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The Role of Coronary Artery Disease in Demand Mediated Myocardial Infarction: A Retrospective Study from a Community Hospital

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The Role of Coronary Artery Disease in Demand Mediated Myocardial Infarction: A Retrospective Study from a Community Hospital

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Abstract

Type 2 Myocardial Infarction (T2MI) is an increasingly recognized clinical entity due to the availability of highly sensitive troponin assays for patients admitted due to common medical diagnoses. However, there is little epidemiological data on the significance and long-term prognosis of T2MI, which occurs secondary to an increase in myocardial oxygen demand and/or a decrease in myocardial blood flow. Arrhythmia, hypoxia, and sepsis are the major etiologies for T2MI. Therefore, sepsis was the identified area of interest for the study giving how common it is in a community hospital. We studied the cardiac workup of patients with elevated troponin in the context of sepsis due to acute medical illness to find out the prevalence of obstructive coronary artery disease (CAD) in this population. In this two-year retrospective, descriptive study, electronic medical records (EMR) were reviewed for all patients aged 18 years and older admitted to a single community teaching hospital with a diagnosis of sepsis and elevated troponin I (> 0.07 ug/L). The primary outcome was the presence of obstructive CAD. The secondary outcome was time to peak serum troponin. Of 222 patients, 40 patients underwent invasive or/and noninvasive cardiac testing for CAD. The study revealed 30% of patients admitted with T2MI due to sepsis have underlying obstructive coronary artery lesions. Troponin rose slower in patients with T2MI with underlying obstructive CAD. Pneumonia was the most common underlying cause of sepsis in both groups. Given the considerable prevalence of underlying flow-limiting coronary artery lesions, it may be advisable to evaluate for obstructive CAD sooner than later, during the index hospitalization, when patients developed elevated troponin secondary to sepsis.

Keywords

Type 2 Myocardial Infarction; Demand Mediated Myocardial Infarction; Cardiac work up; Sepsis; Coronary Artery Disease

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Cover Page Footnote

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Introduction

In 2007, the Task Force for the Universal Definition of Myocardial Infarction (MI) defined five subtypes of MI.¹ Type 1 MI is the result of atherosclerotic coronary artery disease (CAD) with coronary arterial obstruction secondary to plaque rupture, ulceration, fissuring, erosion, or dissection. In contrast, Type 2 Myocardial Infarction (T2MI) does not have an atherosclerotic plaque rupture as an underlying pathology, but, rather, myocardial ischemia and necrosis secondary to a mismatch between myocardial oxygen supply and demand.² Oxygen-carrying capacity and coronary blood flow are the primary determinants of the myocardial oxygen supply, while heart rate, systolic wall tension, and contractility define the myocardial demand. The most common causes of T2MI are sepsis, arrhythmia, and anemia.³ Septic patients with myocardial dysfunction have a dramatic increase in mortality, as much as three-fold, compared to those with normal cardiac function.⁴ The study aimed to explore the association between T2MI and obstructive CAD among patients with T2MI secondary to sepsis, one of the most common conditions admitted to the general medical floors at community hospitals.

Study Design and Population

The study was approved by the Rochester Regional Health Institutional Review Board. In this two-year (October 2014 to October 2016) retrospective descriptive study, electronic charts were reviewed for all patients aged 18 years and older, admitted to a single community teaching hospital with elevated troponin and a diagnosis of sepsis.

The hospital used a sensitive cardiac troponin assay (Siemens Centaur TnI-Ultra, Siemens Medical Solutions USA, Inc., Malvern, PA) with a positive value greater than 0.05 ug/L (above the 99th percentile). In addition, a cut-off troponin level > 0.07 ug/L was selected to increase the specificity of the selected sample. Diagnosis of sepsis was based on the International Classification of Diseases (ICD) 9 code. Cases were verified against the 2001 Society of Critical Care Medicine (SCCM) International Sepsis Definition⁵.

T2MI was therefore defined as a significant rise of the troponin level > 0.07 ug/L in the setting of sepsis without anginal symptoms or ischemic electrocardiogram (ECG) changes. The diagnosis of T2MI was confirmed by the consulting cardiologists who were blinded to the study. All selected patients underwent a cardiac evaluation for ischemia by either noninvasive cardiac stress testing or coronary angiography. The choice of the test was clinician-dependent. The study population was then divided into positive and negative cardiac testing. The positive cardiac testing group is patients who ruled in for T2MI and were found to have either positive coronary angiography or noninvasive cardiac stress testing. At the same time, the negative cardiac testing group is those patients who ruled in for T2MI and were found to have negative coronary angiography or noninvasive cardiac testing.

Exclusion criteria included: age less than 18 years, severe sepsis, septic shock, any history of CAD prior to the index admission, ST-elevation myocardial infarction (STEMI), new left bundle branch block on ECG, and/or resting wall motion abnormalities on transthoracic or transesophageal echocardiogram suggestive of significant underlying CAD.

Data collection

Multiple variables were studied to examine their association with the primary outcome: age, gender, body mass index (BMI), hypertension, hyperlipidemia, diabetes mellitus, current or

prior tobacco use, previous cerebrovascular disease, peripheral vascular disease, chronic kidney disease, chronic obstructive pulmonary disease, atrial fibrillation, medications, acute kidney injury, underlying cause of sepsis, vital signs, ECG, echocardiogram, first troponin, peak troponin, time to peak troponin, hemoglobin and white blood count.

Study objectives

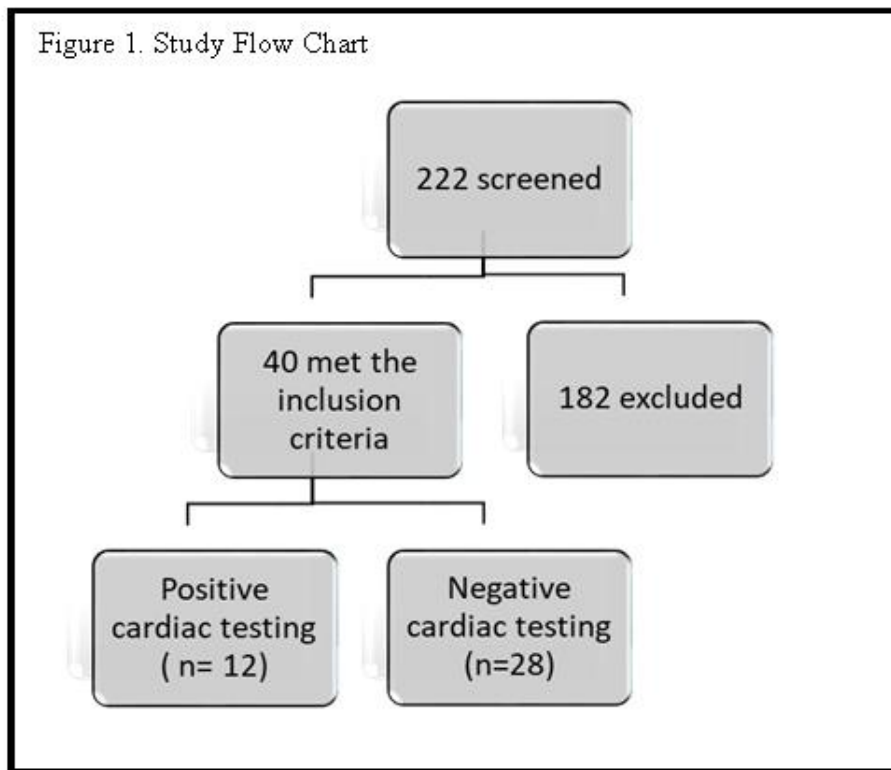
The primary outcome of the study was the presence of obstructive CAD in patients with sepsis and T2MI. The secondary outcome was time to peak serum troponin in T2MI. Subgroup analyses of multiple clinical variables were performed to examine for prognostic value. An obstructive coronary artery lesion was defined as any intraluminal coronary lesion requiring medical intervention, percutaneous coronary intervention, or cardiac surgery. Multi-vessel coronary artery disease is defined as more than one obstructive coronary lesion necessitating percutaneous intervention or cardiac bypass surgery.

Statistical Analysis

Frequencies and percentages were calculated for the categorical and discrete variables, respectively. A two-tailed P-value < 0.05 was considered statistically significant. Continuous variables were summarized as means and standard deviations or median and interquartile range (IQR) as appropriate. Means were compared with t-test and medians via Kruskal Wallis test. Clinical significance for categorical variables was assessed using Pearson Chi-Square and Fisher's exact test. All analyses were performed using Minitab 17 (Minitab, Inc., State College, Pennsylvania, USA).

Results

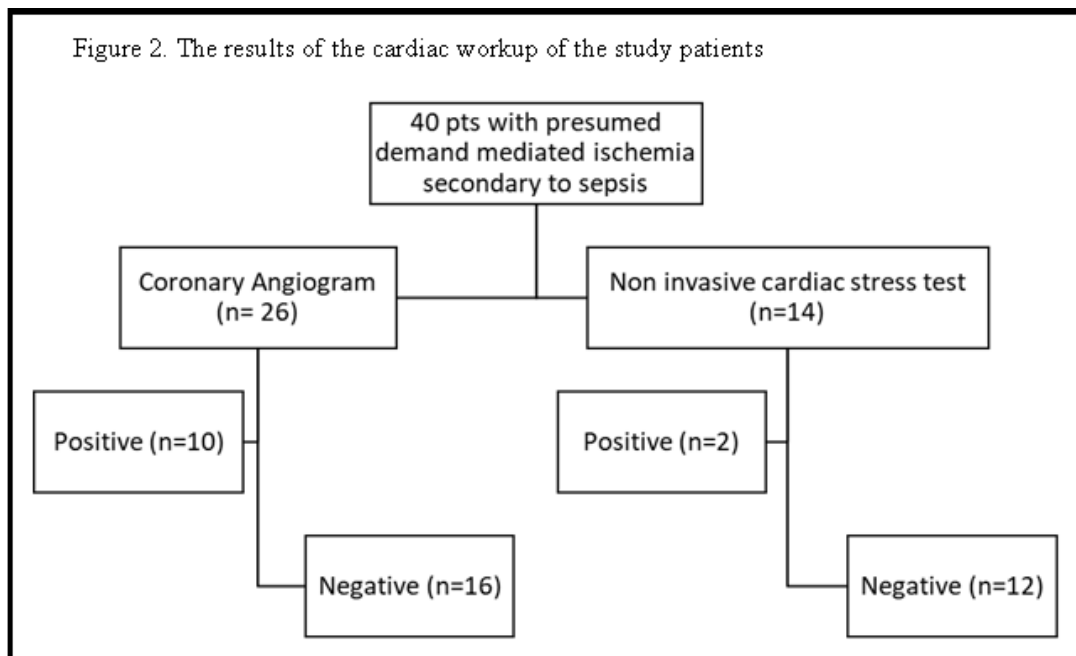
There were 222 patients reviewed after being identified with a diagnosis of sepsis and elevated troponin. Of those, 40 met the inclusion criteria (Figure 1). Reasons for exclusion were a known history of CAD (72 patients), lack of cardiac workup (52 patients), comfort care (36 patients), cardiac arrhythmia (7 patients), death (4 patients), refused cardiac evaluation (3 patients), ST-elevation MI (1 patient), and pericarditis (1 patient).



Of the 40 patients in the study population, 26 underwent a coronary angiogram, while 14 patients underwent non-invasive cardiac stress testing. Baseline characteristics of the study population and comparison of clinical variables between the two groups are shown in Table 1 and Figure 2. The clinical rationale behind selecting the ischemic evaluation test (coronary angiogram vs. noninvasive stress test) was based on the assessment of the consulting cardiologist.

Table 1: Demographic and Clinical Characteristics of the Patients in the two study groups

Variables	Positive cardiac workup (n=12)	Negative cardiac workup (n=28)	P value
Age, Median (IQR), Y	71 (64, 83)	73 (61, 82)	0.96
Female, n (%)	8 (67)	18 (64)	1
BMI, Median (IQR)	28 (23, 38)	32 (28,39)	0.16
Diabetes, n (%)	6 (50)	12 (43)	0.67
Hypertension, n (%)	11 (92)	24 (86)	1
Hyperlipidemia, n (%)	8 (67)	14 (50)	0.49
Current or ex-smoker, n (%)	8 (67)	16 (57)	0.73
Prior CVA, n (%)	1 (8)	1 (4)	0.52
COPD, n (%)	3 (25)	7 (25)	1
CKD, n (%)	3 (25)	6 (21)	1
Atrial Fibrillation, n (%)	3 (25)	5 (18)	0.68
Aspirin, n (%)	6 (50)	12 (43)	0.68
Beta-blocker, n (%)	7 (58)	10 (36)	0.19
Statin, n (%)	8 (67)	12 (43)	0.30
Nitrates, n (%)	1 (8)	1 (4)	0.52
Pneumonia, n (%)	7 (58)	16 (57)	0.94
Bacteremia, n (%)	2 (17)	6 (21)	1

Figure 2. The results of the cardiac workup of the study patients

The study revealed 30% of patients admitted with T2MI due to sepsis have underlying flow-limiting coronary artery lesions (10 patients with positive coronary angiogram and 2 patients with positive cardiac stress testing, total 12 out of the 40 included patients). Of the 40 patients, 23% had underlying single-vessel coronary artery disease, while the multi-vessel disease was diagnosed in 15% (Table 2). Three patients underwent PCI/PTCA, and two patients underwent CABG.

Table 2. Summary of the coronary angiography results

Type of the coronary lesion	Number/Percent of patients
Single vessel disease, n (%)	6 (23)
Multi-vessel disease, n (%)	4 (15)
Non-obstructive coronary artery disease (CAD), n (%)	16 (62)

Acute kidney injury was higher in T2MI with negative cardiac workup than those with positive cardiac workup (50% vs. 8%, $P=0.015$). Trends approaching significance were seen with left ventricular hypertrophy (LVH) in T2MI with negative cardiac workup (26% vs. 17%, $P=0.08$). Vital signs, median ejection fraction, first troponin level, and peak troponin level, among the rest, were not statistically different between the positive and negative workup groups (Table 3). The most common underlying cause for sepsis was pneumonia in both the positive and negative cardiac workup groups (58% vs. 57%, $p=0.94$), followed by unknown source of bacteremia (17% vs. 21%, $p=1.00$).

Table 3. Comparison between vital signs and the troponin measurements of the two study groups

Variables	Positive cardiac workup (n=12)	Negative cardiac workup (n=28)	P value
Febrile, n (%)	8 (67)	15 (54)	0.50
Maximum heart rate, Mean (+/- SD)	126.1 (18.5)	118 (23)	0.25
Hemoglobin, Mean (+/- SD), mg/dl	12.28 (2.88)	11.84 (2.27)	0.64
1st Trop, Median (IQR)	0.16 (0.03, 1.95)	0.57 (0.50, 1.28)	0.81
Peak Trop, Median (IQR)	4.38 (3, 9.63)	3.40 (1.15, 5.38)	0.16
Time to peak Trop, Median (IQR), hrs	24 (16, 28)	9 (0, 26)	0.06
Ejection Fraction, Median (IQR)	50 (30, 59)	55 (38,60)	0.39
LVH, n(%)	17 (2)	26 (10)	0.08
AKI, n(%)	1 (8)	14 (50)	0.015
Noninvasive stress test, n (%)	2 (17)	12 (43)	0.06
Coronary angiography, n (%)	10 (83)	16 (57)	0.06

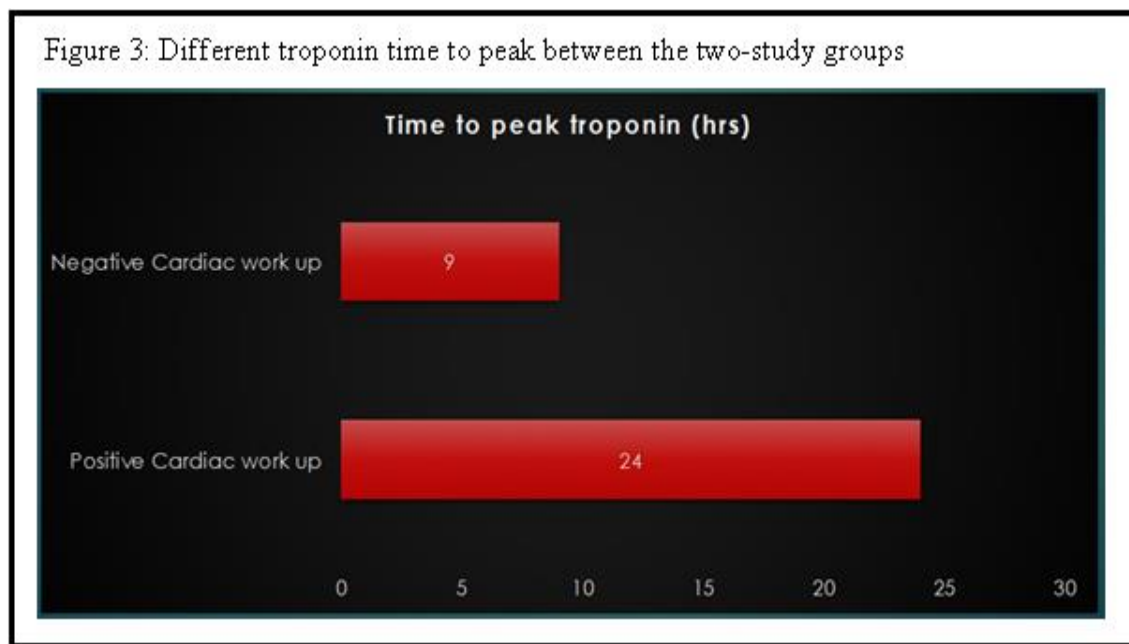
Discussion

The prevalence of underlying CAD in the T2MI population and the optimal means of evaluation and treatment remain unclear.⁶ The Centers for Medicare & Medicaid Services (CMS) adopted a new MI classification schema with the release of ICD 10 codes in October 2017, including code I21.A1 for Myocardial infarction type 2.^{6,7} However, little epidemiological data is available regarding T2MI. This is further compounded by the relatively recent introduction of the term, suspected underreporting, and lack of established diagnostic criteria.⁸ In our study, the incidence of obstructive CAD in patients hospitalized for sepsis and T2MI was 30%, consistent with other reports that showed an incidence between 15-40%.^{9,10} However, most of these studies did not focus solely on sepsis as the underlying etiology for T2MI. Myocardial dysfunction and endothelial injury have been proposed as an underlying mechanism for transient biventricular impairment of the left ventricle in septic patients, owing to the inflammatory cytokine release and subsequent loss in membrane integrity with eventual troponin leakage.¹¹ However, the inflammatory release with resultant myocardial dysfunction cannot account for the high prevalence of obstructive CAD in T2MI.¹¹ Other than the clinical context, the rise and/or fall pattern of cardiac troponin values differentiates between acute myocardial injury and acute myocardial ischemia. The latter could be type 1 or type 2, depending on the underlying etiology.²

Our cohort had a preponderance of female and elderly patients. The population in the study was generally healthy, with medical history mainly significant for hypertension and

hyperlipidemia. Pre-existing CAD was excluded, as were other etiologies for T2MI, such as arrhythmias and anemia, to empower the study results.

Troponin in the patients with T2MI and underlying obstructive CAD was detected as late as 24 hours, compared to 9 hours in the group with negative testing for underlying CAD (Figure 3). This might suggest that following troponin for at least 24 hours would improve specificity for diagnosing CAD among patients admitted with sepsis. However, larger prospective studies are needed to confirm this hypothesis.



Pneumonia was the most common cause of sepsis in the study population; however, the finding was not statistically significant (58% vs. 57%, $p=0.94$).

Acute kidney injury was higher in T2MI with negative cardiac workup, which can be explained by the decreased renal clearance of cardiac troponin due to sepsis. LVH was more common in T2MI patients with negative cardiac workup group, though not statistically significant, likely explained by the higher oxygen requirement of the hypertrophied myocardium and therefore is more likely to be stressed by any minor oxygen supply mismatch.

The observed mortality rate of 18% in our study is similar to previous studies, showing a 30-day mortality rate of 12.5% for patients with T2MI.^{9,12} Overall, the mortality rates for the patients with T2MI were generally higher than T1MI due to an increased prevalence of comorbid medical conditions.² The observed mortality rate is all-cause mortality, so estimating disease-specific mortality rate is difficult given the confounding factors, e.g., high incidence of sepsis and comfort care measures in our population. Nearly half of the patients in the study were previously prescribed beta-blockers and statins, which may have reduced their overall mortality; however, there was no statistically significant difference in drug utilization rates among the groups.

The most recent guidelines do not address the acute or long-term management of T2MI sufficiently. The question remains whether performing a cardiac evaluation, such as stress testing or angiography, is necessary for T2MI. There is, however, a proposed algorithm to approach patients with elevated cardiac troponin in the setting of acute illness, in which cardiac

catheterization or C.T. coronary angiography were suggested in patients without a history of CAD.¹³ Our findings support the validity of this approach giving the high proportion of the underlying obstructive CAD in T2MI population. No firm evidence for medications such as aspirin and beta-blockers in the T2MI population.⁹

Study Limitation

The retrospective nature limits our study. Also, the small number of patients, and single-center design, putting the generalizability of the results in need of validation by a larger sample. Additionally, since some patients received interventional procedures and others underwent stress tests, it is possible that the prevalence of CAD in those who underwent the stress test group was underestimated. Also, we could not prove cause and effect due to the study's retrospective nature.

Conclusion

Almost one-third of patients admitted with T2MI due to sepsis may have underlying flow-limiting coronary artery lesions. It may, therefore, be reasonable to evaluate for obstructive disease when patients present with sepsis and T2MI. There is an urgent need for evidence-based diagnostic and therapeutic strategies, primarily randomized, controlled clinical trials to guide the management of T2MI.

Funding

None

Conflict of Interest

None

Authorship

All authors had access to the manuscript and contributed to the manuscript.

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