Falsely Elevated Cardiac Troponin-I in Patients with Seropositive Rheumatoid Arthritis

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ABSTRACT. ***Objective.*** To determine if patients with seropositive rheumatoid arthritis (RA) have abnormally elevated concentrations of cardiac troponin-I (cTnI). Reports suggest the presence of serum rheumatoid factor (RF) may interfere with the cTnI assay, leading to falsely elevated cTnI levels. One study reported a falsely elevated cTnI in 15 out of 100 serum samples with elevated RF using the Abbott assay, but no elevated level using the Bayer assay. It is unclear how many of these samples came from patients with RA.

Methods. Serum samples were drawn from 60 patients with seropositive RA. We measured RF and cTnI levels using both the Abbott AxSYM assay and the Bayer ADVIA Centaur assay.

Results. Of 60 RA patients with RF ranging from 15 to 2724 IU/ml, none was found to have an elevated cTnI on either assay.

Conclusion. Using 2 commercial assays for cTnI, we found that patients with seropositive RA do not have falsely elevated serum cTnI levels. (J Rheumatol 2005;32:1258–60)

Key Indexing Terms:
RHEUMATOID FACTOR
TROPONIN I
RHEUMATOID ARTHRITIS
FALSE POSITIVE REACTIONS

Cardiac troponin-I (cTnI) is a highly sensitive and specific biochemical marker used for the diagnosis of acute myocardial infarction. Studies suggest the presence of rheumatoid factor (RF) may cause cTnI to be falsely elevated[1-13]. Other factors such as the presence of heterophile antibodies, excess fibrin, and albumin have also been shown to interfere with cTnI assays, causing false-positive results[2,3]. We investigated if patients with seropositive rheumatoid arthritis (RA) have falsely elevated concentrations of cTnI. Three studies and several case reports have previously investigated the possibility of RF causing an elevation in cTnI[1-13].

Krahn, *et al* reported a false elevation of cTnI to a range consistent with myocardial injury in 15 of 100 subjects with elevated RF, when measured using the Abbott AxSYM assay. These same 100 patients' serum samples were also run on the Bayer Immuno 1 assay and were found to have no falsely elevated cTnI[1].

Onuska and Hill[4] highlighted the improvement made by Abbott Laboratories to eliminate heterophile antibody interference by modifying the reagent for the cTnI AxSYM system. One arm of their study performed seroanalysis of 19 RF-positive patients with both the original and modified cTnI reagents. Four patients had elevations of cTnI to a level consistent with myocardial infarction when analyzed with the original reagent, while no patient had an elevation of cTnI analyzed with the modified reagent[4].

We performed a comparison of Abbott's AxSYM cTnI assay (Abbott, Abbott Park, IL, USA) and Bayer's ADVIA Centaur cTnI assay (Bayer, Tarrytown, NY, USA). Our study exclusively tested patients known to have seropositive RA in order to examine the incidence of falsely elevated cTnI in this subset of patients. By performing an independent analysis on this select patient population, we sought to test the diagnostic accuracy of 2 cTnI assays in patients with seropositive RA.

MATERIALS AND METHODS

We studied serum samples from 60 patients over the age of 18 years with seropositive RA at our facility. All patients met the 1987 American Rheumatism Association revised criteria for the classification of RA. Patients were considered seropositive if they had a history of elevated RF (determined by immunoturbidimetric analysis using the Cobas Integra 800 assay by Roche, Roche, Indianapolis, IN, USA) over the last 3 years, or if they were ever documented as being "seropositive" or having a "positive RF" on review of prior evaluations by staff rheumatologists.

Our patient population consisted of 43 women (age 22–79 yrs) and 17 men (age 23–78 yrs). The age range of all patients was 22–79 years (mean 57 yrs). Through electronic record review, laboratory review, and patient interviews, patients were excluded for the following reasons: pregnancy, age < 18 yrs, chronic renal failure (defined as serum creatinine ≥ 1.5), myocarditis, pericarditis, congestive heart failure, unstable angina, invasive cardiac testing within the past 6 months, history of typical anginal symptoms within the past 2 weeks, or patients with known coronary artery disease.

All 60 patients underwent phlebotomy, and serum was tested for RF and for cTnI using both the Abbott assay and the Bayer assay. Blood samples were saved for further testing should their test results reveal an elevation in cTnI. The study protocol was approved by the Human Use Committee at Tripler Army Medical Center and investigators adhered to the policies for protection of human subjects as prescribed in 45 CFR 46.

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RESULTS

Of 74 patients screened, all fulfilled the inclusion criteria and none were eliminated due to exclusion criteria. A prescreening selection bias existed since patients had an electronic medical database available for review. Patients with a cardiac history or who could be excluded by means of existing laboratory data were not asked to participate. Of the initial 74 patients enrolled, one did not report for her initial laboratory investigation and 13 failed to complete the required Health Insurance Portability and Accountability Act consent form and were excluded.

A total of 60 patients underwent serologic analysis for current RF levels and cTnI on both the Bayer and Abbott assays. Serum RF ranged from 15 to 2724 IU/ml (normal < 14) with a mean of 210. No patient tested was found to have elevation of cTnI on either of the 2 assays.

DISCUSSION

Although highly specific for myocardial injury, cTnI assays are not free from antibody interference. Antibodies directed against *Escherichia coli* and etanercept have been suggested to interfere with cTnI monoclonal antibody assays[3,12]. Other causes of elevated cTnI are outlined in Table 1[12]. Current cTnI assays utilize 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, simulating cTnI and causing a false-positive result[7]. In 1999 Abbott Laboratories modified its cTnI reagent system to address the issue of heterophile antibody interference.

Table 1. Reported etiologies and mechanisms of falsely elevated troponin assay[12].

System	Condition
Coronary artery disease	Acute myocardial infarction
	Unstable angina
Noncoronary heart disease	Pericarditis
	Myocardial injury (trauma)
	Myocarditis
	Congestive heart failure
	Arrhythmia
	Pulmonary embolism
Renal failure	
Assay interference	Heterophile antibody
	Rheumatoid factor
	Specialized fluids (albumin, plasmin)
	Excess fibrin

Our results suggest the presence of RF in patients with seropositive RF does not lead to falsely elevated cTnI levels when tests are run on either the Bayer Immuno 1 or the Abbott AxSYM cTnI assays. Our results on the Bayer assay were similar to those reported from previous studies[1,4,6]. However, our results on the Abbott assay, similar to those of Onuska and Hill, showed significant improvement in the diagnostic accuracy of the current Abbott assay with the modified cTnI reagent[4]. A comparison of patient characteristics and test results from our study with those from prior studies is given in Table 2.

The literature reveals evidence of several sources of interference with monoclonal antibody assays, and this should be taken into consideration in any clinical situation that does not correlate with laboratory results. Further study would be beneficial to define patient populations that may be at higher risk of false-positive results on current cTnI assays, although our results suggest that patients with seropositive RA do not have an increased incidence of falsely elevated cTnI.

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Table 2. Combined results and patient characteristics from current and previous studies.

Study	Total Patients (all RF+), n	False-Positive cTnl	cTnl Range, µg/l	Abbott AxSYM Test	Bayer Immunol Test	Range of RF	Age Range, yrs (mean)
Current study	60	0	0–0.8	0/60*	0/60	15–2724 IU/ml	22–79 (57)
Banerjee[13]	1	1	14.4–35.4	1/1	NA	1280 IU/ml	52
Dasgupta[6]	12	7	0.2–>50	7/12	0/10	23–485 IU/ml	Unknown
Katwa[7]	1	1	473–1280	1/1	NA	1240 IU/ml	68
Krahn[1]	100	15	0–32	15/100	0/100	104–7320 IU/ml	17–89 (53)
Onuska[4]	42	13	0–13.1	13/42, 0/19*	NA	83–2938 IU/l	Unknown
Total	212	37	0–1280	37/156, 0/79*	0/170	15–7320 IU/ml	—

* Assay run with the modified cTnl reagent system.

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