

COMPARISON OF CARDIAC BIOMARKERS AND ECHOCARDIOGRAPHY IN DIAGNOSING MYOCARDITIS

Nimi Bharathan¹, Cibu Mathew², Radhika Mutteth³, Rajany Jose⁴, Pushpalatha Mukkadakkattil⁵

¹Assistant Professor, Department of Biochemistry, Government Medical College, Thrissur, Kerala.

²Additional Professor, Department of Cardiology, Government Medical College, Thrissur, Kerala.

³Assistant Professor, Department of Medicine, Government Medical College, Thrissur, Kerala.

⁴Assistant Professor, Department of Community Medicine, Government Medical College, Thrissur, Kerala.

⁵Professor, Department of Biochemistry, Government Medical College, Thrissur, Kerala.

ABSTRACT

BACKGROUND

Conventional methods used to diagnose or rule out myocarditis is not useful in detecting cardiac myocyte injury in clinically suspected cases. Endomyocardial biopsy and histopathological examination is not feasible in most government hospitals in India. Sensitive parameters have yet to be found out. The study was conducted to find out whether diagnosis of myocarditis in clinically suspected cases can be done by measurement of serum levels of cardiac troponinI (cTnI) and MB isoform of creatine kinase (CK-MB).

MATERIALS AND METHODS

19 patients with clinically suspected myocarditis were screened for CK-MB activity and cTnI. Echocardiography, ECG and IgM for leptospirosis were also checked in these patients.

RESULTS

cTnI was elevated in 10 out of 19 patients with clinically suspected myocarditis. CK-MB was elevated in 7 patients.

CONCLUSION

Elevation of cTnI level in blood can be taken as an indicator of cardiac muscle cell injury in suspected cases of myocarditis.

KEYWORDS

Myocarditis, Troponin I, Cardiac Troponins, Cardiac Biomarkers, cTnI.

HOW TO CITE THIS ARTICLE: Bharathan N, Mathew C, Mutteth R, et al. Comparison of cardiac biomarkers and echocardiography in diagnosing myocarditis. J. Evid. Based Med. Healthc. 2017; 4(22), 1287-1290. DOI: 10.18410/jebmh/2017/251

BACKGROUND

Myocardial involvement is a very common complication of various infections like influenza, tonsillitis, hepatitis etc.^{1,2} Routine investigations that are indicators of inflammation are nonspecific and failed to show cardiac myocyte injury. Echocardiography is helpful in only those cases, which show cardiac wall motion abnormalities or other types of ventricular dysfunctions. Endomyocardial biopsy, which is the most accurate diagnostic investigation in myocarditis is not being practiced in our clinical setup where facilities for invasive cardiac procedures are not available. In routine practice, diagnosis of myocarditis is based on history, clinical presentation, examination findings, ECG and echocardiographic findings in our hospital.

In this situation, it seemed rational to look for easier and more accurate methods by which cardiac myocyte injury can be assessed sensitively. Measurement of serum levels of cardiac troponin I (cTnI) and Creatine Kinase-MB Fraction (CK-MB) in patients with clinically-suspected myocarditis is an area of interest in this context. Plenty of studies are available, which show that blood level of cardiac biomarkers become elevated even before ECG changes become evident in cases of myocardial infarction.^{3,4} But, such studies are scanty in India in case of suspected myocarditis. It is mainly from western literature that we assume that elevated levels of cardiac biomarkers can be taken a diagnostic feature of myocarditis. In clinically suspected myocarditis, the variables conventionally used to indicate myocardial cell damage like CK-MB are usually within normal limits probably because a small amount of myocardial necrosis does not lead to increases beyond the normal range. Development of new sensitive assay techniques to estimate serum cTnI using monoclonal antibodies to cTnI has made this assay a better investigation of choice in unstable angina pectoris. In this study, it is investigated whether measurement of cTnI in serum can provide evidence of myocardial cell damage in patients with clinically-suspected myocarditis.

Financial or Other, Competing Interest: None.

Submission 20-02-2017, Peer Review 27-02-2017,

Acceptance 13-03-2017, Published 16-03-2017.

Corresponding Author:

Dr. NimiBharathan,

Houe No. 5, 'Deepthi', Pranavam Nagar,

Ollukara P.O., Thrissur, Kerala.

E-mail: nimi.binoj@gmail.com

DOI: 10.18410/jebmh/2017/251



Leptospirosis is a common cause of myocarditis in Kerala especially among agricultural workers and manual labourers. Increased incidence of Leptospirosis among labourers, working in paddy fields especially in rainy season has made testing for IgM antibody to Leptospira a routine practice during investigation of suspected myocarditis cases. Presence or absence of IgM Leptospira antibody is taken as corroborative evidence in diagnosis.

Aims and Objectives

Aims

To find out whether estimating blood levels of cTnI will help in diagnosing myocarditis in suspicious cases.

Objectives

To compare the blood levels of cTnI and CK-MB with echocardiography in suspected cases of myocarditis.

MATERIALS AND METHODS

Inclusion Criteria

Patients admitted with fever and ECG changes suggestive of myocardial damage along with either hypotension or dyspnoea are included for study.

Exclusion Criteria

Patients diagnosed to have myocardial ischaemia, pulmonary embolism, sepsis and acute stroke are excluded from the study.

Co-intervention- Nil.

22 patients who were admitted to the ICU with clinical suspicion of myocarditis were enrolled for the study. Out of them, 3 patients died before echocardiographic evaluation could be completed. The remaining 19 patients were studied completely. Clinical diagnosis of suspected myocarditis was made when patients presenting with fever and chest pain/dyspnoea/hypotension showed changes in ECG suggestive of myocardial damage. Echocardiography was done for all these patients.

Measurement of CK-MB and cTnI - Blood samples were taken on admission and serum separated. Serum was analysed for cTnI and CK-MB.

Estimation of cTnI was done manually by solid phase sandwich immunoassay using four monoclonal antibodies directed against cTnI using CE certified reagent kit manufactured by Calbiotech Inc., and read on ELISA reader manufactured by Bio-Rad Ltd. Levels above 0.01 mcg/L were taken as positive.

Estimation of CK-MB activity was done by immunoinhibition/modified IFCC method using reagent kit manufactured by Crest Biosystems on clinical chemistry analyser EM360 manufactured by ERBA Mannheim, Germany. CK-MB levels above 24 IU/L were taken as positive.

Presence of IgM antibody to Leptospira was also checked in all these patients. Echocardiographic assessment was also done for detecting presence of myocardial damage and changes in cardiac blood flow pattern. Antibiotics were started for these patients as soon

as clinical diagnosis of myocarditis was made. Clinical and symptomatic improvement along with normalisation of ECG changes was taken as a corroborative evidence of response to treatment.

Statistical Analysis

All results were expressed as mean±SD. Validity of cTnI, CK-MB and echocardiography were calculated using sensitivity, specificity, Positive Predictive Value (PPV) and Negative Predictive Value (NPV). Sensitivity, specificity, PPV and NPV of CK-MB, cTnI and echocardiography were calculated separately and in combination.

RESULTS

Patients included 12 (63.2%) males and 7 (36.8%) females.

Mean serum cTnI level was 1.08±1.47 microg/L. Highest value was 5.39microg/L and lowest value was 0.01microg/L. Elevated levels of cTnI (>0.01µg/L) was detected in 10 (52.63%) out of 19 samples and was undetectable in 9 (47.37%) samples. Among patients with elevated cTnI levels (cTnI+ patients), clinical diagnosis of myocarditis was made in 6 patients (60%), in 3 patients (30%) the diagnosis was that of acute myocardial infarction. One patient who was cTnI+ was diagnosed to have left lower lobe pneumonia in chest x-ray. In patients with normal cTnI levels (cTnI- patients), 3 were clinically diagnosed to have myocarditis (33.33%), 3 patients were diagnosed to have pericarditis (33.33%) and one patient each were diagnosed to have infective endocarditis, pneumonia and upper respiratory infection.

The sensitivity of cTnI assay for detection of myocarditis was found to be 66.66% and specificity was found to be 60%. PPV was 60% and NPV was 66.66% as demonstrated in Table 1.

	Patients Diagnosed to have Myocarditis	Patients not Diagnosed to have Myocarditis
cTnI +	6	4
cTnI -	3	6
Table 1. Number of Patients Showing High (+) and Normal (-) cTnI Values		

Serum levels of CK-MB levels were found to be high in 7 patients (36.84%) and within normal limits in 12 patients (63.16%). Mean CK-MB level was found to be 38.21±40.98 IU/L. In the case of CK-MB, sensitivity was 44.44%, specificity 70%, PPV 57.14% and NPV 58.33% as shown in Table 2.

	Patients Diagnosed to have Myocarditis	Patients not Diagnosed to have Myocarditis
CK-MB+	4	3
CK-MB-	5	7
Table 2. Number of Patients Showing High (+) and Normal (-) CK-MB Values		

The sensitivity of echocardiography in diagnosing myocarditis was found to be 11.11%, specificity 60%, PPV 20% and NPV 42.86% as shown in Table 3.

	Patients Diagnosed to have Myocarditis	Patients not Diagnosed to have Myocarditis
Echocardiography +	1	4
Echocardiography -	8	6

Table 3. Number of Patients Showing Abnormal (+) and Normal (-) Echocardiography Findings

When abnormality in both cTnI and echocardiography together were taken into consideration, sensitivity was found to be 0%, specificity 90%, PPV 0% and NPV 50% as given in Table 4.

	Patients Diagnosed to have Myocarditis	Patients not Diagnosed to have Myocarditis
cTnI + and echocardiography +	0	1
cTnI - and echocardiography -	9	9

Table 4. Number of Patients Showing Abnormality (+) and Normality (-) in cTnI Value and Echocardiography Findings

Similarly, when positivity to cTnI and Leptospira IgM were considered together. They showed 44.44% sensitivity and 90% specificity with PPV 80% and NPV 64.29% (Table 5).

	Patients Diagnosed to have Myocarditis	Patients not Diagnosed to have Myocarditis
cTnI + and Leptospira IgM +	4	1
cTnI - and Leptospira IgM +	5	9

Table 5. Number of Patients Showing Abnormality (+) and Normality (-) in cTnI and Leptospira IgM Values

Leptospira IgM was found to be positive in 6 (31.58%) patients. It was negative in the remaining 13 patients (68.42%).

DISCUSSION

There are previous studies, which show that cTnI is a more sensitive indicator of myocardial damage than CK-MB in diagnosing myocarditis.⁵ There are studies showing that CK-MB has limited value as an index for myocardial injury in suspected myocarditis.⁶ In this study, among 9 patients who were diagnosed to have myocarditis, 66.66% showed high cTnI levels, whereas CK-MB was elevated in only

44.44%. Even though, CK-MB showed higher specificity, it has proven to be inferior to cTnI in predictive value.

Cardiac troponin I is a 22.5 KD protein that exists as part of the troponin complex.⁷ It is one of the three subunits of troponin that regulate the interaction of actin and myosin and thus regulates cardiac contraction. Troponin I subunit is seen to exist in three different isoforms. This isoform of troponin I is seen to exist in cardiac muscle tissue while the other two isoforms are seen in fast twitch and slow twitch skeletal muscle fibres.^{8,9} cTnI and cTnT have amino acid sequences that are different from troponins found in other muscles like skeletal muscles. Human cTnI has additional 31 amino acids at the aminoterminal end that makes it cardiac specific.¹⁰ cTnI has been useful in the diagnosis of patients reaching the emergency department with myocardial infarction.^{11,12} cTnI is normally hardly detectable in the serum of healthy persons. Cardiac troponin I and T are being described and preferred as biomarkers of myocardial damage.¹³ cTnI assay was found to be useful in diagnosis of myocarditis in cattle as shown in a study conducted by Karapinar et al.¹⁴ Noutsias et al have already documented that cardiac troponins can predict the severity and prognosis of inflammatory and non-inflammatory cardiomyopathy.¹⁵

Echocardiography is found to show specificity in those few patients having abnormalities in cardiac blood flow pattern or wall movement.

Both sensitivity and specificity can be increased by combining different noninvasive parameters like cardiac troponins, echocardiography and specific immunoglobulins, so that early treatment can be instituted in centres like ours where facilities for invasive procedures like endomyocardial biopsy are not present.

Presence of IgM antibody to Leptospira was not taken as a diagnostic parameter in this study, but it was done as a tool to identify one of the common causes of myocarditis. So, statistical analysis of that parameter was not done.

Endomyocardial biopsy even though considered as the gold standard in diagnosis of myocarditis is not the most sensitive investigation as specimens collected from areas of inflammation alone will yield positive result. As biopsy from left ventricle is infrequently performed due to higher mortality, localised areas of inflammation arising from left ventricle can be totally missed.⁵ These facts along with lack of infrastructural and technical support for taking endomyocardial biopsy has made it impossible in some institutions. In such situations, combining noninvasive investigations like cTnI, antibodies and echocardiography can help in increasing the accuracy of diagnosis.

MRI is nowadays proving to be helpful in diagnosis of myocarditis when other investigations often fail.¹⁶ Newer markers like miR-1 and miR-146b are also coming to aid diagnosis of myocarditis.¹⁷

CONCLUSION

It was found in this study that measurement of cardiac biomarkers in blood can indicate damage to myocardial

cells in patients with clinically suspected myocarditis better than echocardiography.

Among the cardiac biomarkers, cTnI showed better sensitivity and predictive value than CK-MB. Combining cTnI and echocardiography improved specificity more than when each of these was used individually. Similarly, combined assessment of cTnI and IgM for *Leptospira* also improved specificity, PPV and NPV.

ACKNOWLEDGEMENTS

This study was conducted with financial support from SBMR, Kerala. We acknowledge the support provided for the study by Institutional Research Committee, Government Medical College, Thrissur, Kerala.

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