Serum concentrations of cardiac troponin-I in patients with rheumatoid arthritis, systemic lupus erythematosus, primary Sjogren's syndrome and Graves' disease

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ABSTRACT

Introduction: Some reports in the literature suggest that cardiac troponin-I (cTnI) is falsely elevated in patients with seropositive rheumatoid arthritis (RA) because of the presence of rheumatoid factor (RF). But, there are no reports in the literature on cTnI concentrations in other autoimmune diseases. We therefore decided to measure the serum concentrations of cTnI in patients with seropositive and seronegative RA, systemic lupus erythematosus (SLE), primary Sjogren's syndrome (pSS) and Graves' disease (GD), in order to find out if this cardiac marker is falsely elevated or not.

Methods: Serum samples were drawn from 50 patients with seropositive RA, 50 patients with seronegative RA, 50 patients with SLE, 20 patients with pSS and 15 patients with GD. We measured cTnI levels using the Beckman Access Immunoassay System in these serum samples.

Results: Of the 50 patients with seropositive RA, five had cTnI levels higher than 0.1 ng per ml (the diagnostic value for myocardial infarction in our hospital laboratory), while none of the patients with seronegative RA, SLE, pSS, or GD had levels above this value. Furthermore, univariate regression analysis showed a positive association (r equals 0.35, p-value equals 0.02) between cTnI and RF in patients with seropositive RA.

Conclusion: Using the Beckman Access Immunoassay System for cTnI quantification, it was found that some patients with seropositive RA had falsely-elevated cTnI, while none of the patients with seronegative RA, SLE, pSS, or GD had falsely-elevated cTnI.

Keywords: cardiac troponin-I, Grave's disease, primary Sjogren's disease, rheumatoid arthritis, serum rheumatoid factor, systemic lupus erythematosus

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INTRODUCTION

Despite decades of investigation, the diagnosis of acute myocardial infarction (AMI) is still quite clinically daunting, because the majority of patients with chest pain falls in the low or medium risk category, and present with atypical symptoms and non-specific electrocardiographic changes.[1] In September 2000, the definition of myocardial infarction (MI) was revised by the Joint European Society of Cardiology/American College of Cardiology Committee utilising cardiac troponins (cTn) as new biochemical markers for myocardial damage.[2] Release of cTns occurs after irreversible cardiac myocyte damage. The troponin complex comprises three subunits. Each subunit is a protein, and together they regulate the calcium-dependent interactions between actin and myosin, which result in contraction and relaxation of striated muscle. Whereas the identical troponin-C is expressed by both skeletal and cardiac muscles, the amino acid sequences of cardiac troponin-I (cTnI) and T (cTnT) differ from the sequences in skeletal muscles. This has allowed monoclonal antibodies to be developed against these troponins. These monoclonal antibodies have very little cross-reactivity with the skeletal isoforms.[3] Both are, therefore, very sensitive and specific indicators of myocardial damage.[4-10]

As sensitive and specific as these proteins are, their assays have been beset by some analytical problems. For example, while some reports in the literature suggest that the presence of antibodies may cause serum cTnI

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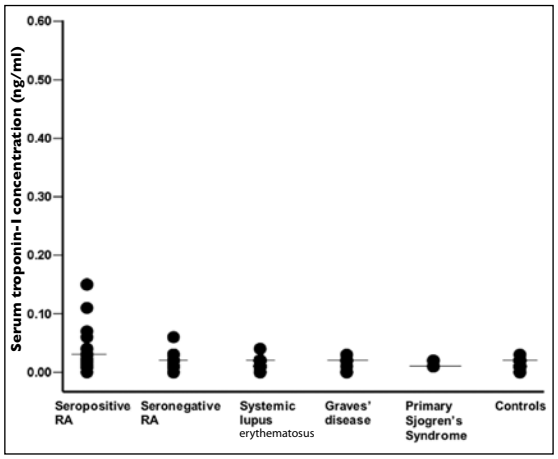

Fig. 1 Scatter plot for serum concentrations of cardiac troponin-I in the different autoimmune diseases.

to be falsely elevated;[11-23] others suggest that this troponin is not affected by rheumatoid factor (RF).[24] Other factors, such as the presence of heterophilic antibodies and excess fibrin and albumin, have also been shown to interfere with cTnI assays.[12,13] Since rheumatoid arthritis (RA) and other autoimmune disorders are common in Kuwait,[25] we decided to find out if patients with RA, systemic lupus erythematosus (SLE), primary Sjogren's syndrome (pSS) and Graves' disease (GD) also have falsely-elevated concentrations of serum cTnI. This is important for the accurate diagnosis of MI in these autoimmune disorders. There has been no report to date on the serum concentrations of cTnI in SLE, pSS, and GD.

METHODS

We investigated serum samples from 50 patients, aged 18 years and above, with seropositive RA, 50 patients with seronegative RA, 50 patients with SLE, 20 patients with pSS, 20 patients with GD and 60 healthy controls. All recruited patients were seen on regular follow-up basis in rheumatic disease and endocrine clinics of Al-Amiri teaching hospital in Kuwait. None of them had infection or flares of their diseases at the time of blood sampling. The diagnosis of RA and SLE were according to the American College of Rheumatology criteria for RA and SLE,[26,27] respectively. The diagnosis of pSS was based on the 2002 American-European Consensus Classification Criteria,[28] while the diagnosis of GD was based on the presence of hyperthyroidism and detection of anti-thyrotropin receptor antibody in the blood.

Through electronic case record review, laboratory review and patient interviews, patients were excluded from the study for the following reasons: age < 18 years, chronic renal failure (defined on the basis of clinical conditions and serum creatinine of more than 120 umol/L), pregnancy, congestive heart failure, unstable angina, invasive cardiac testing within the past six months, history of typical angina symptoms within the past two weeks, and known history of coronary artery disease. The 60 healthy controls were recruited from the Central Blood Bank and were also subjected to the above exclusion criteria. All the patients and healthy controls underwent phlebotomy and serum was tested for cTnI using the Beckman Access® Immunoassay System (Beckman Coulter Inc, Fullerton, CA, USA). The IgG RF concentrations in both healthy controls and patients were measured on the Beckman IMMAGE Nephelometer (Beckman Coulter Inc, Fullerton, CA, USA). Informed consent was obtained from each subject investigated. Since the troponin data were not normally distributed, non-parametric methods were applied in the statistical analysis of data. Correlations were evaluated using Spearman's rank correlation coefficient (r) and a p-value of less than 0.05 was considered to be significant.

RESULTS

Of the 50 patients with seropositive RA, five had serum cTnI values greater than 0.1 ng/ml (the diagnostic value for myocardial infarction in our hospital laboratory). They were admitted to the coronary care unit, where they had serial ECG and serum concentrations of creatinine kinase and its isoenzyme measurements for three days. None of them developed any abnormality suggestive of AMI. The RF concentrations in these five patients were 633, 496, 546, 600, and 480 IU/ml. The serum concentrations of RF in the seropositive RA patients was significantly positively associated with serum cTnI ($r = 0.35$, $p = 0.02$), suggesting that the presence of RF in the sera of patients with RA may cause falsely-elevated serum concentration of cTnI. In this study none of our healthy controls nor SLE or pSS patients had a serum concentration of RF greater than the normal reference range (0–20 IU/ml). None of the patients with seronegative RA, SLE, pSS, or GD had cTnI concentration greater than 0.1ng/ml, suggesting that cTnI is not falsely elevated in these patients (Fig. 1).

DISCUSSION

Our results using the Beckman Access® Immunoassay System for testing serum cTnI suggest that about 10% of patients with seropositive RA had falsely-elevated cTnI levels and that there was a positive correlation between IgG RF and cTnI concentrations. We did not however, measure IgM RF, which may affect this conclusion. This finding is in agreement with previous studies that

reported falsely-elevated cTnI values in the presence of heterophilic antibodies,[11-23] but is at variance with the report of Kenny and Finger, who found that cTnI is not falsely-elevated in RA.[24] Current cTnI assays utilise enzyme-linked immunosorbent assays, with mouse or goat monoclonal antibodies as both the capture and conjugate antibodies. RF antibodies can bind to the Fc receptors of both the monoclonal antibodies at the capture and the conjugate portion of the assay, stimulating cTnI and causing a falsely-elevated result. It is therefore important that cTnI results in patients with seropositive RA be interpreted with caution.

In this study, no patient with seronegative RA, SLE, pSS, or GD had falsely-elevated cTnI levels, suggesting that cTnI can be used for the diagnosis of MI in these patients. This is the first study to report on cTnI assay in patients with SLE, pSS and GD. Unfortunately, the validity of our results for pSS and GD is limited by our small sample size, but nevertheless, it can be concluded that heterophilic antibodies from these diseases do not interfere with cTnI assay on the Beckman Access® Immunoassay System.

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