*Original Research*

# Predictive value of serum HIF-1α and VEGF for arrhythmia in acute coronary syndrome patients

**Bin Li[1], Qiuting Feng[2], Cheng Yu[2], Jun Yang[2], Xian Qin[2], Xing Li[2], Jianing Cao[2], Xin Xu[2], Chenjian Yang[2] and Yan Jin[1,2]**

[1]Wuxi No.2 People's Hospital, The Affiliated Wuxi Clinical College of Nantong University, Wuxi 214002, China; [2]Department of Cardiology, Jiangnan University Medical Center (JUMC), Wuxi 214002, China
Corresponding author: Yan Jin. Email: epjinyan@njmu.edu.cn

**Impact Statement**

The study demonstrated that Lown grade was positively correlated with the serum HIF-1α and VEGF concentrations.

**Abstract**

Percutaneous coronary intervention (PCI) has been widely used in the alleviation of myocardial ischemia in patients with acute coronary syndrome (ACS). However, the incidence of reperfusion arrhythmia (RA) after PCI is high, which seriously affects the prognosis of ACS patients. Therefore, this study aimed to study the predictive value of serum HIF-1α and VEGF levels before PCI for RA in ACS patients post PCI. A total of 200 ACS patients who underwent PCI were selected and divided into those with RA after PCI (RA, $n=93$) and those without RA after PCI (non-RA, $n=107$) according to Lown grade. Spearman correlation analysis was applied for the relationship between serum hypoxia inducible factor-1α (HIF-1α) and vascular endothelial growth factor (VEGF) levels and Lown grade. Patients with RA after PCI tended to have higher levels of creatine kinase muscle and brain isoenzyme (CK-MB), serum HIF-1α and VEGF before surgery. Low left ventricular ejection fraction (LVEF), high CK-MB, high serum VEGF and HIF-1α were risk factors for RA in ACS patients within 24 h after PCI. Receiver operating characteristic (ROC) analysis revealed that serum HIF-1α and VEGF levels could predict RA in ACS patients after PCI, and the combined detection could increase the sensitivity of single HIF-1α detection and the specificity of single VEGF detection. Lown grade was positively correlated with the serum HIF-1α and VEGF concentrations. In conclusion, serum HIF-1α and VEGF levels before PCI are risk factors for the occurrence of RA in ACS patients after PCI, and have certain predictive values for the occurrence of RA in ACS patients after PCI.

**Keywords:** PCI, ACS, RA, VEGF, HIF-1α

***Experimental Biology and Medicine* 2023; 248: 685–690. DOI: 10.1177/15353702231171902**

## Introduction

Acute coronary syndrome (ACS) is related to the rupture of unstable plaques in coronary artery sclerosis.[1,2] The clinical manifestations of ACS are episodic chest tightness and chest pain.[3] In severe cases, heart failure and even sudden death may occur.[3] At present, percutaneous coronary intervention (PCI) is a common method to improve myocardial ischemia in patients with ACS.[4] It could effectively dredge occluded blood vessels and improve myocardial perfusion of patients.[5] However, after coronary recanalization, ACS patients have a high probability of reperfusion arrhythmia (RA), which seriously affects the prognosis of PCI.[6] Relevant studies have shown that RA could increase the risk of re-infarction after PCI in patients with myocardial infarction, and even lead to death.[7] Therefore, exploring the factors related to RA in patients with ACS after PCI is conducive to early intervention to reduce the occurrence of complications after PCI.

Hypoxia-inducible factor-1 (HIF-1) is a heterodimeric transcription factor composed of a constitutively expressed β subunit (HIF-1β) and an oxygen-dependent α subunit (HIF-1α).[8] Among them, HIF-1α is the main regulator of hypoxia signaling pathway.[9] HIF-1α degradation is blocked under hypoxia, resulting in rapid accumulation.[10] Numerous studies have confirmed that HIF-1α is widely expressed in cardiovascular dysfunctions, such as acute myocardial infarction and cardiomyopathy, and plays an important role in regulating cellular oxygen supply and energy metabolism, cell proliferation and apoptosis, and new angiogenesis.[11,12] HIF-1α regulates a variety of downstream genes involved in multiple physiological and pathological processes,[13,14] including vascular endothelial growth factor (VEGF). VEGF plays a critical role in promoting the blood vessels generation and is important in the pathological process of ACS.[15] Currently, it has been revealed that there was a correlation between serum HIF-1α and VEGFa levels and myocardial

injury,[16] but few studies have been done on the correlation between ACS patients with RA after PCI. In view of this, this study explored the predictive value of serum HIF-1α and VEGF levels before PCI for RA in ACS patients post PCI.

## Materials and methods

### Patients

A total of 200 ACS patients were selected. This study was approved by the ethics committee of Wuxi No.2 People's Hospital. All diagnosis and treatment measures were collected from patients and their families with informed consent and signed informed consent.

The diagnostic criteria of ACS refer to the "2015 China Emergency Acute Coronary Syndrome Clinical Practice Guidelines Diagnostic Criteria."

ST-segment elevation myocardial infarction (STEMI): severe chest pain lasting >30 min; ST-segment arched dorsal elevation on ECG; cardiac troponin T or I positive; hybrid creatine kinase isoenzyme level >2 times of the reference value.

Diagnosis of non-ST-segment elevation myocardial infarction (NSTEMI): persistent chest pain; transient or new ST-segment depression, or T wave inversion and flattening on ECG; cardiac troponin T or I positive; hybrid creatine kinase isoenzyme levels >2 times of the reference value.

Diagnosis of unstable angina (UA): chest pain; ST-segment depression or T wave inversion and flattening on ECG; cardiac troponin T or I negative; hybrid creatine kinase isoenzyme levels may be elevated but ⩽2 times of the reference value.

Inclusion criteria: patients diagnosed with ACS by the above diagnostic criteria for the first time; the time from onset to admission was ⩽48 h; PCI was performed; informed consent was given. Exclusion criteria: old myocardial infarction; associated with heart failure, valvular heart disease and other heart diseases; contraindications to PCI; history of preoperative arrhythmia; arrhythmia or taking antiarrhythmic drugs at admission; infection, autoimmune disease, malignant tumor, and abnormal liver and kidney function.

### Lown grade

All patients underwent 24-h Holter monitoring during PCI to monitor the occurrence of RA at any time. RA was graded using the Lown grading methods. In this study, patients with RA were classified as Lown grade ⩾ 1.

Grade 0: normal;
Grade 1: Occasional premature ventricular contractions with a frequency of less than 30 beats/h or 6 beats/min;
Grade 2: Premature ventricular contractions frequently occur, with a frequency of more than 30 times/h or 6 times/min;
Grade 3: Occurrence of polygenic or polymorphic premature ventricular contractions;
Grade 4: Frequent paired premature ventricular contractions or recurrent ventricular tachycardia;
Grade 5: Ron T or ventricular fibrillation occurs.

### Determination of serum HIF-1α and VEGF levels

Before PCI, 3 mL of fasting venous blood was collected from ACS patients, and was placed in a vacuum anticoagulation tube. Serum HIF-1α and VEGF concentrations were measured using the enzyme-linked immunosorbent assay (ELISA) following standard instructions. Human/Mouse HIF-1α ELISA Kit was purchased from Beyotime (PH368, Shanghai, China) and Human VEGF ELISA Kit (ab222510) was purchased from Abcam (Cambridge, MA).

### Statistical methods

The data presented are mean ± standard deviation (SD) or $n$ (percentage). The comparisons of data were done by Mann–Whitney test or Fisher's exact test or chi-square test. Anderson–Darling test, D'Agostino & Pearson test, Shapiro–Wilk test and Kolmogorov–Smirnov test were used to test the normality of the data before analysis. Multivariate logistic regression analysis was used to analyze the risk factors of RA in patients with ACS after PCI. $P < 0.05$ was regarded as statistically significant.

## Results

### Baseline characteristics of ACS patients before PCI with or without RA onset

A total of 200 patients with ACS who underwent PCI were included in this study. All patients underwent 24 h dynamic electrocardiography during PCI to monitor the occurrence of RA. The patients with RA were classified by the Lown grading method. In this study, the patients with RA were considered to have a Lown grading ⩾ 1. According to this grading standard, we divided patients into those with RA after PCI (RA, $n = 93$) and those without RA after PCI (non-RA, $n = 107$). We then compared the demographic data of ACS patients before PCI (Table 1). No significant differences were found between the two groups in age (56.8 ± 9.2 versus 57.6 ± 9.9, $P = 0.217$), gender (47.7% versus 55.9%, $P = 0.259$), ACS type ($P = 0.555$), BMI (23.45 ± 3.92 versus 24.01 ± 4.13, $P = 0.183$), smoking history (41.1% versus 52.7%, $P = 0.119$), diabetes history (26.2% versus 37.6%, $P = 0.094$), hypertension (29.9% versus 41.9%, $P = 0.103$), and hyperlipidemia (40.2% versus 50.5%, $P = 0.156$). In addition, there were no significant differences in heart rate (76.81 ± 13.29 versus 79.32 ± 14.46, $P = 0.139$), blood pressure (128.47 ± 24.96 versus 135.28 ± 26.72, $P = 0.269$), high density lipoprotein cholesterol (1.52 ± 0.63 versus 1.35 ± 0.74, $P = 0.219$), low density lipoprotein cholesterol (2.81 ± 1.02 versus 3.07 ± 0.94, $P = 0.132$), and total cholesterol (3.81 ± 1.21 versus 4.19 ± 1.37, $P = 0.224$) before PCI. However, there were significant differences between the two groups in left ventricular ejection fraction (LVEF) (58.97 ± 8.68 versus 51.25 ± 9.16, $P < 0.001$), creatine kinase muscle, and brain isoenzyme (CK-MB) (118.95 ± 45.73 versus 205.44 ± 51.26, $P < 0.001$), HIF-1α (328.43 ± 133.41 versus 422.54 ± 163.51, $P < 0.001$), and VEGF (61.62 ± 24.37 versus 75.33 ± 29.90, $P < 0.001$) levels.

### Risk factors for RA in ACS patients after PCI

We then used multivariate logistic regression analysis to analyze the risk factors for RA within 24 h post PCI. The

**Table 1.** Baseline characteristics of ACS patients with and without arrhythmia (RA) onset after percutaneous coronary intervention (PCI).

| | Non-RA ($n=107$) | RA ($n=93$) | *P* value |
|---|---|---|---|
| Age (years) | 56.8 ± 9.2 | 57.6 ± 9.9 | 0.217 |
| Gender | | | |
| Male | 51 (47.7%) | 52 (55.9%) | 0.259 |
| Female | 56 (52.3%) | 41 (44.1%) | |
| Body mass index (kg/m$^2$) | 23.45 ± 3.92 | 24.01 ± 4.13 | 0.183 |
| Prior or current smoke | 44 (41.1%) | 49 (52.7%) | 0.119 |
| Prior or current diabetes mellitus | 28 (26.2%) | 35 (37.6%) | 0.094 |
| Prior or current hypertension | 32 (29.9%) | 39 (41.9%) | 0.103 |
| Prior or current hyperlipidemia | 43 (40.2%) | 47 (50.5%) | 0.156 |
| Heart rate (b.p.m.) | 76.81 ± 13.29 | 79.32 ± 14.46 | 0.139 |
| LVEF (%) | 58.97 ± 8.68 | 51.25 ± 9.16 | <0.001 |
| SBP (mmHg) | 128.47 ± 24.96 | 135.28 ± 26.72 | 0.296 |
| DBP (mmHg) | 87.16 ± 15.95 | 91.98 ± 17.26 | 0.382 |
| HDL-C (mmol/L) | 1.52 ± 0.63 | 1.35 ± 0.74 | 0.219 |
| LDL-C (mmol/L) | 2.81 ± 1.02 | 3.07 ± 0.94 | 0.132 |
| TC (mmol/L) | 3.81 ± 1.21 | 4.19 ± 1.37 | 0.224 |
| TG (mmol/L) | 1.47 ± 0.63 | 1.73 ± 0.71 | 0.118 |
| CK- MB (ng/mL) | 118.95 ± 45.73 | 205.44 ± 51.26 | <0.001 |
| Serum HIF-1α (pg/mL) | 328.43 ± 133.41 | 422.54 ± 163.51 | <0.001 |
| Serum VEGF (pg/mL) | 61.62 ± 24.37 | 75.33 ± 29.90 | <0.001 |
| ACS classification | | | |
| STEMI | 20 (18.7%) | 23 (24.7%) | 0.555 |
| NSTEMI | 45 (42.1%) | 38 (40.9%) | |
| UA | 42 (39.2%) | 32 (34.4%) | |

RA: reperfusion arrhythmia; LVEF: left ventricular ejection fraction; SBP: systolic blood pressure; DBP: diastolic blood pressure; HDL-C: high density lipoprotein cholesterol; LDL-C: low density lipoprotein cholesterol; TC: total cholesterol; TG: triglyceride; CK-MB: creatine kinase-muscle/brain; HIF-1α: hypoxia inducible factor 1α; VEGF: vascular endothelial growth factor; ACS: acute coronary syndrome; STEMI: ST-elevation myocardial infarction; NSTEMI: non-ST-elevation myocardial infarction; UA: unstable angina; SD: standard deviation.
The data presented are mean ± SD or n (percentage). The comparisons of data were done by Mann–Whitney test or Fisher's exact test or Chi-square test.

**Table 2.** Multivariate logistic analysis of predictors for arrhythmia in acute coronary syndrome (ACS) patients after percutaneous coronary intervention (PCI).

| | OR | 95% CI | *P* value |
|---|---|---|---|
| Low LVEF (%) | 2.794 | 2.164 to 4.693 | <0.001 |
| High CK-MB | 1.968 | 1.216 to 3.023 | 0.002 |
| High serum HIF-1α | 1.428 | 1.119 to 1.907 | 0.015 |
| High serum VEGF | 1.652 | 1.085 to 2.273 | 0.006 |

OR: odds ratio; CI: confidence interval; LVEF: left ventricular ejection fraction; CK-MB: creatine kinase-muscle/brain; HIF-1α: hypoxia inducible factor 1α; VEGF: vascular endothelial growth factor.

occurrence of RA (0 = no, 1 = yes) was used as the dependent variable, the detection indicators in Table 1 were used as independent variables, and the stepwise method was used to exclude irrelevant items ($P > 0.05$). The results showed that low LVEF (OR = 2.794, 95% CI 2.164 to 4.693, $P < 0.001$), high CK-MB (OR = 1.968, 95% CI 1.216 to 3.023, $P = 0.002$), high serum HIF-1α (OR = 1.428, 95% CI 1.119 to 1.907, $P = 0.015$), and high serum VEGF (OR = 1.428, 95% CI 1.119 to 1.907, $P = 0.006$) concentrations were risk factors for RA in ACS patients within 24 h after PCI (Table 2).

### Correlation of serum HIF-1α and VEGF concentrations in ACS patients

Compared with patients without RA, HIF-1α (Figure 1(a), $P < 0.001$) and VEGF (Figure 1(b), $P < 0.001$) were significantly increased in patients with RA. A statistical positive correlation was revealed on HIF-1α and VEGF concentrations in all ACS patients (Figure 1(c), $r = 0.44$, $P < 0.001$).

### Predictive values of serum HIF-1α, VEGF, and their combination at admission for RA onset after PCI in ACS patients

We explored the predictive value of serum HIF-1α and VEGF concentrations at admission and their combined detection for the occurrence of RA within 24 h after PCI in ACS patients undergoing PCI by ROC analysis (Figure 2(a) to (c)). As shown in Table 3, the area under curve (AUC) of HIF-1α level predicting AR after PCI in ACS patients was 0.66 (95% CI, 0.59 to 0.74, sensitivity 44.09%, specificity 85.05%, Youden index 0.29, $P < 0.001$). The AUC of serum VEGF level predicting AR after PCI in ACS patients was 0.64 (95% CI, 0.56 to 0.72, sensitivity 68.82%, specificity 57.01%, Youden index 0.26, $P < 0.001$). The AUC of serum HIF-1α combined VEGF level predicting AR after PCI in ACS patients was 0.72 (95% CI, 0.65 to 0.79, sensitivity 70.97%, specificity 67.29%, Youden index 0.38, $P < 0.001$).

### Correlation of serum HIF-1α/VEGF concentrations and Lown grade in ACS patients following RA onset after PCI

In this study, the Lown grading method was used to classify the arrhythmia of patients. The higher the grade, the more serious the arrhythmia. Therefore, we analyzed the

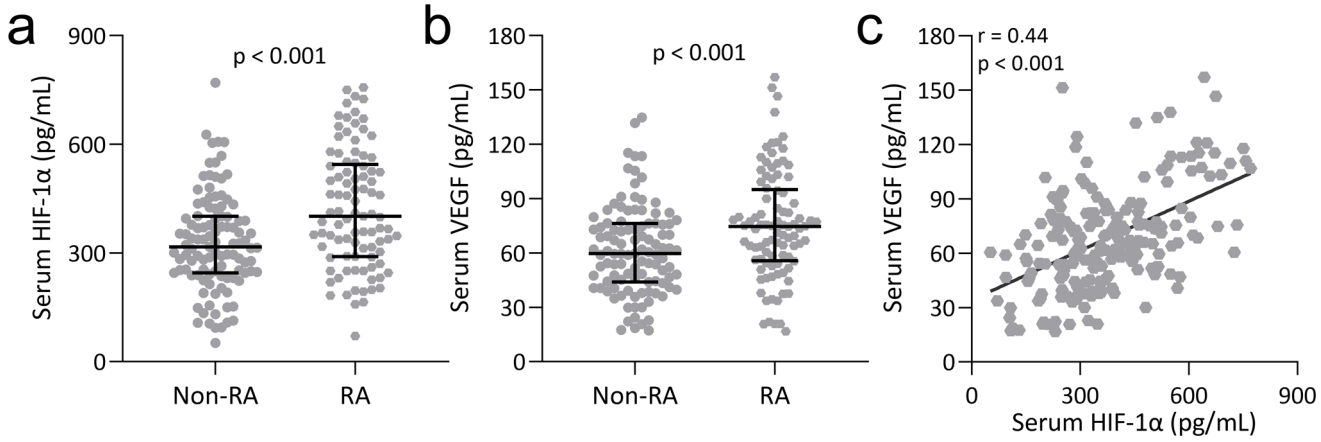


**Figure 1.** Comparisons of serum HIF-1α (a) and VEGF (b) at admission between ACS patients with RA (RA, $n=93$) and without RA (non-RA, $n=107$) onset after PCI. Data were shown with median (interquartile range). The comparisons of data were done by Mann–Whitney test. (c) Spearman correlation analysis of serum HIF-1α with VEGF at admission in ACS patients ($n=200$).

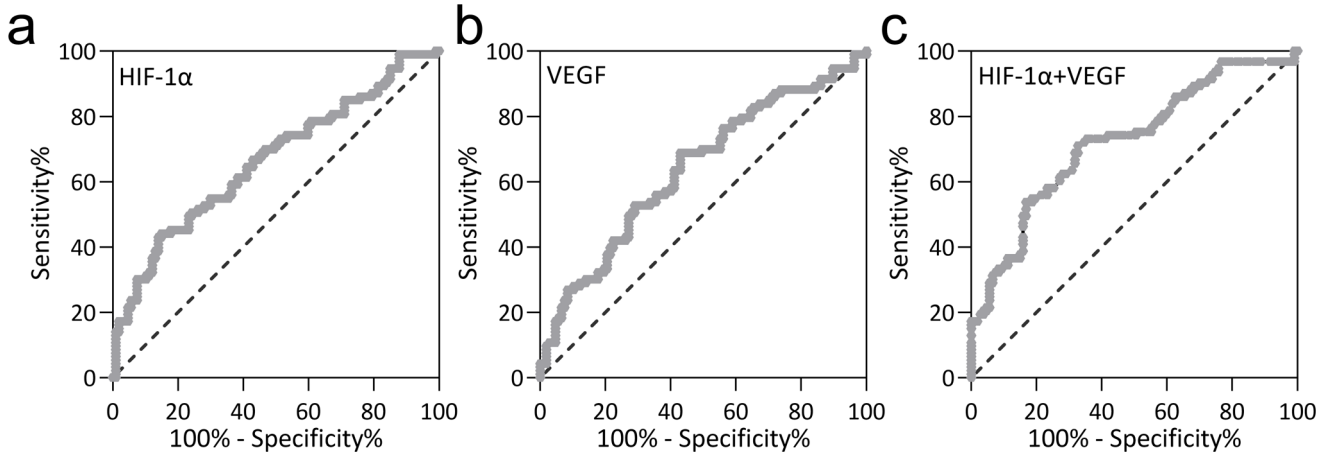


**Figure 2.** ROC analysis of predictive values of (a) serum HIF-1α, (b) VEGF and (c) their combination at admission for RA onset after PCI in ACS patients.

**Table 3.** Predictive values in ROC analysis.

| | AUC (95% CI) | Sensitivity (%) | Specificity (%) | *P* | Youden index |
|---|---|---|---|---|---|
| Serum HIF-1α | 0.66 (0.59 to 0.74) | 44.09 | 85.05 | <0.001 | 0.29 |
| Serum VEGF | 0.64 (0.56 to 0.72) | 68.82 | 57.01 | <0.001 | 0.26 |
| HIF-1α + VEGF | 0.72 (0.65 to 0.79) | 70.97 | 67.29 | <0.001 | 0.38 |

ROC: receiver operating characteristic; AUC: area under curve; CI: confidence interval; HIF-1α: hypoxia inducible factor-1α; VEGF: vascular endothelial growth factor.

correlation between the Lown grade and HIF-1α and VEGF concentrations at admission in 93 patients who developed RA after PCI. With the increase of Lown grade, the serum HIF-1α (Figure 3(a), $r=0.31$, $P=0.002$) and VEGF (Figure 3(b), $r=0.29$, $P=0.005$) concentrations also increased gradually at admission, showing a significant positive correlation.

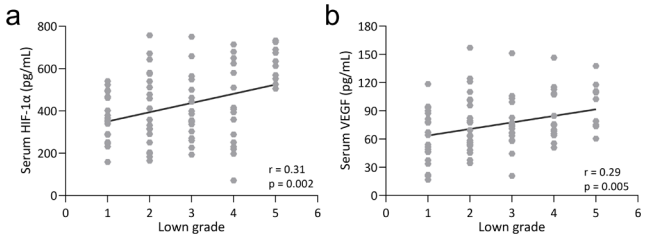


**Figure 3.** Spearman correlation analysis of Lown grade in ACS patients following RA ($n=93$) onset after PCI with their (a) serum HIF-1α and (b) VEGF at admission.

## Discussion

RA is a common complication caused by myocardial reperfusion injury during PCI in ACS patients.[17] During

recanalization of diseased coronary vessels during PCI, due to the influence of energy metabolism disorder, calcium iron overload, inflammatory reaction, formation of oxygen free radicals, and other factors, myocardial damage is not improved but aggravated, which will induce RA.[18] The occurrence of RA indicates that the myocardium of ACS patients is further damaged, which predicts the poor prognosis of the patients.[19] Therefore, preventive treatment for high-risk RA patients is required before PCI to reduce the incidence of RA and ensure a good prognosis for patients. At present, there is a lack of clinical serum markers that could assess the risk of RA in patients with ACS during PCI. This study selected 200 ACS patients admitted to our hospital from December 2020 to March 2022, and evaluated the correlation between HIF-1α and VEGF concentration at admission and RA onset in ACS patients after PCI. We wanted to demonstrate the predictive effect of the two indicators and their combined detection on the occurrence of RA, so as to provide reasonable suggestions for the early intervention of RA after PCI in patients with ACS.

HIF-1α is a heterodimer composed of an α subunit precisely regulated by oxygen concentration and a stably expressed β subunit.[20] The half-life of HIF-1α protein in most cells is only 5–10 min.[21] Its proline residue is hydroxylated by proline hydroxylase (PHD), which is rapidly degraded by the oxygen-dependent-ubiquitin protease pathway.[22] Therefore, HIF-1α protein is maintained at lower levels in cells under normal conditions.[23] Hypoxic environment leads to inhibition of PHD activity.[23] HIF-1α begins to express stably and migrates from the cytoplasm to the nucleus, where it combines with HIF-1β in the nucleus to form an active dimer.[24] The activated HIF-1 binds to the hypoxia response element and transcriptional coactivator p30 in the regulatory region of the target gene to form a transcription initiation complex and induce the expression of downstream genes.[24] The number of genes regulated by HIF-1α exceeds 1000, including erythropoietin, VEGF, inducible nitric oxide synthase (iNO), glucose transporter 1 (GLUT1), endothelin-1 (ET-1), and so on.[25] In terms of heart disease, HIF-1α could increase myocardial glucose uptake and transport by regulating the expression of myocardial GLUT4 and pyruvate kinase M2 isoform (PKM2) to continuously provide compensatory energy supply.[26] In addition, HIF-1α regulates the expression of GLUT1 by targeting in the process of cardiac ischemia and hypoxia, which increases the transport of peripheral blood glucose to vascular endothelial cells, and participates in the protection of mitochondrial function of vascular endothelial cells in hemorrhagic shock.[27] In this research, we found that HIF-1α was remarkably elevated in patients with RA, and in all ACS patients, HIF-1α and VEGF concentrations were significantly positively correlated, which is consistent with our description of other studies above. Innovatively, we demonstrated that HIF-1α concentrations at admission in ACS patients undergoing PCI have a statistically predictive value for the occurrence of RA within 24 h after surgery.

VEGF plays important physiological functions by binding to related receptors.[28] VEGF has important roles such as inducing endothelial cell migration and proliferation, increasing vascular permeability, and regulating thrombosis.[29] Previous researches have revealed that VEGF plays a role in the occurrence and development of certain cardiovascular diseases.[30] Inhibition of VEGFs and the receptors can cause a variety of cardiovascular disease complications.[30] The more severe the lesion, the higher the level of VEGF.[30] The concentration of serum VEGF was positively correlated with myocardial oxidative damage indicators such as myeloperoxidase and advanced oxidation protein products, suggesting that VEGF can accurately reflect the degree of myocardial damage in ACS. In addition, a study indicated that the isoform of VEGF-A, VEGF-A165b, has anti-angiogenic effects, and the ratio of VEGF-A to VEGF-A may be a tool for predicting cardiovascular dysfunctions in patients with AMI after PCI.[31]

VEGF and HIF-1α have been studied extensively in the context of cardiovascular disease. Both molecules are involved in the regulation of angiogenesis and are upregulated in various cardiovascular diseases.[32] Studies have shown that both molecules are involved in the regulation of cardiac remodeling and can protect the heart from ischemic injury.[33] In addition, VEGF and HIF-1α can induce cardiomyocyte proliferation and protect the heart from ischemic injury. Many studies have focused on the role of VEGF and HIF-1α in the context of cardiac disease.[34] For example, a recent study has demonstrated that VEGF and HIF-1α can induce cardiomyocyte proliferation and protect the heart from ischemic injury in a mouse model of myocardial infarction.[35] In this study, we demonstrated that patients who developed RA after PCI tended to have higher levels of serum VEGF and HIF-1α preoperatively, which is consistent with the statistical findings of previous studies in blood samples from patients with other cardiovascular diseases. More importantly, we demonstrated that with increasing Lown grade, serum VEGF and HIF-1α levels tended to increase in patients on admission, showing a significant positive correlation. Our data suggest that the higher the serum HIF-1α and VEGF concentration at admission, the more severe the RA after PCI. In addition, our results suggest that combined detection could increase the sensitivity of single HIF-1α detection and the specificity of single VEGF detection.

In conclusion, we found that preoperative serum HIF-1α and VEGF levels were significantly elevated in ACS patients with RA after PCI compared with patients without arrhythmias. We demonstrated that HIF-1α and VEGF were risk factors for RA within 24 h after emergency PCI in patients with ACS.

#### AUTHORS' CONTRIBUTIONS

BL, QTF, CY, JY, XQ, XL, JNC, XX, CJY, and YJ performed the experiments, and analyzed and interpreted the data. YJ was a major contributor in writing the manuscript. All authors read and approved the final manuscript.

#### DECLARATION OF CONFLICTING INTERESTS

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

**FUNDING**

The author(s) received no financial support for the research, authorship, and/or publication of this article.

**ORCID ID**

Yan Jin https://orcid.org/0000-0003-2234-195X

**REFERENCES**

1. Gach O, El HZ, Lancellotti P. Acute coronary syndrome. *Rev Med Liege* 2018;**73**:243–50
2. Feng H, Pan H, Yao W. Uric acid levels are associated with severity and mortality in patients with acute coronary syndrome. *STEMedicine* 2022;**3**:e131
3. Makki N, Brennan TM, Girotra S. Acute coronary syndrome. *J Intensive Care Med* 2015;**30**:186–200
4. Smith JN, Negrelli JM, Manek MB, Hawes EM, Viera AJ. Diagnosis and management of acute coronary syndrome: an evidence-based update. *J Am Board Fam Med* 2015;**28**:283–93
5. Bhatt DL. Percutaneous coronary intervention in 2018. *JAMA* 2018; **319**:2127–8
6. Taha H, Shaker MM. Percutaneous management of reperfusion arrhythmias during primary percutaneous coronary intervention: a case report. *Egypt Heart J* 2021;**73**:30
7. Lee MS, Dahodwala MQ. Percutaneous coronary intervention for acute myocardial infarction due to unprotected left main coronary artery occlusion: status update 2014. *Catheter Cardiovasc Interv* 2015; **85**:416–20
8. Ke Q, Costa M. Hypoxia-inducible factor-1 (HIF-1). *Mol Pharmacol* 2006;**70**:1469–80
9. Zhang FJ, Luo W, Lei GH. Role of HIF-1alpha and HIF-2alpha in osteoarthritis. *Joint Bone Spine* 2015;**82**:144–7
10. Shukla SD, Walters EH, Simpson JL, Keely S, Wark PAB, O'Toole RF, Hansbro PM. Hypoxia-inducible factor and bacterial infections in chronic obstructive pulmonary disease. *Respirology* 2020;**25**:53–63
11. Luo Y, Teng X, Zhang L, Chen J, Liu Z, Chen X, Zhao S, Yang S, Feng J, Yan X. CD146-HIF-1alpha hypoxic reprogramming drives vascular remodeling and pulmonary arterial hypertension. *Nat Commun* 2019; **10**:3551
12. Warbrick I, Rabkin SW. Hypoxia-inducible factor 1-alpha (HIF-1alpha) as a factor mediating the relationship between obesity and heart failure with preserved ejection fraction. *Obes Rev* 2019;**20**:701–12
13. Fitzpatrick SF. Immunometabolism and sepsis: a role for HIF? *Front Mol Biosci* 2019;**6**:85
14. Archid R, Solass W, Tempfer C, Konigsrainer A, Adolph M, Reymond MA, Wilson RB. Cachexia anorexia syndrome and associated metabolic dysfunction in peritoneal metastasis. *Int J Mol Sci* 2019;**20**:5444
15. Claesson-Welsh L, Welsh M. VEGFA and tumour angiogenesis. *J Intern Med* 2013;**273**:114–27
16. Guo BQ, Xu JB, Xiao M, Ding M, Duan LJ. Puerarin reduces ischemia/reperfusion-induced myocardial injury in diabetic rats via upregulation of vascular endothelial growth factor A/angiotensin-1 and suppression of apoptosis. *Mol Med Rep* 2018;**17**:7421–7
17. Ilia R, Zahger D, Cafri C, Abu-Ful A, Weinstein JM, Yaroslavtsev S, Gilutz H, Amit G. Predicting survival with reperfusion arrhythmias during primary percutaneous coronary intervention for acute myocardial infarction. *Isr Med Assoc J* 2007;**9**:21–3
18. Kumar S, Sivagangabalan G, Thiagalingam A, West EB, Narayan A, Sadick N, Ong AT, Kovoor P. Effect of reperfusion time on inducible ventricular tachycardia early and spontaneous ventricular arrhythmias late after ST elevation myocardial infarction treated with primary percutaneous coronary intervention. *Heart Rhythm* 2011;**8**:493–9
19. Angiolillo DJ, Bhatt DL, Cannon CP, Eikelboom JW, Gibson CM, Goodman SG, Granger CB, Holmes DR, Lopes RD, Mehran R, Moliterno DJ, Price MJ, Saw J, Tanguay JF, Faxon DP. Antithrombotic therapy in patients with atrial fibrillation treated with oral anticoagulation undergoing percutaneous coronary intervention: a North American perspective: 2021 update. *Circulation* 2021;**143**:583–96
20. Güven Bağla A, Içkin Gülen M, Ercan F, Aşgün F, Ercan E, Bakar C. Changes in kidney tissue and effects of erythropoietin after acute heart failure. *Biotech Histochem* 2018;**93**:340–53
21. Han HJ, Saeidi S, Kim SJ, Piao JY, Lim S, Guillen-Quispe YN, Choi BY, Surh YJ. Alternative regulation of HIF-1alpha stability through phosphorylation on Ser451. *Biochem Biophys Res Commun* 2021;**545**:150–6
22. Jaakkola P, Mole DR, Tian YM, Wilson MI, Gielbert J, Gaskell SJ, von Kriegsheim A, Hebestreit HF, Mukherji M, Schofield CJ, Maxwell PH, Pugh CW, Ratcliffe PJ. Targeting of HIF-alpha to the von Hippel-Lindau ubiquitylation complex by O2-regulated prolyl hydroxylation. *Science* 2001;**292**:468–72
23. Semenza GL. Hypoxia-inducible factor 1 (HIF-1) pathway. *Sci STKE* 2007;**2007**:cm8
24. Vriend J, Reiter RJ. Melatonin and the von Hippel-Lindau/HIF-1 oxygen sensing mechanism: a review. *Biochim Biophys Acta* 2016;**1865**:176–83
25. Lee JW, Bae SH, Jeong JW, Kim SH, Kim KW. Hypoxia-inducible factor (HIF-1)alpha: its protein stability and biological functions. *Exp Mol Med* 2004;**36**:1–12
26. Sakagami H, Makino Y, Mizumoto K, Isoe T, Takeda Y, Watanabe J, Fujita Y, Takiyama Y, Abiko A, Haneda M. Loss of HIF-1alpha impairs GLUT4 translocation and glucose uptake by the skeletal muscle cells. *Am J Physiol Endocrinol Metab* 2014;**306**:E1065–76
27. Tang W, Long T, Li F, Peng C, Zhao S, Chen X, Su J. HIF-1alpha may promote glycolysis in psoriasis vulgaris via upregulation of CD147 and GLUT1. *Zhong Nan Da Xue Xue Bao Yi Xue Ban* 2021;**46**:333–44
28. Melincovici CS, Boşca AB, Şuşman S, Mărginean M, Mihu C, Istrate M, Moldovan IM, Roman AL, Mihu CM. Vascular endothelial growth factor (VEGF) – key factor in normal and pathological angiogenesis. *Rom J Morphol Embryol* 2018;**59**:455–67
29. Porta M, Striglia E. Intravitreal anti-VEGF agents and cardiovascular risk. *Intern Emerg Med* 2020;**15**:199–210
30. Yla-Herttuala S, Baker AH. Cardiovascular gene therapy: past, present, and future. *Mol Ther* 2017;**25**:1095–106
31. Harada K, Kikuchi R, Ishii H, Shibata Y, Suzuki S, Tanaka A, Suzuki A, Hirayama K, Murohara T. Association between the ratio of anti-angiogenic isoform of VEGF-A to total VEGF-A and adverse clinical outcomes in patients after acute myocardial infarction. *Int J Cardiol Heart Vasc* 2018;**19**:3–7
32. Xiang Y, Yao X, Wang X, Zhao H, Zou H, Wang L, Zhang QX. Houshiheisan promotes angiogenesis via HIF-1alpha/VEGF and SDF-1/CXCR4 pathways: in vivo and in vitro. *Biosci Rep* 2019;**39**: BSR20191006
33. Zhang D, Lv FL, Wang GH. Effects of HIF-1alpha on diabetic retinopathy angiogenesis and VEGF expression. *Eur Rev Med Pharmacol Sci* 2018;**22**:5071–6
34. Fan J, Lv H, Li J, Che Y, Xu B, Tao Z, Jiang W. Roles of Nrf2/HO-1 and HIF-1alpha/VEGF in lung tissue injury and repair following cerebral ischemia/reperfusion injury. *J Cell Physiol* 2019;**234**:7695–707
35. Liu J, Wang W, Wang L, Chen S, Tian B, Huang K, Corrigan CJ, Ying S, Wang W, Wang C. IL-33 initiates vascular remodelling in hypoxic pulmonary hypertension by up-regulating HIF-1alpha and VEGF expression in vascular endothelial cells. *EbioMedicine* 2018;**33**:196–210

*(Received December 28, 2022, Accepted February 22, 2023)*