Lack of Association Between Cardiac Troponin T and D-Dimer in the Evaluation of Myocardial Damage

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Acute myocardial infarction (AMI) disrupts cardiac cell membranes, releasing intracellular cardiac proteins into the vascular system. Some of these proteins, including the cardiac troponin subunits T and I, have proven useful for diagnosing myocardial damage. Intracoronary thrombosis plays a key role in the pathogenesis of AMI, and the formation of an occlusive thrombus usually precedes the development of myocardial damage. To evaluate whether there is an association between the size of intracoronary thrombosis and myocardial damage, we analyzed D-dimer and cTnT levels in blood samples from patients suspected to have myocardial damage. We investigated 102 patients who were admitted to emergency service

for suspected myocardial damage. D-dimer was assessed with the use of the immunoassay Liatest D-dimer, and cTnT levels were measured with an electrochemiluminescence immunoassay (Troponin T STAT). D-dimer levels were lower in patients with cTnT < 0.01 than in patients presenting cTnT > 0.01 ng/mL. We investigated the relationship between D-dimer and cTnT levels in the patients with cTnT > 0.01 ng/mL (0.40 ± 0.10 ng/mL), and no significant agreement ($r = 0.20$, $P > 0.05$) was observed. The levels of D-dimer were not associated with the levels of cTnT in patients with cTnT > 0.01 ng/mL. *J. Clin. Lab. Anal.* 19:282–284, 2005.

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INTRODUCTION

Acute myocardial infarction (AMI) disrupts cardiac cell membranes, releasing intracellular cardiac proteins into the vascular system. Some of these proteins, including myoglobin, creatine kinase (CK)-MB, lactate dehydrogenase (LDH) type 1, and cardiac troponin subunits T and I, have proven useful for diagnosing AMI (1). In many patients with chest pain, the correct diagnosis of myocardial cell injury depends mainly on cardiac markers because the electrocardiogram is often nondiagnostic (2). Traditional biochemical markers, including CK, CK-MB isoenzyme, LDH, and aspartate aminotransferase, play a limited role in the diagnosis of AMI because their specificity and sensitivity are unsatisfactory (3). The measurement of serum cardiac troponin T (cTnT) and I (cTnI) levels can contribute to a correct diagnosis of AMI because they are sensitive

and specific markers for evaluating myocardial damage (2–9).

Intracoronary thrombosis plays a key role in the pathogenesis of AMI, and the formation of an occlusive thrombus usually precedes the development of myocardial damage. Thus, sensitive markers for an activated coagulation system could be useful for making an early diagnosis of AMI (10). During thrombus formation, plasmin degrades cross-linked fibrin polymers, resulting in the formation of a number of soluble cross-linked

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fibrin degradation products of various molecular weights. The smallest and best characterized of these products is D-dimer (11,12). D-dimer levels are elevated in patients with deep venous thrombosis (12–14), pulmonary embolism (15–19), disseminated intravascular coagulation (14) trauma (20), and malignancy, including hepatocellular carcinoma (21). To evaluate whether there is an association between the size of intracoronary thrombosis and myocardial damage, we analyzed D-dimer and cTnT levels in blood samples from patients suspected of having myocardial damage.

MATERIALS AND METHODS

We investigated 102 patients who were admitted to emergency service for suspected myocardial damage. A blood sample was collected from each patient at the moment of admittance to emergency service by venous puncture into serum tubes or tubes containing 0.109 mol/L trisodium citrate at a ratio of nine parts blood to one part citrate. Serum and plasma were obtained by centrifuging the samples for 10 min at 2,800 g. D-dimer and cardiac troponin T immunoassays were performed in plasma and serum, respectively. This protocol was approved by the Ethics Committee of Santa Casa Hospital.

D-dimer was assessed in plasma with the use of a quantitative and automated immunoassay, Liatest D-dimer (Diagnostica Stago, Asnières, France). A microlatex suspension was coated covalently with two complementary monoclonal antibodies specific for fibrin degradation products. The assay was performed by mixing 50 μ L of undiluted plasma with 100 μ L of reaction buffer, and the test was initiated with 150 μ L of latex suspension. The change in absorbance, measured at 540 nm on STA Compact analyzer (Diagnostica Stago, Asnières, France), was automatically recorded for 140 sec and represented a direct relationship to D-dimer concentration in the specimen. The results were expressed in ng/mL of fibrinogen equivalent units. The normal level of D-dimer in the adult population is generally less than 500 ng/mL.

Serum cTnT levels were measured with the use of a quantitative electrochemiluminescence immunoassay (Troponin T STAT, Roche Mannheim, Germany) in the Roche Elecsys 2010 analyzer. This assay is based on a sandwich principle. The sample, a biotinylated monoclonal troponin T-specific antibody, and a monoclonal troponin T-specific antibody labeled with a ruthenium complex react to form a sandwich complex. After the addition of streptavidin-coated microparticles, the complex becomes bound to the solid phase via the interaction of biotin and streptavidin. The reaction mixture is aspirated into the measuring cell, where the

microparticles are magnetically captured on the surface of the electrode. Unbound substances are then removed. The application of voltage to the electrode then induces chemiluminescent emission, which is measured by a photomultiplier. The results are determined using a calibration curve. The lower detection limit of this assay is 0.01 ng/mL (range = 0.01–25 ng/mL). The expected values of cTnT for healthy individuals are lower than 0.01 ng/mL.

The association between cTnT and D-dimer levels was evaluated by Student's *t*-test, and the relationship between D-dimer and cTnT > 0.01 ng/mL was investigated by linear regression. The results were expressed as mean $\pm$ SEM, and $P < 0.05$ was considered statistically significant.

RESULTS

In this study we found an association between cTnT and D-dimer levels in the patients with suspected myocardial damage. D-dimer levels were lower in patients with cTnT < 0.01 than those with cTnT > 0.01 ng/mL (Table 1). We also investigated the relationship between D-dimer and cTnT levels in the patients with cTnT > 0.01 ng/mL (0.40 ± 0.10 ng/mL), and no significant agreement ($r = 0.20$, $P > 0.05$) was observed (Fig. 1). Although D-dimer levels were

TABLE 1. Levels of cTnT and D-dimer observed in the patients

cTnT	<0.01	>0.01
n	56	46
D-dimer	1371 ± 234	$3920^* \pm 1020$

Values of D-dimer are given as mean $\pm$ SEM.

* $P < 0.01$ cTnT and D-dimer values were expressed in ng/mL.

Fig. 1. Association between the levels of cTnT and D-dimer in patients with cTnT > 0.01 ng/mL. No significant agreement ($r = 0.20$, $P > 0.05$) was observed.

increased in patients with cTnT > 0.01, their alterations were not directly proportional to cTnT variations.

DISCUSSION

Although previous studies have shown an association between hemostatic markers and cTnT, the association between higher levels of cTnT and D-dimer has been unclear. Intracoronary thrombosis plays a key role in the pathogenesis of AMI. The formation of an intracoronary thrombus in stenosed coronary arteries after the rupture of atherosclerotic plaques precedes the development of myocardial necrosis, with the subsequent release of intramyocardial macromolecules. During the development of thrombosis, thrombin activation precedes fibrin degradation. Early endogenous activation of fibrinolysis, on the other hand, may limit infarct size (10).

The most promising approaches for detecting coronary thrombosis and its complications involve the measurement of markers of fibrin formation and degradation in plasma (22). In a previous study, D-dimer levels were significantly higher in patients with ischemia than in patients without ischemia, and D-dimer appeared to be useful for the diagnosis of AMI during index admission in patients without elevation of CK/CK-MB at presentation (23). Although we found that D-dimer levels were increased in patients with cTnT > 0.01, these alterations were not directly proportional to cTnT variations. There was no statistically significant relationship between cTnT and D-dimer, and our results show that the degree of activation of fibrinolysis is not directly associated with the extension of myocardial damage. It is important to note that D-dimer levels may be affected by other illnesses, such as pulmonary embolus, cerebrovascular disease, peripheral vascular disease, and renal or hepatic insufficiency (23). In summary, the D-dimer levels were not associated with cTnT levels in the patients who presented with cTnT > 0.01 ng/mL. However, D-dimer constitutes an important complementary instrument for investigating myocardial damage, because of the importance of intracoronary thrombosis in the pathogenesis of AMI and other cardiac disorders.

REFERENCES

1. Le Moigne F, Beauviex MC, Derache P, Darmon YM. Determination of myoglobin: comparative evaluation of the new automated VIDAS assay with two other immunoassays. *Clin Biochem* 2002;35:255–262.
2. Penttilä K, Koukkunen H, Kemppainen A, et al. Myoglobin, creatine kinase MB, troponin T, troponin I—rapid bedside assays in patients with acute chest pain. *Int J Clin Lab Res* 1999;29:93–101.
3. Plebani M, Zaninotto M. Cardiac markers: present and future. *Int J Clin Lab Res* 1999;29:56–63.
4. Sarko J, Pollack CV. Cardiac troponins. *J Emerg Med* 2002;23:57–65.
5. Speth M, Seibold K, Katz N. Interaction between heparin and cardiac troponin T and troponin I from patients after coronary bypass surgery. *Clin Biochem* 2002;35:355–362.
6. Christenson RH, Azzazy HME. Biochemical markers of the acute coronary syndromes. *Clin Chem* 1998;44:1855–1864.
7. Mullen JC, Bentley MJ, Scherr KD, et al. Troponin T and I are not reliable markers of cardiac transplant rejection. *Eur J Cardiothorac Surg* 2002;22:233–237.
8. Apple FS, Falahati A, Paulsen PR, Miller EA, Sharkey SW. Improved detection of minor ischemic myocardial injury with measurement of serum cardiac troponin I. *Clin Chem* 1997;43:2047–2051.
9. Katus HA, Looser S, Hallermayer K, et al. Development and *in vitro* characterization of a new immunoassay of cardiac troponin T. *Clin Chem* 1992;38:386–393.
10. Mair J, Genser N, Maier J, Lechleitner P, Dienstl F, Puschendorf B. Markers of activated coagulation for early diagnosis of acute myocardial infarction. *Clin Chim Acta* 1997;267:239–245.
11. Rowe CA, Bolitho JS, Jane A, et al. Rapid detection of D-dimer using a fiber optic biosensor. *Thromb Haemost* 1998;79:94–98.
12. Kearon C, Ginsberg JS, Douketis J, et al. Management of suspected deep venous thrombosis in outpatients by using clinical assessment and D-dimer testing. *Ann Intern Med* 2001;135:108–111.
13. Kovacs MJ, MacKinnon KM, Anderson D, et al. A comparison of three rapid D-dimer methods for the diagnosis of venous thromboembolism. *Br J Haematol* 2001;115:140–144.
14. Wilde JT, Kitchen S, Kinsey S, Greaves M, Preston FE. Plasma D-dimer levels and their relationship to serum fibrinogen/fibrin degradation products in hypercoagulable states. *Br J Haematol* 1989;71:65–70.
15. Flores J, Lancha C, Rodriguez EP, Avello AG, Bollo E, Frade LJG. Efficacy of D-dimer and total fibrin degradation products evaluation in suspected pulmonary embolism. *Respiration* 1995;62:258–262.
16. Perrier A, Desmarais S, Goehring C, et al. D-dimer testing for suspected pulmonary embolism in outpatients. *Am J Respir Crit Care Med* 1997;156:492–496.
17. Oger E, Leroyer C, Bressollette L, et al. Evaluation of a new, rapid and quantitative D-dimer test in patients with suspected pulmonary embolism. *Am J Respir Crit Care Med* 1998;158:65–70.
18. Duet M, Benelhadj S, Kedra W, et al. A new quantitative D-dimer assay appropriate in emergency: reliability of the assay for pulmonary embolism exclusion diagnosis. *Thromb Res* 1998;91:1–5.
19. Bounameaux H, Cirafo P, De Moerloose P, et al. Measurement of D-dimer in plasma as diagnostic aid in suspected pulmonary embolism. *Lancet* 1991;337:196–200.
20. Kelley J, Rudd A, Lewis RR, Hunt BJ. Plasma D-dimers in the diagnosis of venous thromboembolism. *Arch Intern Med* 2002;162:747–756.
21. Kim HK, Lee KR, Yang JH, et al. Plasma levels of D-dimer and soluble fibrin polymer in patients with hepatocellular carcinoma: a possible predictor of tumor thrombosis. *Thromb Res* 2003;109:125–129.
22. Ottani F, Galvani M. Prognostic role of hemostatic markers in acute coronary syndromes patients. *Clin Chim Acta* 2001;311:33–39.
23. Menown IBA, Mathew TP, Gracey HM, et al. Prediction of recurrent events by D-dimer and inflammatory markers in patients with normal cardiac troponin I (PREDICT) study. *Am Heart J* 2003;145:986–992.