Early use of beta-blockers attenuates systemic inflammatory response and lung oxygenation impairment after distal type acute aortic dissection

Abstract We have reported that serum C-reactive protein (CRP) elevation is an independent predictor of lung oxygenation impairment (LOI) after distal type acute aortic dissection (AAD). Systemic activation of the inflammatory system after aortic injury may play a role in the development of LOI. The aim of this study is to clarify the effect of beta-blockers on systemic inflammation and the development of LOI after distal type AAD. A total of 49 patients, who were admitted with distal type AAD and treated conservatively, were examined. White blood cell (WBC) count, serum CRP level, and arterial blood gases were measured serially. Forty patients received beta-blocker treatment within 24 h of the onset, while 9 patients received no beta-blocker treatment. Maximum WBC count, maximum CRP level, lowest PaO2/FiO2 (P/F) ratio, and patient background were compared between the two groups. There was no difference between the groups according to age, sex, coronary risk factors, blood pressure, serum level of CRP, WBC count, and oxygenation index on admission. Beta-blocker treatment was associated with lower maximum WBC count \( (P = 0.0028) \) and lower maximum serum CRP level \( (P = 0.0004) \). The minimum P/F ratio was higher in patients with beta-blocker treatment than in those without \( (P = 0.0076) \). Multivariate analysis revealed that administration of a beta-blocker was an independent negative determinant of LOI \( (P/F \text{ ratio } \leq 200 \text{ mmHg}) \). In conclusion, early use of beta-blockers prevented excessive inflammation and LOI after distal type AAD, suggesting a pleiotropic effect of beta-blockers on the inflammatory response after AAD.

Key words Acute aortic dissection · Beta-blocker · Inflammation · Lung oxygenation impairment · C-reactive protein

Introduction

Despite significant advances in diagnostic and therapeutic techniques, the morbidity and mortality of acute aortic dissection (AAD) remain high. According to the international registry of AAD, overall in-hospital mortality was 27.4%. Although the mortality of patients with type B dissection treated medically is relatively low,1,2 type B AAD is sometimes complicated by lung oxygenation impairment (LOI) which begins two or three days after the onset of AAD.4,5 We have reported that elevation of serum C-reactive protein (CRP) is an independent predictor of the development of LOI after AAD and that peak CRP level is negatively correlated with the lowest PaO2/FiO2 (P/F) ratio.4 The inflammatory response is a necessary consequence for tissue repair. However, if the inflammatory system is inappropriately activated, a pathological condition similar to the systemic inflammatory response syndrome (SIRS) may develop. Systemic activation of the inflammatory system after aortic injury may play a role in the development of this complication.

Patients with AAD should be managed by strict reduction of systolic pressure to 100–120 mmHg or the lowest level that is tolerated. For blood pressure control, a beta-blocker is recommended as the first-line drug because they reduce not only blood pressure but also heart rate and the rate of rise in systolic pressure, minimizing aortic shear stress. Recently, a pleiotropic effect of beta-blockers has been reported. Some studies have revealed that beta-blockers have an anti-inflammatory effect and attenuate levels of inflammatory cytokines or matrix metalloproteinases in heart failure or acute myocardial infarction.6–8 Moreover, treatment with a beta-blocker was reported to reduce plaque thickness of the carotid artery and to inhibit endothelial dysfunction through a potent antioxidant mechanism, suggesting a beneficial effect on the vascular endothelium.10,11 However, the effect of beta-blockers on the inflammatory response in AAD has not been determined. In the present study, we evaluated the effect of beta-blockers on systemic inflammation and the development of LOI after distal type AAD.
Materials and methods

Study population

Between February 1991 and January 2007, 102 patients diagnosed with distal type AAD were admitted to our hospital. Of them, a total of 76 consecutive patients who were admitted within 24 h of the onset of symptoms and who received conservative treatment were examined. Patients were divided into two groups according to the presence or absence of treatment with beta-blockers, including carvedilol, atenolol, metoprolol, and arotinolol. All beta-blockers were administered orally. The decision to start beta-blocker treatment was made by the patient’s supervising physician. The reasons why beta-blockers were not given were included bradycardia (n = 2), bronchial asthma (n = 1), hypotension (n = 1), and not specified (n = 5) (Table 1). Patients with chronic renal failure (serum level of creatinine on admission >2 mg/dl), advanced liver disease, heart failure, malignant disease, collagen disease, chronic obstructive pulmonary disease, or infectious disease including pneumonia were excluded from this study population. Patients who had received initial administration of a beta-blocker more than 24 h after the onset of symptoms were also excluded. Therefore, all patients with beta-blocker treatment received initial administration within 24 h of the onset of AAD in this study. We also excluded patients who died or underwent a surgical procedure or endovascular aortic repair before determination of peak CRP level. Forty-nine patients were finally included in this study.

Study protocol

The diagnosis of AAD was made based on typical chest and back pain and findings on contrast-enhanced computed tomographic scans of the chest, abdomen, and pelvis on admission. Blood samples were obtained on admission (before administration of beta-blockers) and then every 24 h for at least 4 days. Total white blood cell (WBC) count was measured by an automated hematology analyzer (Sysmex SE-9000, Toa Medical Electronic, Kobe, Japan). Serum samples were stored at −70°C until CRP analysis. CRP level was measured by latex photometric immunoassay (LPIA-CRP, Mitsubishi Chemical, Tokyo, Japan) using an autoanalyzer (Hitachi 7450, Hitachi, Tokyo, Japan). Serum cardiac troponin T and/or creatine kinase were measured in all patients on admission and during hospitalization. Aortic blood samples were obtained on admission and at least every 24 h thereafter for 5 days, and the arterial oxygen tension (PaO₂) was measured using an automatic blood gas analyzer system (ABL-520, Radiometer, Copenhagen, Denmark). The PaO₂/fractional inspired oxygen (P/F) ratio was calculated to evaluate the severity of oxygenation impairment. During the acute phase, arterial blood pressure was monitored and systolic blood pressure was controlled between 100 and 120 mmHg with oral and intravenous administration of antihypertensive agents including calcium channel blockers, nitroglycerin, and/or beta-blockers. No patients received nonsteroidal anti-inflammatory drugs, corticosteroids, immunosuppressive agents, or other medication that could affect the inflammatory response. Blood and sputum cultures were performed when body temperature exceeded 38°C or respiratory infection was suspected clinically. The following data were obtained: age, sex, risk factors for atherosclerosis including smoking, hypertension, diabetes mellitus, hypercholesterolemia (total cholesterol level ≥220 mg/dl), elapsed time from the onset of symptoms to hospital admission, blood pressure on arrival, and concomitant medication before and after hospitalization including beta-blockers, angiotensin converting enzyme inhibitors (ACE-I), angiotensin II receptor blockers (ARB), calcium channel blockers, and statins. The data of computed tomographic scans, including the extent of aortic dissection, and whether the dissection was open or thrombosed type, were analyzed by two independent radiologists without knowledge of the patients’ background. The extent of dissection was determined according to DeBakey’s classification: the dissection process was limited to the descending thoracic aorta (DeBakey IIIa) or extended below the diaphragm to involve the abdominal aorta (DeBakey IIIb). LOI was defined as the lowest P/F ratio ≤200 mmHg. The study protocol was in agreement with the guidelines of the ethics committee of our institution.

Statistical analysis

Continuous data were expressed as mean ± SD. Comparison between the two groups was performed using Student’s t-test or the Mann–Whitney U-test for continuous variables and Fisher’s exact test for categorical variables. Multiple logistic regression analysis was used to assess the effect of various factors on the development of oxygenation impairment. Statistical significance was defined as a P value of less than 0.05. All statistical analyses were performed using SPSS 13.0 for Windows (SPSS, Chicago, IL, USA).

Results

Patient characteristics

The mean age was 64 ± 12 years (range: 29–89). Thirty-four patients (69%) were male. The mean elapsed time from the onset of AAD to admission was 3.6 ± 4.6 h (range: 0.5–20.0). Within 24 h of the onset of symptoms, 40 patients received administration of beta-blockers, including carvedilol (n =
The 9 patients who had not received beta-blockers during hospitalization were compared with the patients who received beta-blockers. Table 2 shows the patient characteristics of the two groups. Age, sex, smoking, history of hypertension, diabetes mellitus, hypercholesterolemia, coronary artery disease, and Marfan syndrome, elapsed time from onset to arrival at hospital, DeBakey classification IIIa/IIIb, false lumen patency, and P/F ratio on admission were comparable between the two groups. Arterial blood pressure was similar on arrival between the two groups and controlled in the range of 100–120 mmHg with oral and intravenous administration of antihypertensive agents. There was no difference in arterial blood pressure during hospitalization between the two groups.

Table 3 shows the medication in the two groups. Prior use of beta-blockers, ACE-I, ARB, calcium channel blockers, nitrates, and statins was comparable between the two groups. Concomitant medication after admission including calcium channel blockers, nitrates, and statins was also comparable between the two groups. Serum level of creatinine on admission was significantly lower in patients with beta-blocker treatment than in those without. No patients showed electrocardiographic signs of myocardial ischemia. Serum cardiac troponin T and creatine kinase levels were not significantly elevated in any patient. Sputum and blood cultures revealed no evidence of pneumonia or bacteremia in any patient.

Beta-blocker treatment and peak CRP level and peak WBC count

Serial changes in serum CRP level are shown in Fig. 1A. Serum CRP levels on days 2–6 in patients with beta-blocker treatment were significantly lower than those in patients without, although serum CRP level on admission was comparable between patients with and without beta-blocker treatment. The mean peak CRP level was 16.8 ± 11.2 mg/dl. Peak CRP level in patients with beta-blocker treatment was lower than that in those without (28.2 ± 20.5 vs. 14.2 ± 5.6 mg/dl, P = 0.0004, Fig. 2A).

Serial changes in peripheral WBC count are shown in Fig. 1B. White blood cell counts on days 2–6 in patients with beta-blocker treatment were significantly lower than those in patients without beta-blocker treatment, despite similar WBC counts on admission in the two groups (11 211 ± 2077 vs. 9 836 ± 3244 /mm³, P = 0.23). The mean maximum WBC

20), atenolol (n = 16), metoprolol (n = 3), and arotinolol (n = 1). The 9 patients who had not received beta-blockers during hospitalization were compared with the patients who received beta-blockers. Table 2 shows the patient characteristics of the two groups. Age, sex, smoking, history of hypertension, diabetes mellitus, hypercholesterolemia, coronary artery disease, and Marfan syndrome, elapsed time from onset to arrival at hospital, DeBakey classification IIIa/IIIb, false lumen patency, and P/F ratio on admission were comparable between the two groups. Arterial blood pressure was similar on arrival between the two groups and controlled in the range of 100–120 mmHg with oral and intravenous administration of antihypertensive agents. There was no difference in arterial blood pressure during hospitalization between the two groups.

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Table 2. Patient characteristics

|                        | Beta-blocker (−) (n = 9) | Beta-blocker (+) (n = 40) | P value |
|------------------------|--------------------------|--------------------------|---------|
| Age, years             | 66 ± 6                   | 63 ± 13                  | 0.51    |
| Male/Female, n         | 8/1                      | 26/14                    | 0.24    |
| Smoking, n (%)         | 5 (56)                   | 24 (60)                  | >.999   |
| Hypertension, n (%)    | 9 (100)                  | 37 (93)                  | >.999   |
| Diabetes mellitus, n (%) | 2 (22)                 | 4 (10)                   | 0.30    |
| Hypercholesterolemia, n (%) | 2 (22)                | 21 (53)                  | 0.15    |
| History of coronary artery disease, n (%) | 1 (11)           | 4 (10)                   | >.999   |
| Marfan syndrome, n (%) | 0 (0)                    | 2 (5)                    | >.999   |
| Elapsed time from onset, h | 3.2 ± 4.0               | 3.7 ± 4.8                | 0.76    |
| Serum creatinine, mg/dl | 1.2 ± 0.4               | 0.9 ± 0.3                | 0.0008  |
| DeBakey IIIa/IIIb, n   | 1/8                      | 17/23                    | >.999   |
| Open/Close type, n     | 3/6                      | 17/23                    | 0.72    |
| P/F ratio on admission, mmHg | 365 ± 91               | 351 ± 81                 | 0.65    |
| Systolic BP on arrival, mmHg | 189 ± 18            | 181 ± 35                 | 0.52    |
| Diastolic BP on arrival, mmHg | 103 ± 11           | 99 ± 26                  | 0.62    |

Continuous variables are presented as mean ± SD
BP, blood pressure; P/F, arterial oxygen tension/fractional inspired oxygen

Table 3. Concomitant cardiovascular drugs

|                        | Beta-blocker (−) (n = 9) | Beta-blocker (+) (n = 40) | P value |
|------------------------|--------------------------|--------------------------|---------|
| Before admission       |                          |                          |         |
| Beta-blocker, n (%)    | 2 (22)                   | 5 (13)                   | 0.60    |
| Ca channel blocker, n (%) | 2 (22)                | 12 (30)                  | >.999   |
| ACE-I/ARB, n (%)       | 1 (11)                   | 7 (18)                   | >.999   |
| Nitrile, n (%)         | 2 (18)                   | 0 (0)                    | 0.18    |
| Statin, n (%)          | 1 (11)                   | 2 (5)                    | 0.46    |
| After admission        |                          |                          |         |
| Ca channel blocker, n (%) | 9 (100)              | 38 (95)                  | >.999   |
| ACE-I/ARB, n (%)       | 2 (22)                   | 28 (70)                  | 0.019   |
| Nitrile, n (%)         | 9 (100)                  | 28 (70)                  | 0.09    |
| Statin, n (%)          | 0 (0)                    | 8 (20)                   | 0.32    |

ACE-I, angiotensin-converting enzyme inhibitors; ARB, angiotensin II receptor blockers
A Serial changes in serum C-reactive protein (CRP) level after distal type acute aortic dissection (AAD). Serum CRP levels on days 2, 3, 4, 5, and 6 in patients with beta-blocker treatment were significantly lower than those in patients without beta-blocker treatment, although serum CRP level on admission was comparable between patients with and without beta-blocker treatment. *P < 0.05. B Serial changes in peripheral white blood cell (WBC) count after distal type acute aortic dissection (AAD). WBC count on days 2, 3, 4, 5, and 6 in patients with beta-blocker treatment was significantly lower than that in those without beta-blocker treatment, although WBC count on admission was comparable between the two groups. *P < 0.05

![Fig. 1](image1.png)

**Fig. 1.** A Serial changes in serum C-reactive protein (CRP) level after distal type acute aortic dissection (AAD). Serum CRP levels on days 2, 3, 4, 5, and 6 in patients with beta-blocker treatment were significantly lower than those in patients without beta-blocker treatment, although serum CRP level on admission was comparable between patients with and without beta-blocker treatment. *P < 0.05. B Serial changes in peripheral white blood cell (WBC) count after distal type acute aortic dissection (AAD). WBC count on days 2, 3, 4, 5, and 6 in patients with beta-blocker treatment was significantly lower than that in those without beta-blocker treatment, although WBC count on admission was comparable between the two groups. *P < 0.05

The mean P/F ratio immediately after admission was 353 ± 82 mmHg and the mean of the lowest P/F ratio was 210 ± 90 mmHg. Lung oxygenation impairment was present in 47% of patients with AAD. Although P/F ratio on admission was similar in the two groups, the lowest P/F ratio was significantly lower in patients with beta-blocker treatment than in those without (140 ± 41 vs. 226 ± 90 mmHg, P = 0.0076, Fig. 3). The use of mechanical ventilatory support because of LOI in patients with beta-blocker treatment was significantly less frequent than that in those without (15% vs. 56%, P = 0.019). Time to the lowest P/F ratio after the onset of AAD was comparable between the two groups (3 ± 1 vs. 3 ± 2 days, P = 0.54).

**Effect of beta-blockers on LOI**

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**Determinants of LOI**

Multiple logistic regression analyses revealed that administration of a beta-blocker within 24 h of the onset of AAD was an independent negative determinant of LOI (P/F ratio
≤200 mmHg) among variables including age ≥70 years, sex, serum creatinine level on admission, and the use of an ACE-I or ARB and nitrite (Table 4).

### Table 4. Multiple logistic regression analysis for oxygenation impairment

| Variable               | Relative risk | 95% CI      | P value |
|------------------------|---------------|-------------|---------|
| Age ≥ 70 years         | 1.31          | 0.26–6.62   | 0.75    |
| Sex (male)             | 1.40          | 0.32–6.22   | 0.65    |
| Cre > 1.2 mg/dl        | 0.44          | 0.05–4.05   | 0.47    |
| Use of ACE-I/ARB       | 2.29          | 0.52–10.2   | 0.28    |
| Use of nitrite         | 0.89          | 0.19–4.22   | 0.89    |
| Use of beta-blocker    | 0.04          | 0.004–0.48  | 0.01    |

CI, confidence interval; Cre, serum creatinine level; ACE-I, angiotensin-converting enzyme inhibitors; ARB, angiotensin II receptor blockers

**Discussion**

The present study revealed that the early use of beta-blockers was associated with lower maximum WBC count and serum CRP level, resulting in suppression of LOI after AAD. These findings suggest that beta-blocker treatment may play an important role in the prevention of LOI after distal type AAD, at least in part, by attenuating the inflammatory response after aortic injury.

Relationship between inflammation and LOI in AAD

Despite improved diagnostic and therapeutic techniques, AAD is a life-threatening medical emergency associated with high morbidity and mortality. In the acute phase of AAD, the aortic injury can cause systemic inflammation. Schillinger et al. reported that an elevated CRP level on admission was related to higher mortality in patients with acute aortic disease. Sugano et al. reported that patients who underwent emergency surgical treatment and/or died including those with multiple organ dysfunction during hospitalization had higher peak CRP levels than those who did not. Therefore, serum CRP elevation could be a predictor of a poor clinical outcome after AAD.

Widespread severe tissue injury is sometimes complicated by SIRS, which is clinically recognized by the presence of a high body temperature, tachycardia, hyperventilation, and an increased white blood cell count. This syndrome exhibits signs of inflammation including vasodilatation, increased microvascular permeability, and leukocyte accumulation, and is responsible for multiple organ dysfunction which leads to a high mortality. Moreover, SIRS is associated with impaired lung oxygenation including acute respiratory distress syndrome (ARDS). We previously reported that oxygenation impairment, defined as the lowest P/F ratio ≤200 mmHg, was present in almost 50% of patients with AAD. Peak CRP level, peak WBC count, and body temperature were significantly higher in patients with LOI than in those without. Marked serum CRP elevation was an independent predictor of the development of LOI after AAD, and peak CRP level was negatively correlated with the lowest P/F ratio. In this regard, LOI in patients suffering from AAD could be a clinical sign of SIRS, which may develop into multiple organ dysfunction.

Previous pathological studies showed that the infiltration of macrophages and leukocytes, and higher expression levels of several genes associated with inflammatory processes, such as interleukin (IL)-6 and IL-8, were observed in the dissected aorta. Recent study revealed that chronic inflammation in the aortic wall contributes substantially to the formation and progression of aortic aneurysm, suggesting an important role of inflammatory response in aortic degeneration. Hasegawa et al. reported that serum IL-8 level, which is associated with inflammatory reaction and is secreted locally by inflammatory cells (macrophages and neutrophils), is increased in patients with AAD. The mechanism of LOI in AAD is speculated to be that activated neutrophils circulate systemically and adhere to the lung capillary endothelium as a consequence of aortic endothelial injury. The lung tends to be a major site of tissue damage because the pulmonary vascular bed is an important reservoir of neutrophils, storing a large amount of the total circulating neutrophil pool. In fact, Furusawa et al. reported that intravenous administration of sivelestat, a specific neutrophil elastase inhibitor, was effective for postoperative respiratory failure in patients with AAD. Alternatively, Munakata et al. reported that continuous hemodiafiltration to remove proinflammatory cytokines was effective for the treatment of SIRS after operation for thoracic aortic dissection, despite slight removal of water from the continuous hemodiafiltration. However, sufficient evidence has not been established regarding therapeutic strategies for the treatment of LOI after AAD.
Effect of early use of beta-blockers on systemic inflammatory response

It is known that sympathetic activation is associated with the enhanced inflammatory response, as well as the renin-angiotensin system. Takahashi et al. reported that the plasma IL-6 level was positively correlated with the plasma level of norepinephrine after acute myocardial infarction. In an in vivo study, Murray et al. revealed that beta-blockers have an anti-inflammatory effect and attenuate levels of inflammatory cytokines and matrix metalloproteinases in heart failure or acute myocardial infarction. Other reports showed that some beta-blockers have antioxidant effects that result in substantial increments in NO bioavailability, in addition to increasing NO synthase III activation. In particular, carvedilol is known to have antioxidant effects to inhibit the direct cytotoxic actions of reactive oxygen radicals, prevent oxygen radical induced activation of inflammatory processes, and preserve endothelial integrity and function. However, it was conversely reported that beta-adrenergic stimulation inhibits the production of proinflammatory cytokines such as tumor necrosis factor (TNF)-α and IL-12 in macrophages and lymphocytes through β2-receptors. Nishio et al. reported that carvedilol improved the mortality of experimental viral myocarditis possibly through increasing the production of IL-12 and interferon (IFN)-γ and reducing myocardial viral replication. They suggested that carvedilol increases the production of these cytokines by blocking β2-receptors and antioxidant effects, because reactive oxygen species are known to suppress IL-12 and IFN-γ production in human peripheral blood mononuclear cells. Therefore, complex interactions exist among stress hormones and the cytokine network. The previous study showed that pre-exposure of mononuclear cells to epinephrine for 3 h strongly inhibited TNF-α synthesis; however, pre-exposure to epinephrine for 24 h was associated with enhanced TNF-α synthesis, suggesting that the influence of epinephrine on cytokine release is determined partially by the duration of inflammatory cell exposure to catecholamines. Although these reports imply a relation between sympathetic activation and inflammatory response, the effect of beta-blockers on the inflammatory response in AAD has not been fully elucidated. The present study showed that beta-blockers might suppress systemic inflammatory activation and improved LOI, resulting in a lower incidence of mechanical ventilation requirement.

In this study, serum creatinine level on admission and the peak serum creatinine level during hospitalization were significantly lower in patients with beta-blocker treatment than in those without. It is possible that the impaired renal function in patients without beta-blocker treatment may affect the inflammatory response after AAD. However, multiple logistic regression analysis revealed that the only significant predictor of LOI was lack of administration of a beta-blocker within 24 h of the onset of AAD, but not elevation of serum creatinine level (>1.2 mg/dl).

ACE-I and ARB are known to have an anti-inflammatory effect besides their reduction of blood pressure. The negative result for ACE-I or ARB administration in terms of CRP elevation and LOI development may have been caused by the fact that the ACE-I or ARB was not always administered in the acute phase of AAD. These medications were added as second- or third-line therapy when blood pressure control was inadequate. The pleiotropic effect of statin may also be beneficial to reduce the inflammation after AAD. However, there was no significant difference in LOI and the peak CRP level between patients with and without statin administration in this study. Therefore, the use of medication other than beta-blockers to affect the inflammatory response and LOI development after AAD is not plausible.

Study limitations

First, this study evaluated a relatively small number of patients; therefore, the statistical power might not be strong enough for any negative data to be conclusive. Second, this is a retrospective registry comparing outcomes and biochemical markers. Although hemodynamics and arterial blood gas on admission were comparable between patients with and without beta-blocker treatment, other uncontrolled factors might influence the results. For example, the presence of bronchial asthma or hypotension might influence the prevalence of LOI. In fact, patients without beta-blocker treatment included one patient who had a history of bronchial asthma and one patient with hypotension who had severe aortic stenosis. However, there was no difference in serum CRP level and P/F ratio on admission between patients with and without beta-blocker treatment. Moreover, the multivariate analysis revealed that beta-blocker treatment was the only independent negative determinant of the development of LOI. Third, the beta-blockers used in this study varied among patients. To assess the effect of each drug on the inflammatory response after distal AAD, beta-blockers should be randomly selected and the dosage should be adjusted among the different drugs. Fourth, we did not measure other plasma proinflammatory cytokines. Further study measuring proinflammatory cytokines such as IL-6 and TNF-α is required.

Conclusion

Early use of beta-blocker prevented excessive inflammation and LOI after distal type AAD, suggesting a pleiotropic effect of beta-blockers on the inflammatory response after AAD.

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