Local upregulation of interleukin-1 beta in aortic dissecting aneurysm: correlation with matrix metalloproteinase-2, 9 expression and biomechanical decrease

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OBJECTIVES: Our goal was to examine whether interleukin-1 beta (IL-1β) originates locally and its possible relationship with matrix metalloproteinases (MMPs), apoptosis, elastin fibres and biomechanics in aortic dissecting aneurysms (DAs).

METHODS: Aortic DAs were induced in 24 rats with β-aminopropionitrile (BAPN); another 12 rats without BAPN were designated as controls. Then IL-1β levels were measured both in the circulation and in local aortic specimens. The expression of MMP-2 and MMP-9 and Victoria blue and TUNEL staining were also detected. Biomechanical parameters such as the elasticity modulus were used to detect the biomechanical changes in the aortic wall. The correlation of IL-1β, MMP-2, MMP-9, apoptosis and biomechanical properties was analysed.

†The first four authors contributed equally to this study.
RESULTS: Seventeen rats (17/24, 71%) in the BAPN-treated group died of DA rupture. IL-1β levels were dramatically increased in the DA specimens but not in the circulation. Victoria blue staining confirmed the formation of the DA and the reduction of elastin content after induction by BAPN. The extent of apoptosis in the aortic media was dramatically higher in rats with BAPN-induced DA than that in the control group and that in rats treated with BAPN but without DA. MMP-2 and MMP-9 levels were significantly increased in BAPN-treated rats compared to the controls, but no statistical significance was found between rats with and without DA. There were significant differences in biomechanical parameters, such as the elasticity modulus. Among the 3 groups, IL-1β was positively correlated with MMP-2 and MMP-9 levels and with the elasticity modulus but not with apoptosis.

CONCLUSIONS: Local IL-1β might participate in the formation of aortic DA through the upregulation of MMP-2 and MMP-9 and the breakage of elastin fibres, which finally weakens the biomechanical properties of the aortic wall.

Keywords: Interleukin-1 beta • Dissecting aneurysm • Matrix metalloproteinase • Biomechanics • Elastin fibres

INTRODUCTION

An aortic dissecting aneurysm (DA) is an extremely lethal condition because of the rapid rupture of the DA [1]. It is widely accepted that a DA forms when haemodynamic abnormalities occur or when the aortic wall is weakened congenitally or postnatally [2]. Two primary mechanisms directly mediate the changes of DA-associated remodelling of the aortic wall. One involves the matrix metalloproteinase (MMP) family, which could cause matrix degradation and increase the turnover of elastin and collagen fibres. The other involves media cell apoptosis, which could alter media cell density and lead to regression of media cell function. Both of the mechanisms could lead to biomechanical changes related to the elasticity modulus, maximum strength and maximum extensibility.

It is evident that the inflammatory process plays a key role in the development of a DA and could damage the integrity of the aortic wall [3, 4]. Several studies have indicated that the local interleukin-1 beta (IL-1β) plays a critical role in aortic diseases [5, 6]. Our previous study demonstrated that expression of IL-1β significantly rose in human aneurysmal tissues and may play a potential role through the phospho-p38 signal transduction pathway [7]. However, whether the overexpression of IL-1β plays a causative role and the way in which it affects the formation of an DA are still unknown. A plausible mechanism is that IL-1β increases the degradation of the media matrix by stimulating the expression of MMPs and media cell apoptosis that lead to the breakage of elastin fibres and cause biomechanical changes that finally lead to the formation of a DA. To test this theory, we focused on detecting changes in IL-1β, MMPs, elastin fibres, apoptosis and biomechanical parameters in a DA rat model that was treated with β-aminopropionitrile (BAPN) and on clarifying whether IL-1β plays a key role locally and whether it is correlated with the parameters just listed.

MATERIALS AND METHODS

Groups and treatments

Thirty-six male Sprague-Dawley rats (3 weeks old) were divided into 2 groups. Group A, which was the control group (n = 12), was randomly given commercial feed pellets. Group B (n = 24) was treated with BAPN. As we described previously [8], the rats in Group B were given feed pellets containing 0.25% BAPN (Millipore-Sigma, Burlington, MA, USA). Body weight was measured once a week. All the procedures carried out on the rats were approved by the ethics committee for animal experimentation.

Measurement of systolic blood pressure

Systolic blood pressure (SBP) was measured in both groups using the tail-cuff apparatus (ALC-NIBP, Shanghai Alcott Biotech, Shanghai, China) at weekly intervals. Before the measurement, the rats were warmed for 30 min at 28°C to allow the detection of tail artery pulsations and to achieve a steady pulse level. SBP was obtained by averaging 10 measurements.

ELISA essay

Blood was obtained from the tail vein at the second, fourth and sixth week after administration of BAPN. IL-1β in plasma was detected with a commercial ELISA kit (CUSABIO, Houston, TX, USA) following the manufacturer’s instruction.

Aortic sample collection and measurements

The animal experiment lasted 6 weeks, and the rats that died of DA rupture during the study were autopsied. The rats that survived were sacrificed by an overdose of sodium pentobarbital at the end of the experiment. The whole aorta was harvested from the aortic root to the aortic-iliac bifurcation, with the innominate artery, left subclavian artery and right renal artery marked. All loose connective tissue from the adventitia was carefully cleared away from the aorta. The diameters of 3 specific parts (Part A: 2 mm proximal to the innominate artery; Part B: 2 mm distal to the left subclavian artery; and Part C: 12 mm distal to left subclavian artery) (Table 1) were measured with Vernier calipers (Anyi Instrument Co. Ltd, Guilin, China).

Half of the aneurysm segment and a 2-mm-high columnar sample from the thoracic aorta were used for haematoxylin and eosin staining, Victoria blue staining, TUNEL staining and immunohistochemical staining to confirm DA formation as well as to detect apoptosis, the breakage of elastic fibres, MMPs and IL-1β. Images of the media and aorta were obtained using a Leica phase contrast microscope (Leica DC100, Wetzlar, Germany) with a measuring scale. Then, the thickness of the media and the area of the aorta were measured using Photoshop CS4 (Adobe, San Jose, CA, USA). The thickness of the media was the average of the measurements in 8 places, each 45° apart. The area of the aortic ring was measured directly in Photoshop CS4. Histological
evaluation of the elastin fibres was performed by analysing Victoria blue staining with Image Pro Plus 6.0.

### Biomechanical analysis

Columnar samples with a height over 10 mm were carefully removed from the central part of the descending thoracic aorta to avoid any stretching. These samples were used immediately for biomechanical testing. The initial area of the aorta was also used in biomechanical analyses. The definition and calculation of other parameters as well as the measuring procedure are shown in Table 2 and described in our previous study [8].

### Protein extraction and western blot analysis

Forty (40) mg of protein from tissue samples was extracted in radioimmunoprecipitation assay buffer (Cell Signaling Technology, Danvers, MA, USA). The primary antibodies, including anti-IL-1β (Santa Cruz Biotechnology, Dallas, TX, USA), anti-MMP-2 (Abcam, Cambridge, MA, USA) and anti-MMP-9 (Epitomics, Burlingame, CA, USA) were used for western blot analysis. The detailed procedures were described in our previous reports [7].

### Histological examination and Victoria blue and TUNEL staining

The paraformaldehyde-fixed paraffin-embedded aortic tissues were segmented at a thickness of 5 μm and then stained with Victoria blue as well as with haematoxylin and eosin. The TUNEL reaction was performed with an in situ cell detection kit (Roche Applied Science, Indianapolis, IN, USA) to detect media cell apoptosis. TUNEL-positive nuclei (stained brown) were counted, and the average of the percentage of elastic fibres was calculated using Motic Images Advanced 3.2. The product of the positive cell area (μm²) and the average degree of staining was used to express levels of IL-1β, MMP-2 and MMP-9.

### Statistical analyses

Continuous data were expressed as mean ± standard deviations. Data were evaluated with respect to normal distribution (Kolmogorov–Smirnov test) and homogeneity of variances (Levene’s test). One-way analysis of variance with post hoc comparisons was used to analyse the difference between the groups, and the Kruskal–Wallis analysis of variance on ranks was used in case of inhomogeneity of variances or deviation from the normal distribution. Pearson’s correlation was used to evaluate the correlation. Data were analysed using SPSS V 13.0 (SPSS, Inc., Chicago, IL, USA), and a 2-tailed P-value < 0.05 was considered statistically significant.

### RESULTS

#### Body weight and general condition

The body weight of the rats gradually increased about 190 to 210 g by the end of the experiment, whereas the body weight significantly decreased in the groups treated with BAPN from the 3rd week compared to the control group (final body weight: 189.1 ± 11.1 g vs 207.3 ± 9.4 g, P = 0.001) (Fig. 1 and Table 1).

No DAs were found in the control group. In the BAPN-treated group, 17 rats (17/24, 71%) died of DA rupture during the experiment, which was confirmed by necropsy. Three DAs were located in the ascending aorta, 1 in the aortic arch and 6 in the proximal descending aorta. The other 7 DAs were located from the ascending aorta to the central area of the descending aorta. Dissections were observed in every case of aneurysm formation. The mean survival time of the rats with aneurysm rupture was 30.6 days after the administration of BAPN.

#### Measurement of the diameter of the aorta and the systolic blood pressure

The diameters of the aortas of the rats are shown in Table 1. The diameters of the DAs of the rats in the control group were

<table>
<thead>
<tr>
<th>Group</th>
<th>Sample size</th>
<th>Aneurysm formation</th>
<th>Elastic fibres (%)</th>
<th>Body weight (g)</th>
<th>Diameter of aneurysm (mm)</th>
<th>Diameter (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Initial</td>
<td>Final</td>
<td>Part A</td>
</tr>
<tr>
<td>Control</td>
<td>12</td>
<td>0</td>
<td>6.58 ± 1.2</td>
<td>50.2 ± 1.2</td>
<td>207.3 ± 9.4</td>
<td>2.11 ± 0.12</td>
</tr>
<tr>
<td>BAPN</td>
<td>24</td>
<td>17</td>
<td>3.35 ± 1.1*</td>
<td>50.5 ± 1.4</td>
<td>189.1 ± 11.1*</td>
<td>5.2 ± 0.9</td>
</tr>
</tbody>
</table>

Data are represented as mean ± standard deviation.

Panel A: 2-mm proximal to innominate artery; Panel B: 2-mm distal to left subclavian artery; Panel C: 12-mm distal to left subclavian artery.

*Two-tailed P-value < 0.05 compared to control group.

BAPN: β-aminopropionitrile; Part A: 2-mm proximal to innominate artery; Part B: 2-mm distal to left subclavian artery; Part C: 12-mm distal to left subclavian artery.

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Table 1: General conditions and percentage of elastic fibres in the control and BAPN-treatment groups

<table>
<thead>
<tr>
<th>Group</th>
<th>Sample size</th>
<th>Aneurysm formation</th>
<th>Elastic fibres (%)</th>
<th>Body weight (g)</th>
<th>Diameter of aneurysm (mm)</th>
<th>Diameter (mm)</th>
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</tbody>
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Panel A: 2-mm proximal to innominate artery; Panel B: 2-mm distal to left subclavian artery; Panel C: 12-mm distal to left subclavian artery.

*Two-tailed P-value < 0.05 compared to control group.
ELISA examination

The plasma IL-1β concentration did not dramatically change between the BAPN-treated group and the control group at the detected time points (60.72 ± 3.21 vs 62.76 ± 2.03 pg/ml, P = 0.052), indicating that circulated IL-1β may not participate in BAPN-induced DA.

Biomechanical analysis

Biomechanical analysis on the middle part of the descending thoracic aorta showed that the draw ratio, maximum load, strength, stretching length, maximum extensibility and elasticity modulus all decreased in the rats with BAPN-induced DA compared with the control rats and the BAPN-treated rats without DA. The foregoing parameters also significantly decreased in BAPN-treated rats without DA compared with the control rats (Table 2).

Western blot of interleukin-1 beta, matrix metalloproteinase-2 and matrix metalloproteinase-9 in the thoracic aorta

The protein levels of IL-1β, MMP-2 and MMP-9 in thoracic aortic tissue were significantly higher in the BAPN-treated group with or without DA than in those in the control group. No significant differences in IL-1β, MMP-2 and MMP-9 expression in the protein level were observed between the BAPN-treated group with and without DA (Fig. 2). This finding indicated that IL-1β, MMP-2 and MMP-9 were induced by BAPN and may be involved throughout the procedure of DA formation.

Haematoxylin and eosin and Victoria blue staining

Thoracic aortic DAs were detected with histological staining methods. No breakage or dissection was observed in the aortic

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**Table 2:** The differences in the biomechanical parameters in the control group and the BAPN group with or without DA

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Control group (A) (n = 12)</th>
<th>BAPN without DA (B1) (n = 7)</th>
<th>BAPN with DA (B2) (n = 17)</th>
<th>A versus B1 (P-value)</th>
<th>A versus B2 (P-value)</th>
<th>B1 versus B2 (P-value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maximum diameter (mm)</td>
<td>1.25 ± 0.26</td>
<td>1.44 ± 0.11</td>
<td>18.48 ± 1.11</td>
<td>0.566</td>
<td>0.000</td>
<td>0.23</td>
</tr>
<tr>
<td>Thickness of media (μm)</td>
<td>0.04 ± 0.00</td>
<td>0.08 ± 0.02</td>
<td>0.61 ± 0.08</td>
<td>0.000</td>
<td>0.000</td>
<td>0.000</td>
</tr>
<tr>
<td>Initial area (A/mm²)</td>
<td>0.21 ± 0.04</td>
<td>0.14 ± 0.02</td>
<td>0.03 ± 0.00</td>
<td>0.000</td>
<td>0.000</td>
<td>0.000</td>
</tr>
<tr>
<td>Initial length (L)/mm</td>
<td>12.0 ± 1.64</td>
<td>12.8 ± 1.00</td>
<td>12.8 ± 1.00</td>
<td>0.000</td>
<td>0.000</td>
<td>0.000</td>
</tr>
<tr>
<td>Maximum stretching length (D)/mm</td>
<td>6.48 ± 1.01</td>
<td>6.81 ± 1.00</td>
<td>6.81 ± 1.00</td>
<td>0.000</td>
<td>0.000</td>
<td>0.000</td>
</tr>
<tr>
<td>Draw ratio (k)</td>
<td>(initial length + maximum stretching length)/initial length</td>
<td>1.35 ± 0.10</td>
<td>1.35 ± 0.10</td>
<td>0.000</td>
<td>0.000</td>
<td>0.000</td>
</tr>
<tr>
<td>Ultimate area (B)/mm²</td>
<td>0.09 ± 0.00</td>
<td>0.09 ± 0.00</td>
<td>0.09 ± 0.00</td>
<td>0.000</td>
<td>0.000</td>
<td>0.000</td>
</tr>
<tr>
<td>Maximum strength (S)/MPa</td>
<td>275.54</td>
<td>293.84</td>
<td>293.84</td>
<td>0.000</td>
<td>0.000</td>
<td>0.000</td>
</tr>
<tr>
<td>Elasticity modulus (E)/MPa</td>
<td>96.17</td>
<td>96.17</td>
<td>96.17</td>
<td>0.000</td>
<td>0.000</td>
<td>0.000</td>
</tr>
<tr>
<td>Maximum load (F)/N</td>
<td>220.2</td>
<td>256.5</td>
<td>256.5</td>
<td>0.000</td>
<td>0.000</td>
<td>0.000</td>
</tr>
<tr>
<td>Maximum strength (S)/ultimate area (B)</td>
<td>104.71 ± 15.83</td>
<td>104.71 ± 15.83</td>
<td>104.71 ± 15.83</td>
<td>0.000</td>
<td>0.000</td>
<td>0.000</td>
</tr>
<tr>
<td>Maximum extensibility (D/L)</td>
<td>15.36</td>
<td>15.36</td>
<td>15.36</td>
<td>0.000</td>
<td>0.000</td>
<td>0.000</td>
</tr>
<tr>
<td>Elasticity modulus (E)/maximum stretch</td>
<td>62.74</td>
<td>62.74</td>
<td>62.74</td>
<td>0.000</td>
<td>0.000</td>
<td>0.000</td>
</tr>
</tbody>
</table>

Data are represented as mean ± standard deviation. Initial area (A)/mm² = the area before stretching. Maximum area (B)/mm² = ultimate length - initial length. Ultimate area (B)/maximum load (F)/N = ultimate strength maximum extensibility / maximum strength. Elasticity modulus (E) = maximum strength (S)/maximum extensibility (D/L).

Two-tailed P-value < 0.05.

BAPN: beta-aminopropionitrile; DA: dissecting aneurysm; MPa: megapascal.
Expression of IL-1\(\beta\), MMP-2 and MMP-9 in aortic tissues measured by western blot. The protein levels of IL-1\(\beta\), MMP-2 and MMP-9 were significantly higher in the BAPN treatment group than in the control group. No significant difference was observed between the BAPN treatment group with DAs and without DAs. *Two-tailed P-value <0.05 compared to control group. Error bars are standard deviations. BAPN: beta-aminopropionitrile; DA: dissecting aneurysm; IL-1\(\beta\): interleukin-1 beta; MMP-2: matrix metalloproteinase-2; MMP-9: matrix metalloproteinase-9.

**Figure 2:** Expression of IL-1\(\beta\), MMP-2 and MMP-9 in aortic tissues measured by western blot. The protein levels of IL-1\(\beta\), MMP-2 and MMP-9 were significantly higher in the BAPN treatment group than in the control group. No significant difference was observed between the BAPN treatment group with DAs and without DAs. *Two-tailed P-value <0.05 compared to control group. Error bars are standard deviations. BAPN: beta-aminopropionitrile; DA: dissecting aneurysm; IL-1\(\beta\): interleukin-1 beta; MMP-2: matrix metalloproteinase-2; MMP-9: matrix metalloproteinase-9.

**Table 1:** Aneurysm formation in BAPN-treated and control rats. The percentage of elastic fibres was significantly lower in the BAPN group than in the control group.

**DISCUSSION**

We showed that the expression of IL-1\(\beta\) and of the MMPs (MMP-2 and MMP-9) was significantly increased in rats treated with BAPN. Apoptosis was also exacerbated in BAPN-treated rats with DA, but not in BAPN-treated rats without DA. In contrast, the percentage of elastic fibres was also significantly decreased in the aortic media of BAPN-treated rats. Furthermore, biomechanical testing showed that both stress and strain parameters were decreased in BAPN-treated rats, particularly in the BAPN-treated rats with DA. Finally, correlation analysis showed that IL-1\(\beta\) was positively correlated with MMP-2 and MMP-9 levels, which in the end affected the percentage of elastic fibres and both the stress and strain parameters, but not with apoptosis. These results might provide clues to the molecular mechanisms involved in the formation of DA.

Based on our preliminary research and that of other researchers, treatment with 0.25% BAPN led to the development of DA in rats [9, 10]. Seventeen rats treated with BAPN (71%) died of aneurysm rupture during the study, which was confirmed by necropsy and Victoria blue staining. All the DA was located in the thoracic aortic artery, and there were no aneurysms detected in the abdominal aortic artery, which was very similar to the results observed in human beings both via visual observation and pathological examination [8]. Compared with the low formation rate induced by BAPN in mice and by other methods or doses of BAPN in rats, treatment with 0.25% BAPN caused a high rate of formation of DA in rats that was extremely similar to that observed in humans [7, 10]. Apart from this observation, the pathological changes associated with BAPN-induced DA in rats are extraordinarily similar to those noted in humans.
As the primary extracellular matrix components, elastin and collagen maintain the integrity and tensile strength of the aortic wall and provide elastic support to the aortic tissue [11, 12]. BAPN inhibits lysyl oxidase, which cross-links elastin and collagen fibres and plays a critical role in maintaining homeostasis of the elastic lamina [13]. Elastin plays a critical role in vascular tensile strength, though its content is lower than that of collagen [14]. Thus, Victoria blue stain was used to detect the change in the elastic architecture. The results showed the rupture of the elastic architecture, a larger gap among the elastic lamina and the increased thickness of the media. Meanwhile, the proportion of the area of elastin fibre in the total area of the vascular section was decreased in the BAPN-treated group. The decreased integrity of the media made the vascular wall more susceptible to fatigue and cardiovascular deficits such as multiple arterial ruptures and DA, which eventually led to all kinds of abnormalities [15].

Previous reports looked into the biomechanical abnormalities of the aortic aneurysm [16]. However, the BAPN-induced

![Figure 3: Victoria blue and TUNEL staining. (A) Victoria blue staining. DA was detected in the BAPN-treated group. Breakage and dissection of elastic fibres were observed in the BAPN-treated group. The arrow indicated lots of erythrocytes in the false lumen. (B) No or weak TUNEL staining was observed in the control group and in the BAPN-without-DA group. Apoptosis was significantly increased in the BAPN-treated group with DA. The arrow indicates TUNEL-positive cells. *Two-tailed P-value <0.05 compared to the BAPN-treated group with DA. #Two-tailed P-value <0.05 compared to control group. Error bars are standard deviations. BAPN: beta-aminopropionitrile; DA: dissecting aneurysm.](image-url)
Figure 4: Immunohistochemical staining of IL-1β, MMP-2 and MMP-9. Larger quantities of IL-1β, MMP-2 and MMP-9 expressed in both the group treated with BAPN with DAs and the group treated with BAPN without DA. IL-1β, MMP-2 and MMP-9 were located mainly in the media with a focus in the area of the dissection.

*Two-tailed P-value <0.05 compared to control group. Error bars are standard deviations. BAPN: beta-aminopropionitrile; DA: dissecting aneurysm; IL-1β: interleukin-1 beta; MMP-2: matrix metalloproteinase-2; MMP-9: matrix metalloproteinase-9.

**Table 3:** Correlation analysis among expression levels of IL-1β, MMP-2, MMP-9, apoptosis, maximum extensibility (r), maximum strength (S) and elasticity modulus (E) in rats with and without DA.

<table>
<thead>
<tr>
<th></th>
<th>BAPN with DA</th>
<th>BAPN without DA</th>
</tr>
</thead>
<tbody>
<tr>
<td>IL-1β versus MMP-2</td>
<td>0.551</td>
<td>0.022*</td>
</tr>
<tr>
<td></td>
<td>0.658</td>
<td>0.108</td>
</tr>
<tr>
<td>IL-1β versus MMP-9</td>
<td>0.543</td>
<td>0.024*</td>
</tr>
<tr>
<td></td>
<td>0.837</td>
<td>0.019*</td>
</tr>
<tr>
<td>IL-1β versus apoptosis</td>
<td>0.421</td>
<td>0.092</td>
</tr>
<tr>
<td></td>
<td>-0.423</td>
<td>0.345</td>
</tr>
<tr>
<td>IL-1β versus maximum extensibility (r)</td>
<td>-0.69</td>
<td>0.002*</td>
</tr>
<tr>
<td></td>
<td>-0.18</td>
<td>0.700</td>
</tr>
<tr>
<td>IL-1β versus maximum strength (S)</td>
<td>0.31</td>
<td>0.234</td>
</tr>
<tr>
<td></td>
<td>0.88</td>
<td>0.009*</td>
</tr>
<tr>
<td>IL-1β versus elasticity modulus (E)</td>
<td>0.78</td>
<td>0.000*</td>
</tr>
<tr>
<td></td>
<td>0.77</td>
<td>0.044</td>
</tr>
</tbody>
</table>

*Two-tailed P-value <0.05.

To summarize, this study shows the upregulation of IL-1β, MMP-2 and MMP-9 and of apoptosis in BAPN-induced aortic DA and a close relationship between IL-1β and MMP. These results suggest that IL-1β might increase the degradation of the media matrix by upregulation of MMP-2 and MMP-9 in DA, which finally decreases the percentage of elastin fibres and weakens the biomechanics of the aortic wall. However, this study was an observational study with a limited number of rats, and we could not establish an exact cause and effect relationship between IL-1β and MMPs during the development of the DA. The verification of this presumption and the demonstration of the mechanism should be pursued in future in vivo and in vitro studies of treatment with IL-1β and anti-IL-1β.

**Conflict of interest:** none declared.

**REFERENCES**


