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Analysis of serum levels of HIF-1α and IL-6 in patients with acute stanford type a aortic dissection

Zheyuan Wang[1†], Junyi Wen[1†], Shaoqin Chen[1] and Lin Lu[1*]

Abstract

Background Studies have reported that Acute Stanford type A aortic dissection (ATAAD) is associated with hypoxia and inflammation. This study aims to explore the levels of HIF-1α and IL-6 in the serum of patients with ATAAD, and to analyze the association between these two factors as well as their potential clinical significance.

Methods Serum samples were collected from 82 ATAAD patients and 19 healthy controls. Subsequently, the levels of HIF-1α and IL-6 in the serum of these samples were measured using the enzyme-linked immunosorbent assay (ELISA).

Results The results showed that the serum HIF-1α level in patients with ATAAD were significantly reduced compared with the healthy control group [10.72 (7.28,14.92) vs. 19.54 ± 8.07 pg/mL, $p < 0.0001$], and the serum IL-6 level were significantly increased [3.12 (1.97, 9.13) vs. 1.13 (0.98, 1.42) pg/mL, $p < 0.0001$]. Moreover, there was no statistical difference of HIF-1α level in ATAAD patients with or without hypoxemia and IL-6. However, there was a significant positive correlation between the levels of IL-6 and the expression of HIF-1α ($r = 0.5435$, $P < 0.0001$).

Conclusion We found that levels of HIF-1α and IL-6 were abnormal in patients with ATAAD. Moreover, the HIF-1α and IL-6 level in ATAAD patients were positively correlated, suggesting that HIF-1α and IL-6 may play roles simultaneously during the development of acute aortic dissection.

Keywords Hypoxia-inducible factor-1 alpha (HIF-1α), Interleukin-6, Acute aortic dissection

Introduction

Acute aortic dissection (AAD) is a disease with rapid onset, rapid progression, high mortality, and complex pathogenesis [1–3]. Accumulating evidences suggested that hypoxia and inflammation play a crucial role in the formation and progression of aortic dissection [4, 5].

HIF-1α is a key transcription factor that is expressed under hypoxic conditions and participates in regulating cell adaptation to hypoxic environments [6]. In recent years, increasing evidence has suggested that HIF-1α plays an important role in cardiovascular disease [7]. In the other hand, IL-6 expression was reported correlates with ATAAD severity and prognosis [8]. Extensive basic research underscores the involvement of interleukin-6 (IL-6) in aortic dissection pathology [9].

However, whether the HIF-1α and IL-6 have synergistic effect on the ATAAD is unclear. In this study, we examine the serum levels of HIF-1α and IL-6 in acute type A aortic dissection, and explore the association between these two factors.

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Materials and methods

Study objects

In our study, we included patients with ATAAD who came to our hospital and treated in our department during the period of June 2022 to July 2023. The diagnosis of ATAAD was primarily confirmed by computed tomography angiography (CTA). Our study encompassed patients who were diagnosed with ATAAD within 24 h of symptom onset. Exclusion criteria were: (1) limb paralysis; (2) severe organ perfusion insufficiency; (3) chronic liver or kidney diseases; (4) coma; (5) massive pleural effusion that cannot be controlled; (6) underlying pulmonary diseases; and (7) preoperative pulmonary infection.

In order to investigate the levels of HIF-1α and IL-6 in acute aortic dissection with and without hypoxemia, we divided patients with acute aortic dissection into two groups: hypoxemia group with OI (PaO2/FiO2) ≤ 300 mmHg and non-hypoxemia group with OI (PaO2/FiO2) > 300 mmHg according to literature [10]. Meanwhile, 19 healthy blood samples were collected as a control group.

This study was approved by the Institutional Review Board of Xiamen Cardiovascular Hospital at Xiamen University.

Research methods

Anticoagulated venous blood samples were collected within 1 h of hospital admission and prior to any surgical interventions to ensure reflection of acute-phase pathological states while avoiding interference from surgical procedures or pharmacological treatments. The supernatant was collected *via* centrifugation and stored in a refrigerator at − 80∘C until use.19 healthy blood samples were collected as a control group. The levels of HIF-1α and IL-6 were tested by ELISA assay (Human Hif-1α ELISA kit, EHC080, NeoBioscience Technology Co.,Ltd, Shenzhen, China; Human IL-6 ELISA kit, EHC007, NeoBioscience Technology Co.,Ltd, Shenzhen, China).The sample dilution used for diluting plasma was analyzed as a blank control. The optical density (OD) of each well was measured at a wavelength of 450 nm in Varioskan Flash Multimode reader (Thermo Scientific, Waltham, Massachusetts, US). The concentration of HIF-1α and IL-6 were calibrated with the HIF-1α and IL-6 standard curve. Assays were repeated in duplicate.

Table 1 Clinical characteristics of the studied population

Characteristics	Healthy (Mean ± SD)	ATAAD(Mean ± SD)	*p* value
Age (years)	47 ± 8.6	49.83 ± 5.57	0.246
Male (%)	12(63.1%)	70(85.4%)	**0.026**
Body weight (kg)	61.59 ± 7.93	62.75 ± 3.82	0.569
Abdominal circumference(cm)	76.05 ± 3.70	83.67 ± 6.26	**0.0001<**
Smoke (%)	2(10.53%)	43(51.81%)	**0.001**
Alcoholism (%)	0	9(12%)	0.202
Hypertension (%)	0	70(85.4%)	**0.0001<**
Diabetes mellitus (%)	0	5(6.1%)	0.58
Coronary artery disease (%)	0	12(14.6%)	0.116
Pericardial effusion	0	23(28%)	**0.006**
HIF-1α (pg/mL)	19.54 ± 8.07	10.72(7.28,14.92)	**0.0001<**
IL-6 (pg/mL)	1.13(0.98,1.42)	3.12(1.97,9.13)	**0.0001<**

Continuous normally distributed variables were expressed as mean(± standard deviation) and not-normally distributed variables as medians (interquartile range)

Statistical analysis

Statistical analyses were performed using SPSS (version 20.0, IBM, USA). The measurement data with normal distribution were expressed as the mean ± standard deviation, while the measurement data with nonnormal distribution were expressed as median and quartile interval. Comparisons of the two independent groups were performed with t tests or Mann-Whitney U tests (for continuous variables) and chi-square tests or Fisher's exact tests (for categorical variables). $p < 0.05$ represented that the difference was statistically significant.

Results

Clinical characteristics of the studied population are shown in Table 1. There were significant differences between the two groups in terms of gender, abdominal circumference, smoking, hypertension, pericardial effusion, HIF-1α, and IL-6 ($P < 0.05$). There were no significant differences in age, body weight, diabetes, alcoholism, coronary heart disease, and other aspects ($P > 0.05$).

Comparison of serum levels of IL-6 and HIF-1α between ATAAD and healthy individuals

Compared to that in healthy individuals, we found that a significant lower serum level of HIF-1α in patients diagnosed with type A acute aortic dissection, (10.72 [7.28, 14.92] pg/mL vs. 19.54 ± 8.07 pg/mL, $p < 0.0001$) (Fig. 1A). Conversely, a significantly higher level of IL-6 was observed in the patient group compared to the control group (3.12 [1.97, 9.13] vs. 1.13 [0.98, 1.42], $p < 0.0001$) (Fig. 1B). These data suggested that the levels of Hif-1α and IL-6 are abnormal in ATAAD.

Comparison of serum levels of HIF-1α and IL-6 in type a acute aortic dissection with or without hypoxemia

To further investigate whether the levels of HIF-1α and IL-6 associate with hypoxemia, we compared these levels in ATAAD patients with or without hypoxemia. The data revealed that in type A acute aortic dissection, regardless of whether it is in hypoxic or non-hypoxic state, there is no significant difference in the serum expression levels of

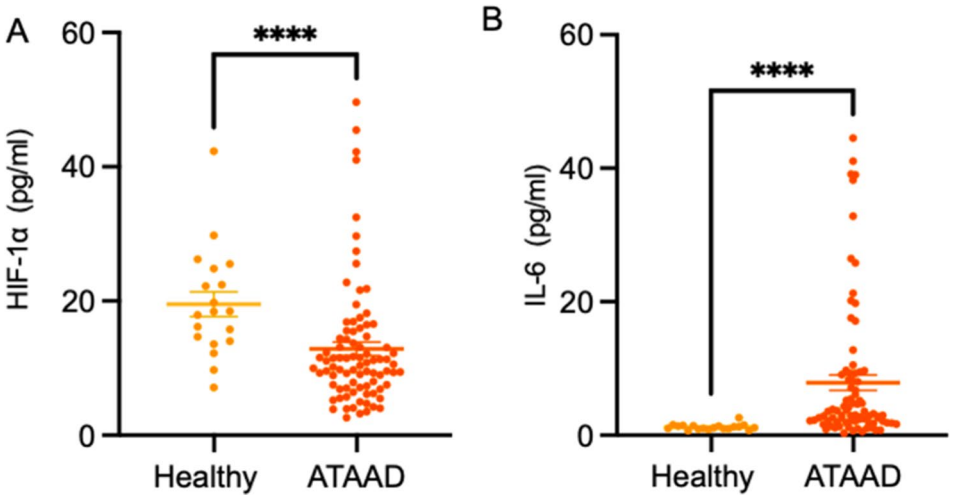

Fig. 1 Comparison of serum levels of HIF-1α (**A**) and IL-6 (**B**) between type A acute aortic dissection and healthy individuals.****, $P < 0.0001$

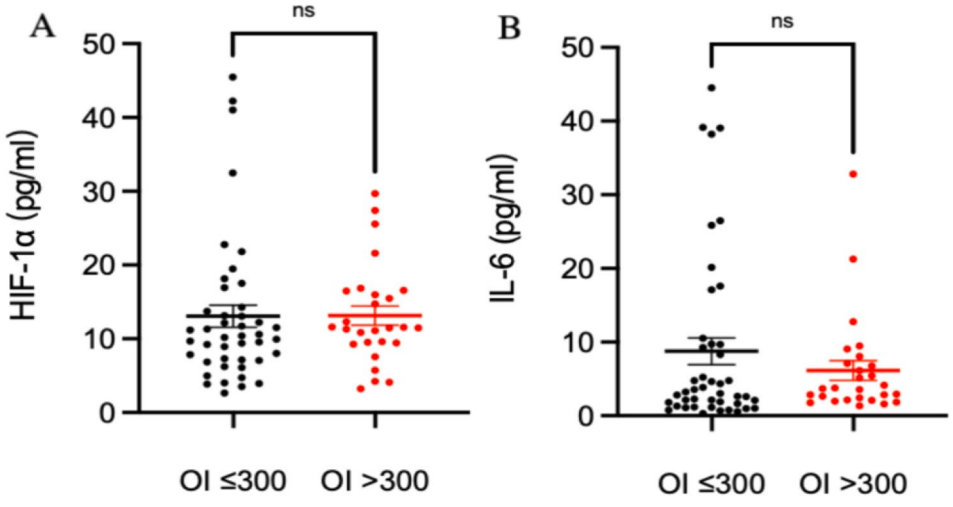

Fig. 2 Comparison of serum levels of HIF-1α (**A**) and IL-6 (**B**) between hypoxemia and non-hypoxemia groups.ns, no significance

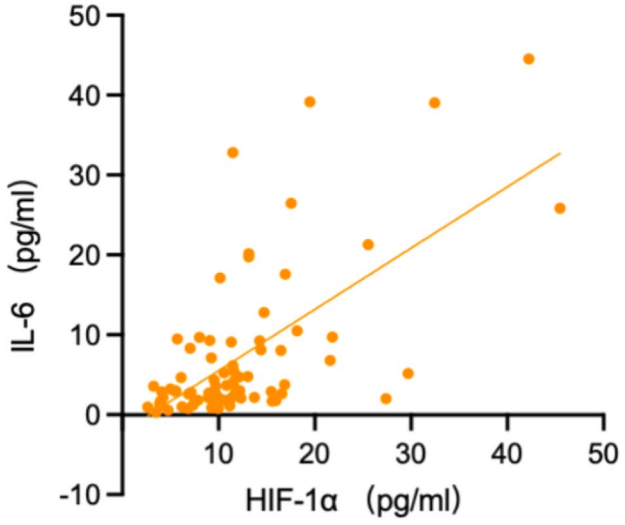

Fig. 3 Correlation between HIF-1α and IL-6($r = 0.5435$)

HIF-1α [10.28 (7.07, 14.13) vs. 11.48 (9.42, 16.48) pg/mL, $p > 0.05$] and IL-6 [3.12 (1.41, 9.71) vs. 3.68 (2.15, 7.12) pg/mL, $p > 0.05$] (Fig. 2A-B).

Correlations of HIF-1α with IL-6 in ATAAD patients

To further elucidate whether there is a combined effect of inflammation and hypoxia in the pathogenesis of ATAAD, we conducted a Spearman's correlation analysis. Our results revealed that there was a significant positive correlation between the levels of IL-6 and HIF-1α ($r = 0.5435$, $P < 0.0001$), indicating a potential relationship or interaction between these two factors that may simultaneously contribute to the occurrence and progression of type A acute aortic dissection (Fig. 3).

Discussion

Acute aortic dissection is an extremely severe cardiovascular disease [1]. Its exact pathogenesis is not yet fully understood. Studies have suggest that hypoxia and inflammation play crucial roles in the formation and progression of aortic dissection [4, 5]. Studies reported that hypoxic environments or HIF-1α not only significantly increase the concentration of macrophages expressing IL-6 around blood vessels, but also induce macrophage proliferation and migration, promote the survival of inflammatory cells, and enhance the inflammatory response, with evidence suggesting that HIF-1α is associated with the IL-6/STAT3 pathway [11–13].

Macrophages can undergo metabolic reprogramming *via* the HIF-1α-ADAM17 pathway, facilitating vascular inflammation, extracellular matrix degradation, and elastic lamina rupture, thereby exacerbating the development of aortic dissection [14]. The onset of aortic dissection is accompanied by a marked rise in both the quantity and proportion of synthetic smooth muscle cells, leading to diminished aortic elasticity and subsequent vessel wall rupture [15–17]. Research suggests that hypoxia-induced HIF-1α may mediate smooth muscle cell phenotype switching via the PI3K/AKT pathway, suppressing proliferation and migration capacities through downregulation of AEG-1 expression [18]. In murine models of aortic dissection, elevated HIF-1α levels are observed in aortic smooth muscle tissues. HIF-1α is implicated in regulating macrophage autophagy in type A aortic dissections and fostering hypoxia-driven proliferation and migration of vascular smooth muscle cells (VSMCs). Under hypoxic conditions, the deletion of HIF-1α has been shown to diminish VSMC proliferation and migration capabilities [19].

In this study, Spearman 's correlation analysis showed a positive correlation between HIF-1α and IL-6 serum levels, suggesting a correlation or interaction between these two factors. This is inconsistent with previous cellular pathway and histological studies. During hypoxia, HIF-1α increases and affects gene expression related to hypoxia adaptation and IL-6 expression. Both are associated with inflammatory response and vascular endothelial function [20, 21]. The positive correlation between HIF-1α and IL-6 in acute aortic dissection suggests that they may jointly promote disease progression. This provides new clues for future directions and treatment strategies.

However, our research found that the expression of HIF-1α in human blood samples from patients with type A aortic dissections is lower than that in healthy individuals. This may due to several possibilities as list below:

1. Acute hypoxia strongly induces the expression of HIF-1α. In the study of hypoxia adaptation in injured epithelia, exposure to chronic hypoxia environments similar to wound microenvironments leads to a decrease in the level of mTOR (mammalian target of rapamycin), which in turn leads to a decrease in HIF-1α levels [22]. The occurrence of acute aortic dissection may also be related to chronic hypoxia. In clinical work, we also find that some AD patients are obesity, they are suffering from obstructive sleep apnea syndrome (OSAS) and are in a state of hypoxia for a long time. This also indicates that they are in a statement of chronic hypoxia. We know that HIF-1α is an easy degradation factor under non-hypoxic environment. All of the AD patients are given oxygen therapy as soon as they are on the way to the hospital when they are in the ambulance. Even if some patients are not sent by ambulance, they are also given oxygen therapy as soon as admission. The hypoxic environment will be changed and the HIF-1α is degradated. In this case, the serum level of HIF-1α may be down-regulated [23–25].
2. It has been reported that high levels of HIF-1α expression were observed in tissue samples of acute aortic dissection, while we observed low levels of HIF-1α in serum [26]. This difference may be due to the different distribution and mechanism of action of HIF-1α inside and outside the cell. Because HIF-1α mainly functions as a transcription factor in the nucleus, when aortic dissection occurs, HIF-1α needs to enter the nucleus to bind to the HRE (hypoxia response element) in DNA to regulate the expression of downstream genes. Therefore, the release of HIF-1α outside the cell will be correspondingly reduced.
3. In aortic dissection, there may be other biological molecules that inhibit HIF-1α. These molecules can reduce its level through signal transduction pathways or directly interact with HIF-1α. The expression of HIF-1α is affected by multiple factors, including but not limited to IL-6. Even if the level of IL-6 increases, other regulatory factors may also lead to a decrease in HIF-1α expression. That can explain our result: although HIF-1α and IL-6 level in ATAAD patients were positively correlated, the serum IL-6 level were significantly increased while the serum HIF-1αlevel were significantly reduced.
4. In ATAAD patients, HIF-1α expression levels exhibit distinct patterns across different stages of the disease, implicating stage-specific variations. Given the dynamic nature and progression of aortic dissection, HIF-1α expression is likely subject to temporal fluctuations throughout the course of the illness. Moreover, the observed discrepancies in serum HIF-1α levels can be attributed to interindividual variability and sample heterogeneity.

The patient response to IL-6 and HIF-1α in the context of aortic dissection shows cell-type and tissue-dependent variability, introducing further complexity. This cellular heterogeneity may result in divergent expressions of HIF-1α within specific cell populations compared to the overall serum concentrations, highlighting the need for nuanced interpretations of HIF-1α's role in the pathophysiology of aortic dissection.

Although animal models can provide useful preliminary data in many cases, there are significant species differences between the physiological systems of humans and rodent. Therefore, there are certain limitations in applying animal experimental results to humans due to species differences in the observed increase in HIF-1α levels in rodent models, and further clinical research is needed.

Due to the limitation of sample collection, the sample size of the measurement is small, and the research results of the experiment have certain limitations. We can increase the sample size in one step to reduce the relevant impact of the offset value. In our study, we only use ELISA to detect the levels of HIF-1α and IL-6 in serum, and can further verify the expression levels of both through retesting using immunofluorescence, Western blot analysis, and other methods.

Conclusion

Our research found that the levels of HIF-1α and IL-6 in ATAAD patients is abnormal. Notably, a positive correlation was observed between the serum levels of HIF-1α and IL-6, suggesting a potential synergistic role in the progression of acute aortic dissection. Further studies is need to elucidate detail roles of HIF-1α and IL-6 in ATAAD.

Abbreviations

ATAAD	Acute Stanford type A Aortic Dissection
AAD	Acute Aortic Dissection
CTA	Computed Tomography angiography
HRE	Hypoxia Response Element
OSAS	Obstructive Sleep Apnea Syndrome

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Author contributions

Zhenyuan Wang: Wrote the manuscript, Designed the research. Performed the research, Analyzed the data, Conceptualization, Investigation, Methodology, Visualization, Project administration. Junyi Wen: Data Curation, Methodology, Validation, Project administration. Shaoqin Chen: Designed the research, Methodology, Conceptualization, Investigation. Lin Lu: Conceptualization, Writing-review and editing, Funding acquisition, Supervision, Project administration. All authors contributed to the article and approved the submitted version.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

This study was conducted in accordance with the principles of the Declaration of Helsinki, and it has been approved by the Ethics Committee of Xiamen Cardiovascular Hospital Xiamen University. Written informed consent was obtained from all participants after they received an explanation of the study.

Consent for publication

All authors are consentient for publication.

Competing interests

The authors declare no competing interests.

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