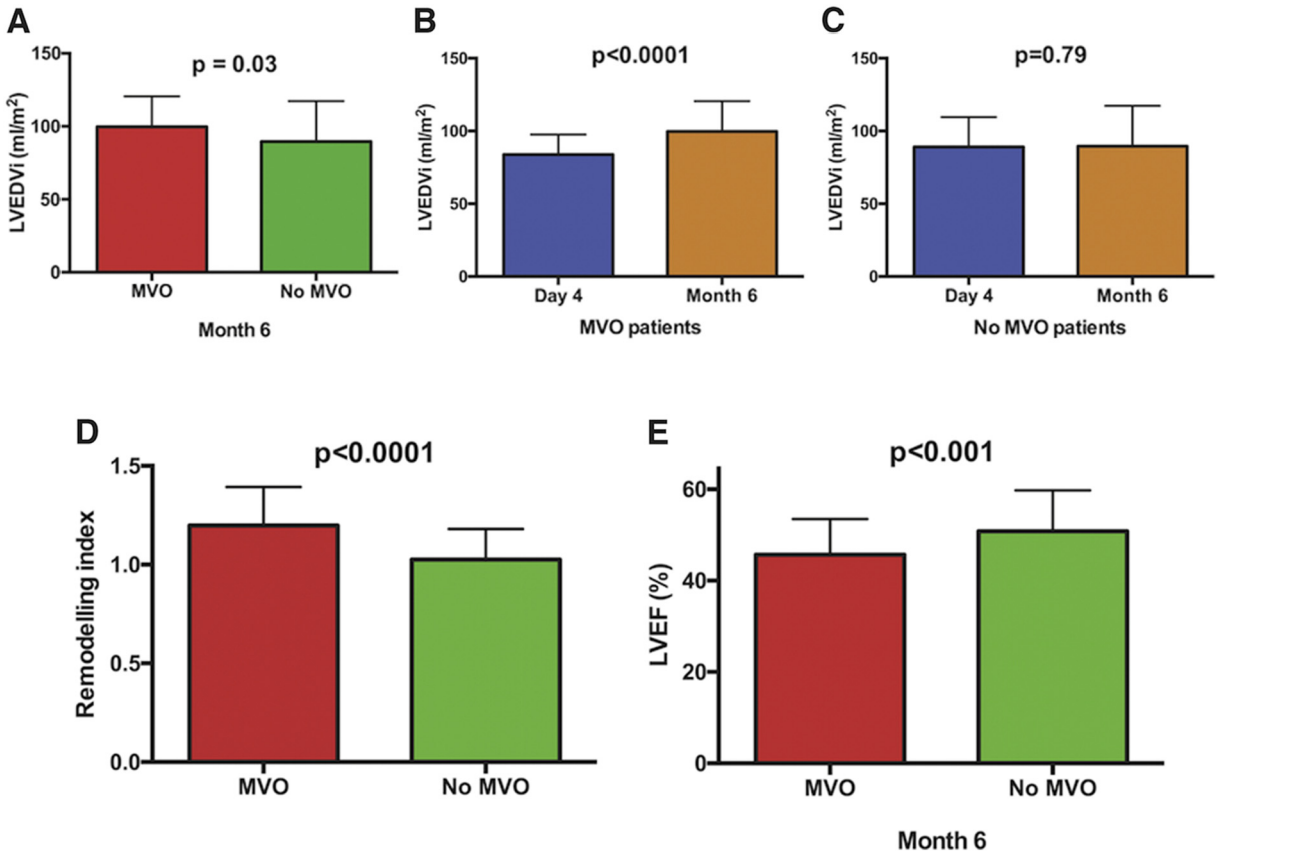

Fig. 3. Myocardial infarction characteristics evolution in patients with post-PCI TIMI flow = 3. A. Indexed left ventricular end-diastolic diameter (LVEDi) at month 6; B. Indexed left ventricular end-diastolic diameter (LVEDi) evolution in patients with microvascular obstruction (MVO); C. Indexed left ventricular end-diastolic diameter (LVEDi) evolution in patients without MVO; D. Remodeling index in patient with and without MVO; E. Left ventricular ejection fraction (LVEF) in patient with and without MVO.

improvement of LVEF through counteraction of its pro-inflammatory properties [28].

In the present study, we have shown an association between increased VEGF-A levels and MVO as diagnosed by cardiac MRI, the reference method, at day 4 ± 2. The peak of circulating VEGF levels was reached between day 1 and day 14 in most studies [8,9,17]. In the detailed study by Panniterri et al., the first peak was established at day 1–2 [8]. Due to cardiac MRI constraints and limited availability in the setting of emergency, it was not possible in this study to assess at the same time MVO and VEGF levels at day 1–2. Here, he measurements were performed at day 4 ± 2, according to the predefined protocol. VEGF-A levels were significantly increased in patients with angiographic NR as compared to patients with final coronary TIMI 3 flow, and were also significantly and independently associated with MVO in the 130 patients with successful PCI. Counteracting or inhibiting the early VEGF-A peak at the acute phase of MI in humans could therefore be of interest to limit MVO and its deleterious consequences. These results are provocative as they seem diametrically opposed to previous thinking on the role of VEGF-A during acute MI in humans. Larger trials are needed to confirm these results but this study opens new perspectives of research for MVO prevention and treatment.

4.2. MVO and VEGF levels are associated with LVEF at 6-month follow-up

The prevention of LV adverse remodeling after acute MI is one of the most important challenges for clinicians given its association with heart failure and its inherent morbimortality [29]. Cardiac MRI is the gold standard non-invasive technique for assessment of LV remodeling [30]. In our STEMI cohort, we found an association between MVO and LV remodeling with a significant increase in LVEDVi between baseline and 6-month follow-up in MVO patients, resulting in a significant decrease in LVEF.

In this study we report an association between VEGF-A levels at baseline and LVEF at 6-month follow-up. Higher VEGF-A levels at admission in the study were indeed significantly correlated with impaired LV function at 6-month follow-up after STEMI ($p = 0.017$).

The present findings suggest that it could be of importance to evaluate VEGF-A levels in clinical practice in order to identify patients at risk of MVO and to predict LVEF impairment at mid-term follow-up after STEMI. Moreover, therapies aimed at counteracting VEGF-A effect at the acute phase of STEMI could have beneficial effect by diminishing MVO and improving systolic function. Patients with high VEGF-A levels during STEMI could consequently benefit from closer follow-up and more aggressive titration of anti-remodeling and heart failure treatments.

4.3. Limitations

Some limitations of this study should be acknowledged. Firstly, as only patients with ≥3 akinetic segments were included, our conclusions may not apply to patients with smaller MI. Secondly, in order to ensure the homogeneity of the population, we selected patients with an initial TIMI flow 0–1 of the culprit artery on admission. For this reason and due to the systematic use of myocardial MRI, our population may not be fully representative of all STEMI patients. Thirdly, as most studies on STEMI patients, we report an important male predominance, thus limiting the generalization of results to female population, although gender did not seem to influence the present results. Finally, it may have been more appropriate to measure VEGF levels at day 1–2 or to have serial VEGF measurements. However, this proof of concept study is the first to highlight the potential deleterious role of VEGF

during STEMI in humans. Larger studies with optimal sampling time points may allow for even better results in this setting.

5. Conclusion

This study demonstrated for the first time that VEGF-A levels after STEMI were associated with MVO as assessed by cardiac MRI, both in patients with angiographic NR and in patients with successful PCI. Moreover, VEGF-A levels were inversely correlated with LVEF at 6-month follow-up. While further studies are needed to confirm our results, early measurement of VEFG-A could be of pronounced interest to stratify patient prognosis and to guide individualized follow-up and treatment.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2019.02.067.

Conflicts of interest

None.

Acknowledgments

We thank Jeffrey Arsham for correcting this manuscript.

References

[1] A.M. van der Laan, J.J. Piek, N. van Royen, Targeting angiogenesis to restore the microcirculation after reperfused MI, Nat. Rev. Cardiol. 6 (2009) 515–523.
[2] C. Bouleti, N. Mewton, S. Germain, The no-reflow phenomenon: state of the art, Arch Cardiovasc Dis. 108 (2015) 661–674.
[3] M. Murakami, M. Simons, Regulation of vascular integrity, J. Mol. Med. (Berl). 87 (2009) 571–582.
[4] G, Heusch, P, Kleinbongard, A, Skyschally, B, Levkau, R. Schulz, R. Erbel, The coronary circulation in cardioprotection: more than just one confounder, Cardiovasc. Res. 2 (2012) 237–245.
[5] G. Ndrepepa, K. Tiroch, M. Fusaro, D. Keta, M. Seyfarth, R.A. Byrne, J. Pache, P. Alger, J. Mehilli, A. Schomig, A. Kastrati, 5-year prognostic value of no-reflow phenomenon after percutaneous coronary intervention in patients with acute myocardial infarction, J. Am. Coll. Cardiol. 55 (2010) 2383–2389.
[6] T.S. Albert, R.J. Kim, R.M. Judd, Assessment of no-reflow regions using cardiac MRI, Basic Res. 101 (2006) 383–390.
[7] D. Garcia-Dorado, J. Oliveras, Myocardial oedema: a preventable cause of reperfusion injury? Cardiovasc. Res. 27 (1993) 1555–1563.
[8] G. Pannitteri, E. Petrucci, U. Testa, Coordinate release of angiogenic growth factors after acute myocardial infarction: evidence of a two-wave production, J. Cardiovasc. Med. (Hagerstown) 7 (2006) 872–879.
[9] A. Kranz, C. Rau, M. Kochs, J. Waltenberger, Elevation of vascular endothelial growth factor-A serum levels following acute myocardial infarction. Evidence for its origin and functional significance, J. Mol. Cell. Cardiol. 32 (2000) 65–72.
[10] C. Bouleti, T. Mathivet, J.M. Serfaty, N. Vignolles, E. Berland, C. Monnot, P. Cluzel, P.G. Steg, G. Montalescot, S. Germain, Angiopoietin-like 4 serum levels on admission for acute myocardial infarction are associated with no-reflow, Int. J. Cardiol. 187 (2015) 511–516.
[11] B. Gellen, L. Biere, D. Logeart, O. Lairez, E. Vicaut, A. Furber, J.J. Mercadier, M. Sirol, Timing of cardiac magnetic resonance imaging impacts on the detection rate of left ventricular thrombus after myocardial infarction, JACC Cardiovasc. Imaging 10 (2017) 1404–1405.
[12] M. Sirol, H. Gzara, E. Gayat, R. Dautry, B. Gellen, D. Logeart, P. Soyer, E. Vicaut, J.J. Mercadier, Comparison between visual grading and planimetric quantification of microvascular obstruction extent assessment in reperfused acute myocardial infarction, Eur. Radiol. 26 (2016) 2166–2175.
[13] S. de Waha, M.R. Patel, C.B. Granger, E.M. Ohman, A. Maehara, I. Eitel, O. Ben-Yehuda, P. Jenkins, H. Thiele, G.W. Stone, Relationship between microvascular obstruction and adverse events following primary percutaneous coronary intervention for ST-segment elevation myocardial infarction: an individual patient data pooled analysis from seven randomized trials, Eur. Heart J. 38 (2017) 3502–3510.
[14] B. Ibanez, S. James, S. Agewall, M.J. Antunes, C. Bucciarelli-Ducci, H. Bueno, A.L.P. Caforio, F. Crea, J.A. Goudevenos, S. Halvorsen, G. Hindricks, A. Kastrati, M.J. Lenzen, E. Prescott, M. Roffi, M. Valgimigli, C. Varenhorst, P. Vranckx, P. Widimsky, Group ESCSD, 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: the Task Force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC), Eur. Heart J. 39 (2018) 119–177.
[15] Group TS, The thrombolysis in myocardial infarction (TIMI) trial. Phase I findings, N. Engl. J. Med. 312 (1985) 932–936.
[16] A. Kawamoto, H. Kawata, Y. Akai, Y. Katsuyama, E. Takase, Y. Sasaki, S. Tsujimura, Y. Sakaguchi, M. Iwano, S. Fujimoto, T. Hashimoto, K. Dohi, Serum levels of VEGF and basic FGF in the subacute phase of myocardial infarction, Int. J. Cardiol. 67 (1998) 47–54.
[17] Y. Hojo, U. Ikeda, Y. Zhu, M. Okada, S. Ueno, H. Arakawa, H. Fujikawa, T. Katsuki, K. Shimada, Expression of vascular endothelial growth factor in patients with acute myocardial infarction, J. Am. Coll. Cardiol. 35 (2000) 968–973.
[18] S. Banai, M.T. Jaklitsch, M. Shou, D.F. Lazarous, M. Scheinowitz, S. Biro, S.E. Epstein, E.F. Unger, Angiogenic-induced enhancement of collateral blood flow to ischemic myocardium by vascular endothelial growth factor in dogs, Circulation. 89 (1994) 2183–2189.
[19] J.D. Pearlman, M.G. Hibberd, M.L. Chuang, K. Harada, J.J. Lopez, S.R. Gladstone, M. Friedman, F.W. Sellke, M. Simons, Magnetic resonance mapping demonstrates benefits of VEGF-induced myocardial angiogenesis, Nat. Med. 1 (1995) 1085–1089.
[20] J. Kastrup, E. Jorgensen, A. Ruck, K. Tagil, D. Glogar, W. Ruzyllo, H.E. Botker, D. Dudek, V. Drvota, B. Hesse, L. Thuesen, P. Blomberg, M. Gyongyosi, C. Sylven, G. Euroinject One, Direct intramyocardial plasmid vascular endothelial growth factor-A165 gene therapy in patients with stable severe angina pectoris, A randomized double-blind placebo-controlled study: the Euroinject One trial. J. Am. Coll. Cardiol. 45 (2005) 982–988.
[21] D.J. Stewart, M.J. Kutryk, D. Fitchett, M. Freeman, N. Camack, Y. Su, A. Della Siega, L. Bilodeau, J.R. Burton, G. Proulx, S. Radhakrishnan, N.T. Investigators, VEGF gene therapy fails to improve perfusion of ischemic myocardium in patients with advanced coronary disease: results of the NORTHERN trial, Mol. Ther. 17 (2009) 1109–1115.
[22] H.F. Dvorak, Discovery of vascular permeability factor (VPF), Exp. Cell Res. 312 (2006) 522–526.
[23] S. Weis, S. Shintani, A. Weber, R. Kirchmair, M. Wood, A. Cravens, H. McSharry, A. Iwakura, Y.S. Yoon, N. Himes, D. Burstein, J. Doukas, R. Soll, D. Losordo, D. Cheresh, Src blockade stabilizes a Flk/cadherin complex, reducing edema and tissue injury following myocardial infarction, J. Clin. Invest. 113 (2004) 885–894.
[24] S.M. Weis, D.A. Cheresh, Pathophysiological consequences of VEGF-induced vascular permeability, Nature. 437 (2005) 497–504.
[25] A. Galaup, E. Gomez, R. Souktani, M. Durand, A. Cazes, C. Monnot, J. Teillon, S. Le Jan, C. Bouleti, G. Briois, J. Philippe, S. Pons, V. Martin, R. Assaly, P. Bonnin, P. Ratajczak, A. Janin, G. Thurston, D.M. Valenzuela, A.J. Murphy, G.D. Yancopoulos, R. Tissier, A. Berdeaux, B. Ghaleb, S. Germain, Protection against myocardial infarction and no-reflow through preservation of vascular integrity by angiopoietin-like 4, Circulation. 125 (2012) 140–149.
[26] C. Bouleti, T. Mathivet, B. Coqueran, J.M. Serfaty, M. Lesage, E. Berland, C. Ardidie-Robouant, G. Kauffenstein, D. Henrion, B. Lapergue, M. Mazighi, C. Duyckaerts, G. Thurston, D.M. Valenzuela, A.J. Murphy, G.D. Yancopoulos, C. Monnot, I. Margaill, S. Germain, Protective effects of angiopoietin-like 4 on cerebrovascular and functional damages in ischaemic stroke, Eur. Heart J. 34 (2013) 3657–3668.
[27] N. van Bruggen, H. Thibodeaux, J.T. Palmer, W.P. Lee, L. Fu, B. Cairns, D. Tumas, R. Gerlai, S.P. Williams, M. van Lookeren Campagne, N. Ferrara, VEGF antagonism reduces edema formation and tissue damage after ischemia/reperfusion injury in the mouse brain, J. Clin. Invest. 104 (1999) 1613–1620.
[28] Y. Kodama, Y. Kitta, T. Nakamura, H. Takano, K. Umetani, D. Fujioka, Y. Saito, K. Kawabata, J.E. Obata, A. Mende, T. Kobayashi, K. Kugiyama, Atorvastatin increases plasma soluble Fms-like tyrosine kinase-1 and decreases vascular endothelial growth factor and placental growth factor in association with improvement of ventricular function in acute myocardial infarction, J. Am. Coll. Cardiol. 48 (2006) 43–50.
[29] S. Funaro, G. La Torre, M. Madonna, L. Galiuto, A. Scara, A. Labbadia, E. Canali, A. Mattatelli, F. Fedele, F. Alessandrini, F. Crea, L. Agati, A. Investigators, Incidence, determinants, and prognostic value of reverse left ventricular remodelling after primary percutaneous coronary intervention: results of the Acute Myocardial Infarction Contrast Imaging (AMICI) multicenter study, Eur. Heart J. 30 (2009) 566–575.
[30] V. Bodi, J.V. Monmeneu, J.T. Ortiz-Perez, M.P. Lopez-Lereu, C. Bonanad, O. Husser, G. Minana, C. Gomez, J. Nunez, M.J. Forteza, A. Hervas, E. de Dios, D. Moratal, X. Bosch, F.J. Chorro, Prediction of reverse remodeling at cardiac MR imaging soon after first ST-segment-elevation myocardial infarction: results of a large prospective registry, Radiology. 278 (2016) 54–63.