Immunome Research

Firoj, et al., Immunome Res 2016, 12:2
DOI: 10.4172/1745-7580.10000121

Review Article Open Access

Role of Plasma Cytokines and Endotoxin in Patients with Acute Aortic Dissection

Firoj KM*, Fa XE, Yu HB and Huang ZF

[1]*Department of Cardio-Vascular Surgery, 2nd Affiliated Hospital of Zhengzhou University, Zhengzhou, Henan, P.R China*

***Corresponding author:** Khan Mohammed Firoj, Department of Cardio-Vascular Surgery, 2nd Affiliated Hospital of Zhengzhou University, Zhengzhou, Henan, P.R China, Tel: 008613027787275; E-mail: falishakhan72@yahoo.com

Received date: May 28, 2016; **Accepted date**: August 25, 2016; **Published date**: August 25, 2016

Abstract

Objective: To analyze the role of plasma cytokines and endotoxin in patients with acute aortic dissection (AAD) in concluding prognostic effect.

Material and methods: A total of 85 patients with acute aortic dissection were admitted in 2nd affiliated hospital of Zhengzhou university from January 2009 to November 2015. Patients were divided into death group and survival group. At the time of admission (T1), 12 hours after admission (T2), 24 hours after admission (T3), the plasma level of
interleukin-6 (IL-6), interleukin- 10 (IL-10), tumor necrosing factor- alpha(TNF-α) and endotoxins were measured.

Results: The plasma level of IL-6, TNF-α and endotoxins in death group at each time point were significantly higher than survival group (F group=3.194, 5.973, 9.156, P<0.05. There were significant difference of IL-6, TNF-α and endotoxins levels among three time points in two groups (F time=5.135, 11.548, 8.875, P<0.05. IL-6, TNF-α levels in the survival group at T3, IL-6 level in death group at T2, IL-6, TNF-α and endotoxins levels in the death group at T3 were significantly higher than T1, P<0.05. There was no significant difference in IL-10 level between two groups and among three time points (F group=1.674, F time=2.901, P>0.05.

Conclusion: Plasma level of IL-6, TNF-α and endotoxin are increased in the acute aortic dissections showing the progressive development of AAD. Our findings in this study indicate the role of inflammation during AAD. The changing pattern of these markers can be used for diagnosis and prophylactic treatment of AAD.

Keywords Acute aortic dissection (AAD); Cytokines; TNF-α; Endotoxin

Introduction

Acute dissection of the aorta is an uncommon yet potentially catastrophic clinical event that mandates prompt recognition and expeditious treatment. Diagnosis begins with a high clinical index of suspicion in a patient presenting with chest pain and one or more predisposing risk factors, most notably, hypertension or an inherited disorder of connective tissue.Aortic dissection is characterized by medial degeneration with intimal tear and crossing of blood into the artery wall, leading to the formation of a false lumen and subsequent systemic inflammatory responses [1]. Interleukin-6 (IL-6), C-reactive protein (CRP), and tumor necrosis factor-α (TNF-α) are major pro-inflammatory cytokines, and their increasing levels have been demonstrated to be closely related to the progression of dissection and TAAD-related complications [2,3].

In clinical practice, TEE or contrast-enhanced CT scanning has become the initially preferred diagnostic strategy for the assessment of patients with suspected acute aortic syndromes. The use of MRI has been limited by the restricted availability of the magnets and by considerations of patient safety while undergoing study.

Our aim of this study is to find out the relationship between the rising of major pro-inflammatory cytokines with the progression of AAD.

Material and Methods

From January 2009 to November 2015, after excluding the patients who died before emergency surgical intervention, 85 cases of acute aortic dissection were admitted and performed successful emergency surgery, including 51 males and 34 females. Aged 35-67 years, duration from onset of disease to the emergency surgery was 18-43 hours. After the surgery, patients were divided into two groups according to the prognosis, survival group (69 cases) and death group (16 cases). In two groups, duration from onset of disease to the emergency surgery, gender, age, systolic and diastolic blood pressure at the time of admission were compared, the differences were not statistically significant as shown in the Table 1 below.

Venous blood of the patients were drawn and the plasma was separated to use for ELISA test through which the plasma level of IL-6, IL-10 and TNF-α were measured out at time, T1=at the time of admission, T2=12 hours after the admission, T3=24 hours after the admission.

Main steps of measurement: in the holes of standard and sample microplate, biotin marker fluid was added, wash gently in microplate washer after incubating the reaction, then an enzyme labeled marker

liquid is added and incubate the reaction in dark at 37, wash again after the reaction in the same way above in the micro plate washer. Termination buffer is added to stop the reaction. Micro-plates are kept on the ELISA reader or micro-plate reader at 450 nm to read the light absorbance and find out the corresponding level of the sample in the standard curve.

Group	N(M/F)	T(/h)	Age/year	SBD/mmHg	DBP/mmHg
Survival	69(41/28)	11.5 ± 7.4	48 ± 14	146 ± 23	96 ± 14
Death	16(10/6)	10.9 ± 8.7	45 ± 13	139 ± 21	97 ± 10
X2/t	0.051	0.283	0.782	1.114	0.270
P	0.821	0.778	0.436	0.269	0.788

Table 1: General comparison of survival and death groups.

Plasma endotoxin levels in both groups were measured by using LIMULUS kit, (endotoxin assay kit). Important steps: draw anticoagulated plasma, water bath, oscillation or shaking, collect the supernatant, adding buffer solution, then add the limulus reagent, after water bath add successively, sodium nitrate, sulfur amino amines, naphthylethylenediamine, and put on the spectrophotometer to see the corresponding color absorbance at spectral light of 721 degree. According to the absorbance value in the standard curve, the plasma levels of endotoxin were checked.

Statistical analysis

SPSS 11.5 was used to analyze the data, plasma level of cytokines and endotoxins in two groups were compared using variance analysis of repeated measured data, test level α=0.05

Result

Comparisons of plasma cytokines and endotoxins in two groups at different time are shown in the Table 2. From the Table 2, compared with the survival group, the plasma levels of IL-6, TNF-α and endotoxins were increased at each time of measurement in the death group. Within the survival and death group, the comparisons of plasma IL-6, TNF-α and endotoxin at each time point were statistically significant. In the survival group, plasma level of IL-6, TNF-α at T3 is higher than in T1, in the death group, plasma level of IL-6 at T2, plasma level of IL-6, TNF-α and endotoxin at T3 are raised. While comparing the Plasma level of IL-10 in each time of measurement in the two groups, the differences were not statistically significant.

Group	n	IL-6	TNF-α	Endotoxin	IL-10
Survival					
T1	69	0.04 ± 0.02	23.32 ± 12.67	31.55 ± 5.78	30.13 ± 19.97
T2	69	0.07 ± 0.13	33.35 ± 17.32	31.74 ± 6.98	33.77 ± 19.21
T3	69	0.15 ± 0.07	46.56 ± 54.42	32.26 ± 4.18	33.38 ± 32.74
Death					
T1	16	0.08 ± 0.02	33.47 ± 13.14	41.13 ± 19.97	31.55 ± 5.78
T2	16	0.18 ± 0.04	53.77 ± 19.21	53.77 ± 19.21	31.74 ± 6.98
T3	16	0.24 ± 0.05	101.38 ± 32.74	101.38 ±32.74	32.26 ± 4.18
F group		3.914(0.041)	5.973(0.023)	9.15(0.014)	1.674(0.195)
F time		5.135(0.036)	11.548(0.005)	8.875(0.015)	2.901(0.089)

Table 2: Comparing plasma level of IL-6, TNF-α, endotoxins and IL-10 in survival and death group mg/L.

Discussion

The Stanford type A Aortic Dissection (TAAD) is associated with severe morbidity and mortality. [1,2]. Patients without optimal medical treatment have a mortality rate of 50-68% during the first 48 hours after an acute event, with a mean mortality of up to 1% per hour, and reaches as high as 90% within 3 months [3]. Despite the continuous advances of diagnostic technologies during recent years [4], it remains difficult to assess the progression of TAAD accurately.

Hospital and long-term survival has improved substantially over the past 40 years, yet there remains ample room for continued progress. For centers with an active interest in the evaluation and management of acute dissection, hospital mortality rates have been lowered to 15% to 25% [5-7]. Five-year actuarial survival rates range between 50% and 70%,[6-9] with a 7% to 20% incidence of late reoperation, usually for aneurysmal enlargement or re-dissection [6,10,11]

Acute aortic dissection is a dreaded, life threatening, rapidly progressing cardiovascular disease with high mortality rates. Aortic dissection may lead to systemic inflammatory response syndrome (SIRS) and even may cause multiple organ dysfunction syndromes (MODS) [12-15]. Aortic dissection leads to the formation of true and false lumen of the aorta, the blood flow in the false lumen causes further development of downstream false lumen. With the progression of dissection, blood volume in the false lumen increases which causes compression of true lumen reducing blood supply to the distal organs including intestines leading to systemic tissue ischemia [16,17]. In addition to the blood occupying false lumen leading to tissue ischemia, plasma cytokines and endotoxin released after the stress in acute aortic dissection can also lead to SIRS. According to authors, whether in survival or death group, after the acute aortic dissection, the plasma endotoxin and pro-inflammatory factors like IL-6, TNF-α are sharply increased; explaining that outbreak of cytokines and endotoxin after the event of acute aortic dissection can lead to SIRS.

Previous studies reported that injury or severe illness, even dirty operation can result in an increase in plasma cytokines and endotoxin [18]. Changes in plasma level of cytokines and endotoxins can also reflect the severity of the patient's condition [19]. Continuous determination of plasma endotoxins and inflammatory mediators can help to predict the prognosis of patients and improve the physician's emphasis on such patients to provide early intervention and treatment [20]. Suitable inflammatory mediators in patients with acute aortic dissection can not only reflect severity of systemic inflammatory response but also can predict the prognosis of patients by monitoring the variations in plasma level of inflammatory mediators with time. In recent years, many articles have reported the variation of SIRS in patients with acute aortic dissection.

Wen et al. analyzed the relationship between the prognosis and plasma level of inflammatory mediators [2]. Nomura et al. compared the plasma levels of inflammatory mediators in patients with and

without the residual dissection [21]. The above studies confirmed that plasma level of cytokines have a strong association with acute aortic dissection. Current evidence demonstrated a significant infiltration of macrophages and neutrophils in the dissected aortic wall [22]. These recruited leukocytes could release a series of pro-inflammatory cytokines, which would further accelerate the progression of dissection and lead to systemic complications. Early detection of pro-inflammatory mediators and increase anti-inflmmatory response can improve the survival rate of the patients [1-3]. A sharp increase of plasma IL-6, TNF-α and endotoxins in patients with AAD may indicate a poor prognosis.

Conclusion

In this small sample size, prospective study, we demonstrated that the plasma level of pro-inflammatory cytokines, IL-6, TNF-α and endotoxins in death group at each time point were higher than the survival group but level of anti-inflammatory cytokines, IL-10 between the two groups did not show any significant difference. It explains clearly that after the onset of AAD, pro-inflammatory mediators are dramatically increased and anti-inflammatory mediators are unable to rise to weaken the SIRS which may be the cause of poor prognosis. So clinicians should try to improve the importance and the best way of treating these diseases as soon as possible.

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