

Elevated plasma D-dimer and hypersensitive C-reactive protein levels may indicate aortic disorders

Níveis plasmáticos elevados do dímero D e da proteína C reativa hipersensíveis podem indicar desordens aórticas

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Abstract

Objective: D-dimer and C-reactive protein are of diagnostic and predictive values in patients have thrombotic tendency, such as vascular thrombosis, coronary artery disease and aortic dissection. However, the comparative study in these biomarkers between the patients with acute aortic dissection and coronary artery disease has not been sufficiently elucidated.

Methods: Consecutive surgical patients for acute type A aortic dissection (20 patients), aortic aneurysm (nine patients) or coronary artery disease (20 patients) were selected into this study. Plasma from preoperative blood samples and supernatant of aortic homogenate of the surgical specimens were detected for D-dimer and hypersensitive C-reactive protein (hs-CRP).

Results: Plasma D-dimer and hs-CRP values in type A aortic dissection or aortic aneurysm were much higher than in coronary artery disease patients or the healthy control (for D-dimer, aortic dissection: coronary artery disease, 0.4344 ± 0.2958 $\mu\text{g/ml}$ vs. 0.0512 ± 0.0845 $\mu\text{g/ml}$, $P < 0.0001$; aortic dissection: healthy control, 0.4344 ± 0.2958 $\mu\text{g/ml}$ vs. 0.1250 ± 0.1295 $\mu\text{g/ml}$, $P = 0.0005$; aortic aneurysm: coronary artery disease, 0.4200 ± 0.4039 $\mu\text{g/ml}$ vs. 0.0512 ± 0.0845 $\mu\text{g/ml}$, $P = 0.0013$; and aortic aneurysm: healthy control, 0.4200 ± 0.4039 $\mu\text{g/ml}$ vs. 0.1250 ± 0.1295 $\mu\text{g/ml}$, $P = 0.0068$; and for hs-CRP, aortic dissection: coronary artery disease, 4.400 ± 3.004 mg/L vs. 1.232 ± 0.601 mg/L , $P < 0.0001$; aortic dissection: healthy control, 4.400 ± 3.004 mg/L vs. 0.790 ± 0.423 mg/L , $P < 0.0001$; aortic aneurysm: coronary artery disease, 2.314 ± 1.399 mg/L

vs. 1.232 ± 0.601 mg/L , $P = 0.0084$; aortic aneurysm: healthy control, 2.314 ± 1.399 mg/L vs. 0.790 ± 0.423 mg/L , $P = 0.0002$; and coronary artery disease: healthy control, 1.232 ± 0.601 mg/L vs. 0.790 ± 0.423 mg/L , $P = 0.0113$). Besides, there were close correlations between plasma D-dimer and hs-CRP in overall ($Y = 4.8798X + 0.8138$, $r^2 = 0.4497$, $r = 0.671$, $P < 0.001$), aortic dissection ($Y = 2.6298X + 1.2098$, $r^2 = 0.5762$, $r = 0.759$, $P < 0.001$), and aortic aneurysm ($Y = 7.1341X + 1.3006$, $r^2 = 0.4935$, $r = 0.7025$, $P = 0.048$) groups rather than in the coronary artery disease or healthy control subjects. In addition, there were no significant differences between D-dimer and hs-CRP values of the aortic supernatant among groups except for undetectable D-dimer in the aortic supernatant of the coronary artery disease group.

Conclusions: The patients with acute aortic dissection and aortic aneurysm may reflect the extensive inflammatory reaction and severe coagulopathies in the patients with acute type A aortic dissection, and thoracic aortic aneurysm in comparison to the coronary patients and healthy control individuals. The detections after onset in the patients with acute chest pain may help making a differential diagnosis between the aortopathies and ischemic heart disease. The scanty significance of the tissue biomarkers may preclude their diagnostic value in clinical practice.

Descriptors: Aorta, thoracic. Clinical laboratory techniques. Coronary artery disease. C-reactive protein. Fibrin fibrinogen degradation products.

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Resumo

Objetivo: D-dímero e proteína C reativa são de valores de diagnóstico e preditivo em pacientes com tendência trombótica, como a trombose vascular, doença arterial coronária e dissecação aórtica. No entanto, o estudo comparativo desses biomarcadores entre os pacientes com dissecação aguda da aorta e doença arterial coronariana não foi suficientemente esclarecido.

Métodos: Pacientes cirúrgicos consecutivos foram selecionados para este estudo por tipo de dissecação aguda aórtica (20 pacientes), aneurisma da aorta (9 pacientes) ou doença arterial coronária (20 pacientes). O plasma a partir de amostras de sangue no pré-operatório e sobrenadante de homogenato de aorta dos espécimes cirúrgicos foi detectado para o D-dímero e proteína C reativa hipersensível.

Resultados: Os valores do plasma de D-dímero e proteína C reativa em dissecação aórtica tipo A ou aneurisma da aorta foram muito superiores em pacientes com doença arterial coronariana ou de controles saudáveis (pelo D-dímero, dissecação aórtica: doença arterial coronariana, $0,4344 \pm 0,2958$ µg/ml vs $0,0512 \pm 0,0845$ µg/ml, $P < 0,0001$; dissecação aórtica: controle saudável, $0,4344 \pm 0,2958$ µg/ml vs $0,1250 \pm 0,1295$ µg/ml, $P = 0,0005$; aneurisma da aorta: doença arterial coronariana, $0,4200 \pm 0,4039$ µg/ml vs $0,0512 \pm 0,0845$ µg/ml, $P = 0,0013$; e aneurisma de aorta: controle saudável, $0,4200 \pm 0,4039$ µg/ml vs $0,1250 \pm 0,1295$ µg/ml, $P = 0,0068$ e para a hs-CRP, dissecação aórtica: doença arterial coronariana, $4,400 \pm 3,004$ mg/L vs $1,232 \pm 0,601$ mg/L, $P < 0,0001$; dissecação aórtica: grupo controle saudável, $4,400 \pm 3,004$ mg/L vs $0,790 \pm 0,423$ mg/L, $P < 0,0001$; aneurisma da aorta: doença arterial

coronariana, $2,314 \pm 1,399$ mg/L vs $1,232 \pm 0,601$ mg/L, $P = 0,0084$; aneurisma da aorta: grupo controle saudável, $2,314 \pm 1,399$ mg/L vs $0,790 \pm 0,423$ mg/L, $P = 0,0002$; e doença arterial coronariana: grupo controle saudável, $1,232 \pm 0,601$ mg/L versus $0,790 \pm 0,423$ mg/L, $P = 0,0113$). Além disso, houve correlações próximas de plasma de D-dímero e proteína C reativa em em todos os pacientes com dissecação aórtica ($Y = 4,8798X + 0,8138$, $r^2 = 0,450$, $r = 0,671$, $P < 0,001$), (Y = $2,6298X + 1,2098$, $r^2 = 0,5762$, $r = 0,759$, $P < 0,001$), e aneurisma de aorta ($Y = 7,1341X + 1,3006$, $r^2 = 0,4935$, $r = 0,7025$, $P = 0,048$) ao contrário dos grupos de doença arterial coronariana ou grupo controle de pacientes saudáveis. Além disso, não houve diferenças significativas dos valores de D-dímero e proteína C reativa de sobrenadante de aorta entre os grupos, exceto para o D-dímero indetectável no sobrenadante de aorta do grupo com doença coronária.

Conclusões: Os pacientes com dissecação aguda da aorta e aneurisma da aorta podem refletir a reação inflamatória extensa e coagulopatias graves nos pacientes com o dissecação aguda aórtica tipo A e aneurisma da aorta torácica em comparação com os doentes coronários e indivíduos-controle saudáveis. As detecções após o acometimento nos pacientes com dor torácica aguda podem ajudar a fazer um diagnóstico diferencial entre a aortopatias e doença isquêmica cardíaca. A escassa significância dos biomarcadores de tecido pode impedir o seu valor diagnóstico na prática clínica.

Descritores: Aorta torácica. Técnicas de laboratório clínico. Doença das coronárias. Proteína C-reativa. Produtos de degradação da fibrina e do fibrinogênio.

INTRODUCTION

D-dimers are fibrin degradation products which are released during local or systemic activation of coagulation. D-dimer testing is widely used in the diagnosis of deep vein thrombosis, pulmonary embolism [1], or disseminated intravascular coagulopathy [2]. Patients with thrombotic tendency such as paroxysmal atrial fibrillation often had increased plasma fibrinogen and D-dimer levels, while the cardioversion of atrial fibrillation to sinus rhythm in such patients may decrease the levels of these markers in the plasma [3]. Yasaka et al. [4] found, in patients with mitral stenosis, significantly higher D-dimer plasma levels with detectable left atrial thrombi. Patients receiving warfarin therapy may have their plasma D-dimer levels reduced [5]. D-dimers in patients with an impaired left ventricular function were higher than those with a normal left ventricular function [6]. Intraoperative elevated D-dimer during cardiopulmonary bypass was considered the result of activation of temperature-dependent enzymes during the rewarming phase, whereas the elevation of D-dimer 24 hours postoperatively in the cardiac surgical patients without the

use of cardiopulmonary bypass was considered a protective mechanism of the body to clear the hemostatic plugs to restore vascular patency [7].

D-dimer is a strong predictor of recurrent coronary events. D-dimer elevation along with dysfunctional apolipoprotein concentrations may predict coronary events [8]. Moreover, D-dimer showed earlier positive test (within 2 hours from the onset) than troponin T in the detection of acute coronary syndrome [9]. D-dimer of the patients with large vessel disease was significantly higher than that of the patients with acute coronary syndrome ($6,99$ µg/ml vs. $0,89$ µg/ml, $P < 0,05$). Nevertheless, increased D-dimer levels are encountered in many non-thrombotic conditions. Recently, normal D-dimers were also taken as exclusion criteria of acute aortic dissection in patients with chest pain [10]. D-dimers may increase progressively during cardiac surgery with cardiopulmonary bypass [11]. D-dimer can be detectable prior to the release of troponin or creatine kinase MB into bloodstream [10]. Nevertheless, this diagnostic criteria was doubted by several authors as it may misjudge some patients with suspected acute aortic dissection, and hence a combined diagnostic strategy

inclusive of alternative coagulation tests and imaging techniques may be mandatory in particular in reaching a definite diagnosis of aortic dissection.

C-reactive protein (CRP) may be significantly elevated in the plasma of the patients with aortic dissection and atherosclerosis, which may be associated with the arterial damage and immune reaction [12]. Aortic dissection and atherosclerosis are low-grade inflammatory reactions for which CRP testing might be less sensitive. Instead, hypersensitive C-reactive protein (hs-CRP) measurements would provide with high sensitive results. Elevated hs-CRP may predict recurrent coronary events, like heart attack, restenosis of coronary arteries after angioplasty, stroke, and peripheral vascular disease, etc. [13].

A comparative study between aortic and ischemic heart diseases was rarely described with regard to the diagnostic values of plasma D-dimer and hs-CRP. This study was designed to test plasma D-dimer and hs-CRP of the patients with acute type A aortic dissection, in comparison to those with thoracic aortic aneurysm or with the coronary artery disease, and healthy control. In addition, we examined the D-dimer and hs-CRP levels of the aortic supernatant of the surgical specimens of the patients with acute type A aortic dissection, thoracic aortic aneurysm and coronary artery disease.

METHODS

From 2008 to present, consecutive surgical patients for type A aortic dissection (20 patients), aortic aneurysm (nine patients) or coronary artery disease (20 patients) were selected into this study. Patients with aortic dissection or aortic aneurysm due to Marfan's syndrome during the study period were excluded from this study.

Blood samples (4 ml) were obtained from the surgical patients from the indwelling catheter of the radial artery in the operating theater after systemic heparinization and before cardiopulmonary bypass, while control fast morning blood samples were drawn from young healthy volunteers. Plasma was collected by centrifugation $3000 \times g$ for 5 min, and stored at -80°C until detection. The surgical specimens of large aortic tissues were obtained immediately after they were severed in the operations of the replacement of the aorta in the patients with aortic dissection or aortic aneurysm. The aortic tissues 0.2-0.4 cm in size taken from the punch holes of the proximal anastomosis on the anterior wall of the ascending aorta in patients receiving coronary artery bypass were collected. The aortic tissue was stored at -80°C , which would be thawed and made into supernatant until detection.

Blood and the aortic tissue specimens were tested for D-dimer with an Sysmex® CA-7000 system coagulation analyzer (Sysmex, Kobe, Japan), and detection of hs-CRP

with a Hitachi Model 7600 Series Automatic Analyzer (Hitachi High-Technologies Corporation, Hitachi, Japan). The kits used in the experiments were D-dimer PLUS (Simens Healthcare Diagnostics Products GmbH) and Reagent kit for hs-CRP test (latex agglutination assay). Their reference values were 0.1417 (90%CL 0.0638 - 0.2464) $\mu\text{g/ml}$ for D-dimer, and < 6 mg/L for hs-CRP, respectively.

All data were expressed in mean \pm standard deviation, and intergroup comparisons were made by *t*-test. $P < 0.05$ was considered of statistical significance.

This study was approved by the institutional ethical committee, and was conducted following the guidelines of the Declaration of Helsinki. Informed consent was obtained from each patient.

RESULTS

Plasma D-dimers of the aortic dissection and aortic aneurysm groups were significantly higher than the reference value. There appeared no statistical significance in plasma D-dimer levels between the aortic dissection and aortic aneurysm groups (0.4344 ± 0.2958 $\mu\text{g/ml}$ vs. 0.4200 ± 0.4039 $\mu\text{g/ml}$, $P = 0.9352$), or between the coronary artery disease and healthy control groups (0.0512 ± 0.0845 $\mu\text{g/ml}$ vs. 0.1250 ± 0.1295 $\mu\text{g/ml}$, $P = 0.0519$). However, plasma D-dimer levels of the aortic dissection or aortic aneurysm were significantly higher than those of the coronary artery disease or healthy control groups (aortic dissection:coronary artery disease, 0.4344 ± 0.2958 $\mu\text{g/ml}$ vs. 0.0512 ± 0.0845 $\mu\text{g/ml}$, $P < 0.0001$; aortic dissection:healthy control, 0.4344 ± 0.2958 $\mu\text{g/ml}$ vs. 0.1250 ± 0.1295 $\mu\text{g/ml}$, $P = 0.0005$; aortic aneurysm:coronary artery disease, 0.4200 ± 0.4039 $\mu\text{g/ml}$ vs. 0.0512 ± 0.0845 $\mu\text{g/ml}$, $P = 0.0013$; and aortic aneurysm:healthy control, 0.4200 ± 0.4039 $\mu\text{g/ml}$ vs. 0.1250 ± 0.1295 $\mu\text{g/ml}$, $P = 0.0068$) (Figure 1).

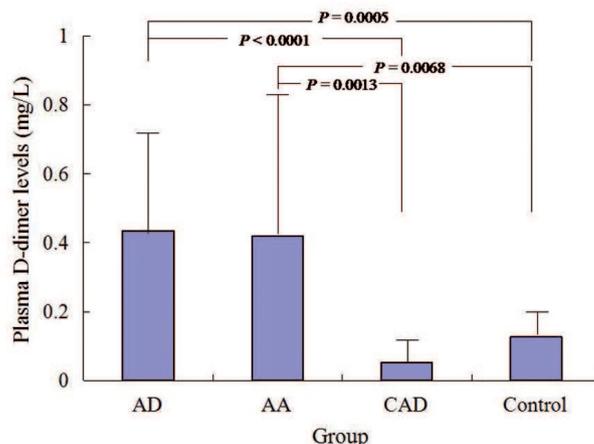


Fig. 1. Plasma D-dimer levels. AA - aortic aneurysm; AD - aortic dissection; CAD - coronary artery disease; Control - healthy control

There was no statistical significance in plasma hs-CRP values between the aortic dissection and aortic aneurysm groups (4.400 ± 3.004 mg/L vs. 2.314 ± 1.399 mg/L, $P = 0.1131$). However, plasma hs-CRP values of the aortic dissection or aortic aneurysm were significantly higher than those of the coronary artery disease or healthy control groups (aortic dissection: coronary artery disease, 4.400 ± 3.004 mg/L vs. 1.232 ± 0.601 mg/L, $P < 0.0001$; aortic dissection: healthy control, 4.400 ± 3.004 mg/L vs. 0.790 ± 0.423 mg/L, $P < 0.0001$; aortic aneurysm: coronary artery disease, 2.314 ± 1.399 mg/L vs. 1.232 ± 0.601 mg/L, $P = 0.0084$; and aortic aneurysm: healthy control, 2.314 ± 1.399 mg/L vs. 0.790 ± 0.423 mg/L, $P = 0.0002$), and between the coronary artery disease and healthy control groups (1.232 ± 0.601 mg/L vs. 0.790 ± 0.423 mg/L, $P = 0.0113$) (Figure 2).

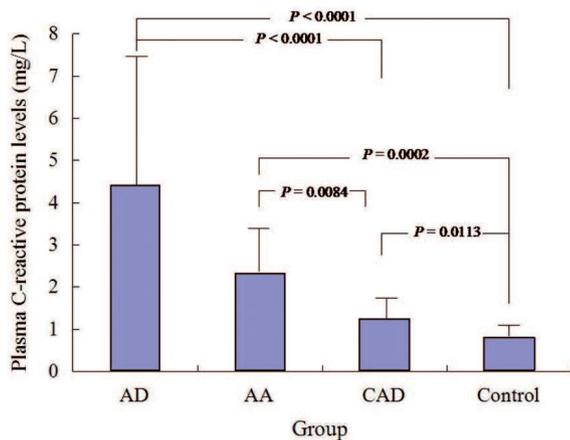


Fig. 2. Plasma hypersensitive C-reactive protein levels. AA - aortic aneurysm; AD - aortic dissection; CAD - coronary artery disease

No significant difference was found in the D-dimer values of the supernatant of the aortic tissues between the aortic dissection and aortic aneurysm groups (37.411 ± 69.865 mg/mg vs. 37.022 ± 37.697 mg/mg, $P = 0.9907$). However, D-dimer was undetectable in the supernatant of the aortic tissues of all cases of the coronary artery disease group (Figure 3).

No significant difference was found in the hs-CRP levels of the supernatant of the aortic tissues among the three investigated groups (aortic dissection: aortic aneurysm, 169.205 ± 134.240 mg/mg vs. 172.873 ± 74.549 mg/mg, $P = 0.9464$; aortic dissection: coronary artery disease, 169.205 ± 134.240 mg/mg vs. 148.413 ± 89.130 mg/mg, $P = 0.709$; aortic aneurysm: coronary artery disease, 172.873 ± 74.549 mg/mg vs. 148.413 ± 89.130 mg/mg, $P = 0.5321$) (Figure 4).

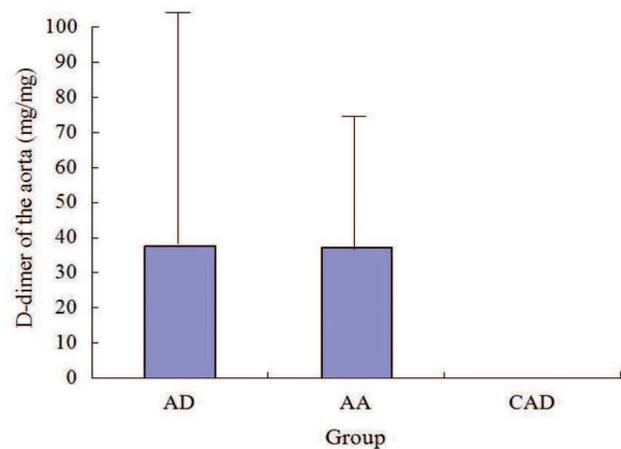


Fig. 3. D-dimers of the supernatant of the aortic tissues. AA - aortic aneurysm; AD - aortic dissection; CAD - coronary artery disease

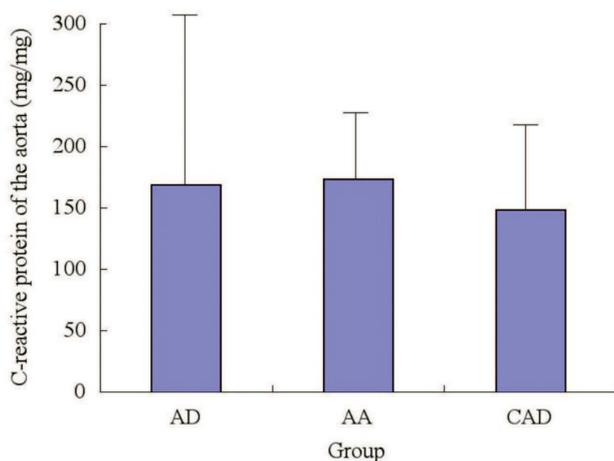


Fig. 4. Hypersensitive C-reactive protein levels of the supernatant of the aortic tissues. AA - aortic aneurysm; AD - aortic dissection; CAD - coronary artery disease; Control - healthy control

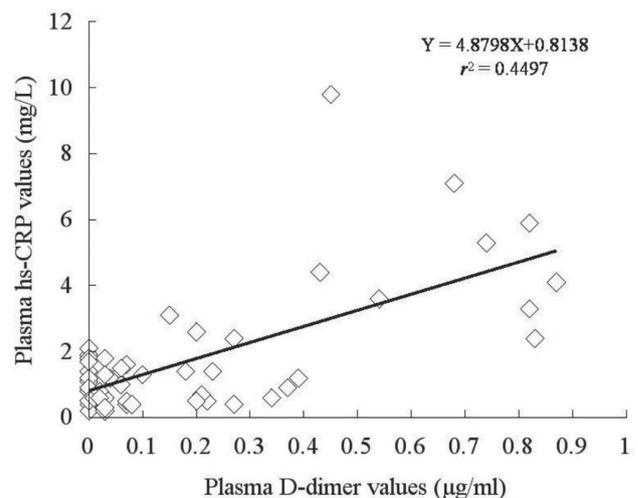


Fig. 5. Linear correlation between plasma D-dimer and plasma hypersensitive C-reactive protein levels of all four investigated groups

There was a significant correlation between plasma D-dimer and plasma hs-CRP when the results of all four groups were included ($Y = 4.8798X + 0.8138$, $r^2 = 0.4497$, $r = 0.671$, $P < 0.001$) (Figure 5). A significant correlation between plasma D-dimer and plasma hs-CRP was also noted in the aortic aneurysm ($Y = 2.6298X + 1.2098$, $r^2 = 0.5762$, $r = 0.759$, $P < 0.001$) (Figure 6), the aortic dissection ($Y = 7.1341X + 1.3006$, $r^2 = 0.4935$, $r = 0.7025$, $P = 0.048$) (Figure 7). However, there appeared no close correlation between plasma D-dimer and plasma hs-CRP in the coronary artery disease ($Y = 0.655X + 1.225$, $r^2 = 0.008$, $r = 0.088$, $P = 0.738$) and in the healthy control ($Y = -0.013X + 0.135$, $r^2 = 0.002$, $r = -0.041$, $P = 0.863$) groups.

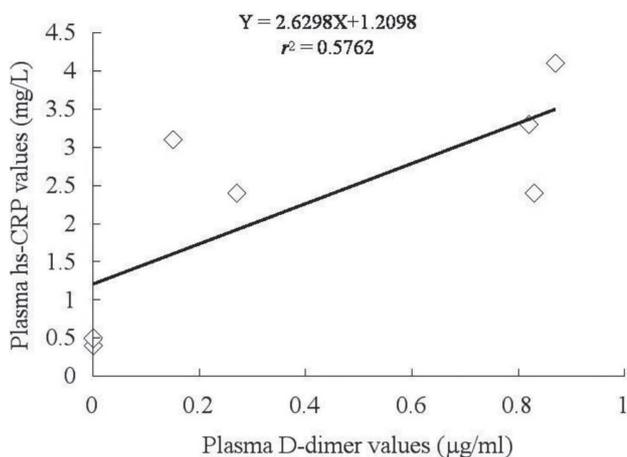


Fig. 6. Linear correlation between plasma D-dimer and plasma hypersensitive C-reactive protein levels of the aortic aneurysm group

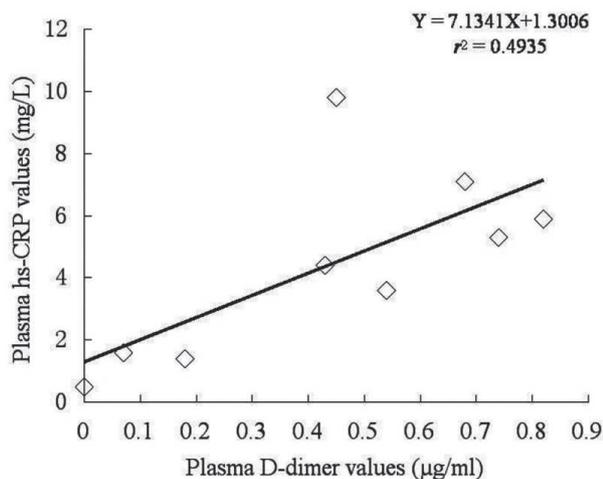


Fig. 7. Linear correlation between plasma D-dimer and plasma hypersensitive C-reactive protein levels of the aortic dissection group

When plasma D-dimer or plasma hs-CRP was taken as an independent variable, no inclusive dependent variables of the aortic dissection group (diseased course, time interval from the onset, preoperative fibrinogen levels, and D-dimer or hs-CRP levels in the supernatant of the aortic tissues) displayed a significant correlation with it.

DISCUSSION

D-dimer

D-dimer is a primary product of the cross-linked fibrin relating to fibrinolytic activation involving in atherosclerotic progression and endogenous fibrinolysis [14]. D-dimer antigen remains undetectable until it is released from cross-linked fibrin by the action of plasmin [15]. D-dimer is usually detectable 1 hour after the formation of the thrombus with a half-life time of 4-6 hours [16]. The D-dimer values could be detectable and remain high in the plasma 1.2 ± 2.5 days after onset of acute aortic dissection, and the mean value could be $8.610 (2.982-20.000) \mu\text{g/ml}$, significantly higher than the control [17].

D-dimer measurement is a rapid, easy-to-use, cost-effective method [18]. Test strip (Roche Diagnostics) for rapid bedside D-dimer assay is highly sensitive for early exclusion of acute aortic dissection in patients with chest pain [19]. A value of $0.5 \mu\text{g/ml}$ was defined as the threshold for a positive D-dimer [20]. Circulating D-dimers and CRP values appear to have prognostic value in the diagnosis of the underlying disorders with sufficient sensitivity and specificity [21].

D-dimer and ischemic heart disease

Lowe et al. [22] reported the positive correlation between CRP and D-dimer, and suggested combination of CRP and D-dimer may potentially predict ischemic heart disease. Bayes-Genis et al. [10] have recently demonstrated that plasma D-dimer values are significantly higher in patients with acute ischemic events than in non-ischemic patients. However, ischemic diseases may cause limited specificity of D-dimer testing as cerebrovascular disease, peripheral vascular disease, prior coronary revascularization, and renal or hepatic insufficiency may cause thrombosis with elevated D-dimer. Multivariate analysis showed that D-dimer levels were a significant independent variable for myocardial infarction, and elevated D-dimers were more likely to be associated with death compared with subjects with the lowest D-dimer values [23]. A five-fold increase in D-dimers was found in patients with unstable angina pectoris [24], and in those with an acute myocardial infarction [25]. D-dimer may reflect the severity of arteriosclerosis [26], indicating an increased formation and splitting of fibrin [6] in coronary patients. During thrombolytic therapy the fibrinogen levels drop to 12%-20% of their original values

and plasma D-dimer concentrations rise to 70-130-fold of the original values [6].

Plasmin has a broad range of actions: degrading fibrin, fibrinogen, factors V and VIII, proteins involved in platelet adhesion (glycoprotein I and vWF), and aggregation (glycoprotein IIb/IIIa), retaining platelet aggregates (thrombospondin, fibronectin, and histidine-rich glycoprotein), and enhancing the attachment of platelets and fibrin to the endothelial surface. α_2 -antiplasmin, also termed as plasmin inhibitor, is a serine protease inhibitor (serpin) responsible for inactivating plasmin, an important enzyme that participates in fibrinolysis and degradation of various other proteins. This protein is encoded by the SERPINF2 gene [27]. If there happens an enhanced plasmin or attenuated α_2 -antiplasmin in the atherosclerotic process, there might be scanty D-dimer production, which may lead to undetectable D-dimer in the plasma or aortic tissues of the coronary patients.

D-dimer and aortic diseases

Serum D-dimers may be remarkably elevated in the patients with acute aortic dissection [28]. The patients with acute aortic dissection had significantly elevated D-dimer values compared to both the chronic aneurysm patients as well as the normal subjects; patients with chronic aortic aneurysms also had significantly higher D-dimer compared to the control [29]. Eggebrecht et al. [21] reported that D-dimers were highly increased in patients with acute aortic dissection similar to those of the patients with pulmonary embolism, but significantly higher than those of the patients with chronic aortic dissection, acute myocardial infarction, or chest pain. These results were in agreement with ours.

The research on the elevations of circulating D-dimers have revealed substantial correlation with the time interval from the onset to the testing, and the type and dissection extent of aortic dissection: type A 8.8 ± 14.5 $\mu\text{g/ml}$, type B 10.1 ± 14.8 $\mu\text{g/ml}$, involvement of thoracic, abdominal aorta, and iliac arteries 18.9 ± 19.9 $\mu\text{g/ml}$, thoracic and abdominal aorta without iliac arteries 11.1 ± 17.8 $\mu\text{g/ml}$, and intramural hematoma 2.7 ± 1.9 $\mu\text{g/ml}$, respectively. Sbarouni et al. [29] reported 18 patients with acute aortic dissection having a mean D-dimer of 0.700 $\mu\text{g/ml}$, significantly higher than the patients with chronic aneurysms and the normal controls. The correlation between D-dimer value and the time interval from onset to detection was emphasized by many authors. However, Paparella et al. [11] described no correlation between these two parameters, suggesting that elevation of D-dimer may not depend on time. In addition, the D-dimer value was significantly lower in patients with a thrombosed false lumen than with a patent false lumen and in patients with De Bakey type II than with De Bakey type I, indicating that the D-dimer value depends on the length of the dissection [30]. The size of false lumen and dissection

length can be closely related to the formation of D-dimer [31]. Mean plasma D-dimer levels may increase or decrease with the progressive enlarging or regressive dwindling aortic dissection [32].

The cutoff level of 0.5 $\mu\text{g/ml}$ within 24 hours after onset was used for excluding pulmonary embolism, now also used for acute aortic dissection [33]. A plasma D-dimer value > 0.25 $\mu\text{g/ml}$ increased the cardiovascular mortality risk almost 4-fold [34]. Elevated D-dimer levels > 0.58 $\mu\text{g/mL}$ was predictive of death or myocardial infarction [10]. Furthermore, a positive relationship between D-dimer and in-hospital mortality rate among patients with acute aortic dissection was observed [35]. In acute type A aortic dissection, Weber et al. [36] proposed that plasma D-dimer may predict mortality. Immer [37] objected this viewpoint, and explained that prediction of mortality in acute aortic dissection based on D-dimer concentrations, may be extremely dangerous, as this may exclude some patients that may survive. D-dimer, but not CRP, troponin, lactate dehydrogenase, or leukocyte count, was predictive of a diagnosis of acute aortic dissection, with a sensitivity and specificity of 99% and 34%, respectively. D-dimer concentration positively correlated with the anatomical extension of the dissection to the different segments of the aorta [17]. D-dimer test could be negative in acute aortic syndrome due to acute aortic dissection, especially in patients without a patent false lumen presenting with an aortic intramural hematoma [38]. D-dimers may become significantly lower in aortic intraluminal hematoma (median 1.230 $\mu\text{g/ml}$, range 0.685 - 2.645 $\mu\text{g/ml}$) than in conventional dissection (median 9.290 , range 3.890 - 20.000). This may be associated with the lack of a thrombotic patent false lumen in the patients with intraluminal hematoma [39].

CRP

CRP can also be produced locally in atherosclerotic lesions [40]. The major part of CRP is synthesized by hepatocytes, driven by interleukin-6 with synergistic enhancement of interleukin-1 or tumor necrosis factor [41,42]. CRP directly influences several phases of atherosclerosis via complement activation, apoptosis, vascular cell activation, monocyte recruitment, lipid accumulation, and thrombosis [43]. Therefore, exaggerated CRP itself might exert harmful effects that promote the atherosclerosis of the dissected aortic wall.

CRP continued to increase at 48 hours after arrival to intensive care unit after surgery [44]. Strong correlations were observed in D-dimer values with circulating CRP values [45]. Contrary to what was reported in the literature, we did not find any correlation between plasma D-dimer and hs-CRP values. Instead, we noted close correlation between plasma D-dimer and hs-CRP values in overall, acute aortic dissection or aortic aneurysm groups.

On multivariate analyses, D-dimer retained a significant association with coronary risk, whereas CRP did not [46]. CRP has been preliminarily shown a less predictive value as an inflammatory risk score for aortic aneurysm endovascular treatment [47]. Maximal CRP was only predicting the impaired oxygenation, but not Stanford type, thrombosed false lumen, pleural effusion, atelectasis, and intravenous vasodilator use. At admission, CRP was normal and increased significantly since day 2 in the impaired oxygenation group [48]. Increased admission CRP correlated with high mortality irrespective of management policy [49]. However, Sakakura et al. [50] proposed that it may take 3-6 days to reach a peak CRP, initial CRP levels might not reflect the whole severity of aortic dissection, and therefore the peak CRP level was a better marker than the initial CRP level in the risk evaluation of type B aortic dissection.

hs-CRP is a useful risk predictor for recurrent coronary events, stroke or peripheral arterial disease [51]. Xu et al. [52] reported that serum hs-CRP was much higher in acute aortic dissection than in chronic aortic dissection and normal control, and serum hs-CRP had significant correlation with hypertension and serum fibrinogen levels.

In this study, we found that plasma D-dimers of the patients with acute type A aortic dissection and aortic aneurysm were significantly higher than the reference value. Plasma D-dimer and hs-CRP values in type A aortic dissection or aortic aneurysm were much higher than in coronary artery disease patients or the healthy control. Besides, there were close correlations plasma D-dimer and hs-CRP in overall, aortic dissection, and aortic aneurysm groups. These results suggested that plasma D-dimer and hs-CRP reflect the severity of the inflammatory reactions in the aortopathies including aortic dissection, aortic aneurysm and atherosclerosis, and could be important diagnostic biomarkers for aortic dissection and aortic aneurysm. In addition, the results of D-dimer and hs-CRP of the supernatant aortic tissues were scanty of intergroup significance, and showed undetectability of D-dimer in the aortic tissue of the coronary patients.

In conclusion, the patients with acute aortic dissection and aortic aneurysm may have remarkable elevations of plasma D-dimer and hs-CRP than the patients with coronary artery disease. The results may reflect the extensive inflammatory reaction and severe coagulopathies in the patients with acute type A aortic dissection, and thoracic aortic aneurysm patients in comparison to the coronary and healthy control subjects. The detections after onset in the patients with acute chest pain may help making a differential diagnosis between the aortopathies and ischemic heart disease. The undetectable D-dimer in aortic tissues of coronary patients may preclude its diagnostic value and require further investigations.

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