Low-risk Non-ST-Elevation Acute Coronary Syndrome and Normal Troponin: Do We Need Further Evaluation?

Erez Marcusohn MD[1], Danny Epstein MD[2], Anees Musallam MD[1], Zohar Keidar MD PHD[3,4] and Ariel Roguin MD PHD[1,4]

Departments of [1]Cardiology, [2]Internal Medicine B, and [3]Nuclear Medicine, Rambam Health Care Campus, Haifa, Israel
[4]Rappaport Faculty of Medicine, Technion–Israel Institute of Technology, Haifa, Israel

ABSTRACT: **Background:** With the recent introduction of high-sensitivity troponin (hsTn), the incremental benefit of stress myocardial perfusion imaging (MPI) in the evaluation of patients who present to the emergency department (ED) with acute coronary syndrome (ACS) is unclear.

Objectives: To assess the added value of stress MPI in low-risk ACS patients with normal range hsTnI.

Methods: We analyzed all patients who were hospitalized at our medical center from February 2016 to November 2017, who presented with low-risk ACS and underwent stress MPI, and in whom hsTnI was in the normal range after the introduction of hsTnI.

Results: During the study period, 161 patients were admitted with a diagnosis of unstable angina (i.e., ACS with normal range hsTnI) and underwent stress MPI during index admission. The study population included 52/161 patients (31.7%) with low-risk ACS who had no indication for initial invasive strategy. No patients had positive MPI. One patient underwent coronary angiography due to suggestive history; however, he did not have a significant coronary artery disease and had no indication for percutaneous coronary intervention.

Conclusions: In patients with low-risk ACS and normal range HsTnI without additional high-risk features, stress MPI has little additional value for the correct diagnosis and management. Prospective studies are warranted to confirm whether resting hsTnI could serve as a powerful triage tool in chest pain patients in the ED before diagnostic testing and thus, improve patient management.

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Chest pain is a common cause of hospital admission worldwide and is a major burden on healthcare resources [1]. The clinical spectrum of non-ST-elevation acute coronary syndrome (ACS) includes patients with biochemical evidence of cardiomyocyte necrosis or non-ST-segment elevation myocardial infarction (NSTEMI) and patients with unstable angina in the absence of cardiomyocyte necrosis. The clinical representation of these syndromes may range from patients free of symptoms at presentation, to individuals with ongoing ischemia, electrical, or hemodynamic instability who may need urgent revascularization [2]. Although patients without myocardial infarction (MI) have much better prognosis and derive less benefit from intensified antiplatelet therapy as well as early invasive strategy, compared to those with NSTEMI, they may still be at risk for short- and long-term events [2,3].

The introduction of high-sensitivity cardiac troponin (hsTn) measurements, instead of the standard troponin assays, in ACS patients presenting to the emergency department (ED), resulted in an increase in the detection of MI (4% absolute and 20% relative) and a reciprocal decrease in the diagnosis of unstable angina [4-7]. Approximately 13% of all ED diagnoses are ACS [7]. Yet despite negative primary assessment, including electrocardiogram (ECG) and serial troponin testing, the majority of these individuals were further referred to an objective functional or anatomic test [7]. This result is in concordance to the current guidelines.

Since introducing the hsTnI assays, many studies have shown that patients presenting to the ED with cardiac chest pain and hsTnI under 5 ng/L have very good prognosis and are at extremely low risk for major cardiovascular events at follow-up [1,8-13]. These selected patients have a very low risk to have a positive stress imaging test [3].

As noted by Smulders and colleagues [11] in their review, hsTn is useful in ruling out acute MI with high confidence and challenge the need for additional testing. Nonetheless, this finding does not apply to unstable angina because HsTn assays do not rule out unstable angina.

Our hypothesis was that selected patients with low-risk ACS and unstable angina who presented with normal range HsTn, lack of ECG changes without indications for early re-vascularization according to the European Society of Cardiology (ESC) 2015 non-ST-elevation acute coronary syndrome (NST-ACS) guidelines can be discharged, directly from the ED or after a short observation, without any further risk stratification.

Our study aimed to examine whether the negative predictive value (NPV) of normal hsTnI is comparable with the NPV results of stress myocardial perfusion imaging (MPI), and therefore has no significant added value in these low-risk patients.

PATIENTS AND METHODS

The study was approved by the institutional review board. Due to the retrospective nature of the study, informed consent was waived. The data were analyzed anonymously.

We conducted a population-based retrospective cohort study, using the data of all patients hospitalized at a large academic tertiary care medical center, with an episode of unstable angina (ICD9 code 411.1) and underwent stress MPI. The ability to assess hsTnI was first introduced to our center in February 2016; therefore, the study period was between February 2016 and November 2017. The hospital is a 1000-bed academic hospital.

The study population included only low-risk NST-ACS patients with normal hsTnI on their first blood draw in the ED, at least 2 hours after the start of symptoms. Patients were further excluded from the study if they had at least one indication for invasive strategy according to the last ESC guidelines [2], including refractory or recurrent angina despite intensive medical therapy, signs or symptoms of new or worsening heart failure, hemodynamic instability, sustained ventricular arrhythmias, GRACE score above 109, elevated hsTnI, new ST depressions, reduced LV systolic function (LVEF < 40%), diabetes mellitus, renal insufficiency (GFR < 60 ml/min/1.73 m^2, percutaneous coronary intervention (PCI) within 6 months, or prior coronary artery bypass surgery. Grace score and GFR were calculated retrospectivly.

All patients included in the study (low-risk patients with unstable angina) underwent a stress MPI during the index hospitalization. The stress test was performed either with a treadmill or using a pharmacological stress (dipyridamole or adenosine). A positive MPI test was considered when showing an ischemic area of more than 5%.

STATISTICAL ANALYSIS

Baseline characteristics of the study population were analyzed with conventional group descriptive statistics according to the study cohort. Quantitative variables were expressed as means and standard deviations, while qualitative variables were expressed as numbers and percentage. Results were pooled for calculation of negative predictive value (NPV).

Data analysis were performed using IBM Statistical Package for the Social Sciences statistics software, version 23 (SPSS, IBM Corp, Armonk, NY, USA) and Microsoft Excel version 14.0 (Redmond, Washington, USA).

RESULTS

During the study period, 161 patients were admitted with a diagnosis of unstable angina (i.e., NST-ACS with normal range hsTnI) and underwent stress MPI. The study population was comprised of 52/161 patients (31.7%) with low-risk ACS who had no indication for initial invasive strategy, based on current ESC guidelines. The study population was managed conservatively and referred for stress MPI. Clinical characteristics and risk factors of the study population are summarized in Table 1.

Table 1. Patient characteristics (n=52)

Age, years*	69.5 ± 12
Male, n (%)	29 (56)
Ischemic heart disease, n (%)	27 (52)
Known coronary artery disease, n (%)	34 (65)
Hyperlipidemia, n (%)	43 (83)
Hypertension, n (%)	39 (75)
Smoker, n (%)	17 (33)
Admission data	
Creatinine on admission, mg/dl*	0.89 ± 0.2
Average heart rate, beats/minute*	69 ± 13.7
Average systolic blood pressure, mmHg*	143.1 ± 24.6

*Mean ± standard deviation

None of the patients had positive MPI and the only patient who underwent coronary angiography, due to suggestive history, did not have significant coronary artery disease and had no intervention.

In the exclusion group, 109 patients underwent stress MPI even though they had an indication for initial invasive approach due to treating physician decision. Of 109 patients, 5 (4.5%) had positive stress MPI, all went through angiography, and 3 (2.75%) were treated with angioplasty. Twelve presented with non-significant ischemia on stress MPI (< 5%) but 6 (50%) were still referred to angiography. Two of these six were treated with angioplasty.

The reasons for exclusion included after CABG (19 patients), diabetes (80 patients), systolic heart failure (40 patients), eGFR under 60 ml/min/1.73 m^2 (22 patients), had ongoing chest pain, and 7 patients had PCI in the previous 6 months. Some Patients had more than one indication 5for invasive approach.

In summary, 52 (32%) of the 161 patients admitted to the ED with the diagnosis of unstable angina and normal range troponin who met the criteria for low-risk ACS, no ischemia was diagnosed on stress MPI and no indication was found for performing PCI. Therefore, normal range troponin was found to have a 100% NPV (95%CI 93.28–100%), in this specific group of patients for both positive MPI and PCI.

DISCUSSION

In the present study, we found that in the era of hsTn measurement, the added value of MPI performed during hospitalization in low-risk NST-ACS patients, is extremely low.

Unlike previous studies, this study emphasized the specific subgroup with true low-risk unstable angina that fulfill the exact definition of unstable angina after reviewing all medical

records and patient descriptions of their chest pain. The majority of previous studies addressing chest pain in the ED relate to all suspected cardiac chest pain admitted to the ED as suspected MI. The issue is in including non-cardiac chest pain and stable angina with true unstable angina in the same category.

Most recent guidelines state that in patients suspected of ACS without ischemic changes on 12-lead ECGs and negative cardiac troponins (preferably high-sensitivity), who are free of chest pain for several hours, a non-invasive stress test (preferably imaging) is recommended before deciding on an invasive strategy. This test can be performed during admission or shortly after discharge and has a class I level A recommendation. However, this strategy is based on several relatively old studies [16-19] performed prior to the incorporation of hsTn assays.

The aim of the present study was to quantify the added value of MPI in this specific population of low-risk NST-ACS patients. We found that in the presence of normal high sensitivity troponin levels, further investigation in this specific group is not mandatory and can be safely omitted from the management algorithm.

The evaluation of patients with ACS is time-consuming and labor-intensive, contributing to overcrowding and lengthy stays in hospital wards. Numerous studies have shown that patients with chest pain and low or undetectable troponin at admission have extremely low-risk for further adverse cardiovascular events and death within one month to 3 years. Some authors even concluded that these low-risk patients can be discharged to home from the ED without the need for further evaluation [1,8-13].

Stress MPI is a well-established imaging tool that has an extremely high NPV for adverse outcome or need for coronary revascularization. Aldous et al. [14] found that stress testing among troponin-negative chest pain patients led to the identification of additional 4.5% in the number of patients who underwent index admission revascularization.

Recently published meta-analysis of 17 studies, which included more than 8000 patients with ACS, showed NPV of 96.6% for revascularization over a mean follow-up of 36 months, corresponding to an annual event rate of 1.25% per year [15]. The risk of MI or cardiac death after a normal test was 1.2% with a NPV of 98.8% over a mean follow-up of 36 months, corresponding to an estimated annualized event rate of 0.45% per year.

The relationship between troponin and stress MPI results has been studied before in various scenarios. However, only a few studies have examined this relationship in the hsTn era [20-22].

Ahmed and co-authors [20] performed an analysis on 136 patients from the ROMICAT I trial (Rule Out Myocardial Infarction Using Computer Assisted Tomography) who had stress MPI and hsTnT measurements. The authors concluded that in patients with acute chest pain, myocardial perfusion abnormalities and coronary artery disease are predicted by resting hsTnT levels. They found a high NPV of 94% and 95% when the cutoff was below 5.73 and 4.26 pg/ml.

In 2017, Goldkorn and colleagues [23] evaluated 3753 patients with presumed cardiac chest pain and normal troponin, no ECG changes, and non-high risk for ACS. Of these patients, 1593 were evaluated with MPI; 1457 (93%) had normal or mild ischemia no justifying further angiography. Interestingly, 51 patients with mild ischemia (22% of that subgroup) underwent angiography with almost a third (31%) treated with PCI. The authors suggested that mild ischemia on stress MPI decreases mortality and re-admissions due to chest pain.

Røsjø et al. [21] examined the levels of hsTn I in patients with stable coronary artery disease undergoing stress MPI and showed that hsTnI concentrations were not closely associated with reversible myocardial ischemia, but rather were influenced by variables associated with structural alterations of the myocardium. By linear regression analysis showed that age, male sex, history of hypertension, angiotensin-converting enzyme inhibitor use, and lower left ventricular ejection fraction were associated with higher baseline hsTn concentrations.

Reinhardt and colleagues [22] analyzed data from the ROMICAT-II trial, which was composed of 1000 patients who presented with chest pain to the EDs at nine hospitals in the United States. The authors concluded that in patients presenting to the ED with acute chest pain, negative biomarkers, and a nonischemic ECG result, the use of noninvasive testing with coronary computed tomography angiography (CCTA) or stress testing leads to longer length of stay, more downstream testing, more radiation exposure, and greater cost without an improvement in clinical outcomes.

Many patients are at low risk for a major cardiac adverse event (MACE). With normal troponin and non-ischemic ECG, the risk of MACE and MI is less than 1%. The American Heart Association and ESC recommend further evaluation in low- to intermediate-risk patients within 72 hours. These modalities add little to further risk stratification. These tests do not appropriately stratify patients who are already at low risk, nor do they diagnose acute MI. CCTA is an anatomic imaging modality of the coronary vasculature and has been shown to decrease length of stay in the ED, although it is associated with downstream testing. Literature concerning further risk stratification in already low-risk patients is controversial [24].

LIMITATIONS

The present study is retrospective in nature and focuses only on a small sample of patients. The clinical diagnosis was conducted by various physicians with a variety of clinical skills who may differ in their interpretation of patient complaints. Therefore, large randomized trials with a clear checklist for defining the anginal status are needed.

CONCLUSIONS

In patients with low-risk ACS with normal hsTnI without additional high-risk features, the NPV for excluding significant

coronary artery disease causing significant ischemia on stress MPI is high enough. Use of stress MPI and/or CCTA for risk stratification of low-risk chest pain patients is controversial. These tests may allow prognostication but do not predict ACS risk beyond ECG and troponin and may be useful for intermediate-risk patients. Our findings sets the stage to reconsider the need for further risk stratification in low-risk patients, and to study this specific population in larger trials.

Correspondence
Dr. E. Marcusohn
Dept. of Cardiology, Rambam Health Care Campus, Haifa 3109601, Israel
Phone: (972-4) 854-2181
Fax: (972-4) 854-3451
email: erezmrc@gmail.com

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Capsule

Conserved cell types with divergent features in human versus mouse cortex

Elucidating the cellular architecture of the human cerebral cortex is central to understanding our cognitive abilities and susceptibility to disease. **Hodges** and colleagues used single-nucleus RNA-sequencing analysis to perform a comprehensive study of cell types in the middle temporal gyrus of human cortex. The authors identified a highly diverse set of excitatory and inhibitory neuron types that are mostly sparse, with excitatory types being less layer-restricted than expected. Comparison to similar mouse cortex single-cell RNA-sequencing datasets revealed a surprisingly well-conserved cellular architecture that enables matching of homologous types and predictions of properties of human cell types. Despite this general conservation, they also found extensive differences between homologous human and mouse cell types, including marked alterations in proportions, laminar distributions, gene expression and morphology. These species-specific features emphasize the importance of directly studying human brain.

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Eitan Israeli