

Acute chest pain of uncertain etiology, the short and long view

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Efforts to triage patients with acute chest pain more efficiently date from the time of the first coronary care units in the 1960s.¹ The admission of patients with acute coronary syndrome (ACS) to dedicated cardiac units improved substantially their outcomes. However, admission of low-risk patients with non-cardiac chest discomfort jeopardized the efficiency of these units.

Triaging patients with acute chest pain in the emergency department (ED) has always been a balancing act between two conflicting interests: on the one hand, the concern of ED physicians to miss acute myocardial infarction (AMI) and face legal consequences; on the other hand, the concern of cardiologists about admitting patients with low likelihood of having ACS.

Until 15 years ago, it was common practice to hospitalize patients with chest discomfort of uncertain cardiac etiology as “rule-out myocardial infarction patients.” Patients were usually hospitalized for 2-3 days and more than one-half of the patients was discharged without a firm diagnosis or explanation for their symptoms. Numerous studies have shown that in fact the incidence of ACS in these patients was very low, 3%-6%. Thus, the “rule-out myocardial infarction” strategy was inefficient and very costly. The cost of this approach was calculated to be \$1.5 million per life saved.^{2,3} It is well understood at this day and age that

“rule-out myocardial infarction” is no longer an allowable diagnosis.

ADMISSION ECG

Observational studies suggested that about 3% of patients with AMI were not recognized in the ED and inappropriately sent home.^{4,5} The latter patients had a worse outcome and missed AMI constitutes about 20% of all the ED malpractice dollars awarded. The percentage of missed infarcts has been extrapolated to the 8 million of patients with chest pain who present yearly to EDs in the US, suggesting that as many as 24,000 acute infarcts might be missed each year. However, this extrapolation is flawed because the actual incidence of AMI in ED patients with chest discomfort and non-diagnostic ECG is very low, about 8%. Of the latter patients 2%-4% may be misdiagnosed, which is only about 0.1% of the total cohort of patients presenting with chest complaints. Because of the large denominator this still may amount to about 8,000 missed infarcts per year. Therefore, strategies to distinguish between high- and low-risk patients with chest discomfort have been the focus of clinical pathways since many years. Of note, when experts reviewed the ECGs of missed infarcts, one-quarter the ECGs was indeed misinterpreted, but three-quarter of the ECGs were in fact non-diagnostic.

One simple diagnostic means that has not been sufficiently appreciated for its prognostic value is the admission ECG.⁶ The ECG of patients presenting with acute chest pain contains important short-term prognostic information. If the initial admission ECG was normal or non-specific, in-hospital life-threatening complications occurred 23 times less frequently than if the admission ECG was abnormal.⁶ In fact, the rate of life-threatening complications was only 0.6% in patients with acute chest pain and normal admission ECG, even if biomarkers for AMI were positive.⁶ Since patients evaluated in Chest Pain Centers (CPCs) typically have normal or non-ischemic ECGs, they do actually represent a very low-risk group.

CHEST PAIN CENTERS

In the mid-1990s many hospitals in the US opened dedicated CPCs. The purpose of these observation units

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has somewhat changed over the years and is now not only to rule out ACS but also to assure that the patients do not have significant underlying chronic CAD. Pre-discharge exercise testing has therefore become an essential component of the evaluation protocol in CPCs.⁷ This is particularly useful because exercise capacity is a strong independent predictor of cardiovascular outcomes, regardless of the presence of CAD.⁸ Patients who cannot achieve 6 METs during exercise testing have a high (>60%) 4-year cardiac mortality rate, whereas patients who exercise >10 METs have a very low (<0.5%) cardiac event rate.⁸ Thus, assessing exercise capacity in a CPC is very useful as a means to assess future cardiovascular risk.

REST MYOCARDIAL PERFUSION IMAGING (MPI)

The potential value of radionuclide MPI as a means to rule out ACS was explored in the mid-1970s using resting thallium-201 MPI.⁹ These early studies revealed a very high negative predictive value of resting MPI for ACS. However, because patient visits to the ED are unpredictable and the need of radiopharmaceuticals was not foreseeable, rest MPI became practical only after the introduction of Tc-99m-labeled MPI agents in the early 1990s. Contemporary studies confirmed the high negative predictive value (99%) of rest MPI for excluding ACS.¹⁰⁻¹² However, the radiopharmaceutical must be injected during ongoing chest pain or within 6 hours after chest discomfort has abated, for optimal results. If rest MPI is normal in a patients with acute chest pain, the likelihood of ACS is extremely low and the 30-day outcome is very favorable.¹⁰

In reality, very few patients evaluated in CPCs still have ongoing chest pain. Rest MPI is therefore rarely performed.

STRESS TESTING AFTER INITIAL OBSERVATION

Since 1997, we have evaluated more than 16,500 patients in our CPC. Usually patients are observed in the CPC for 6-8 hours, have serial biomarkers and serial rest ECGs. If 2-3 sets of biomarkers are normal and the patient remains clinically stable, either physical or pharmacological stress testing is performed before discharge.¹³

During the initial observation period, a small percentage (3%) of patients may be hospitalized directly from the CPC, because of recurrent chest pain, ischemic ECG changes, or positive biomarkers. However, more than 97% of patients will go on to have stress testing.

Symptom-limited physical exercise testing, with or without imaging, is the preferred test because of the

above-mentioned important prognostic information to be gained.

Typically, about 20% of CPC patients have exercise ECG alone, 60% exercise with MPI, and 20% pharmacological stress with MPI. Of note, more than 95% of these stress tests were normal in our unit. The majority of the patients with abnormal stress tests were hospitalized for further evaluation. Overall, including those who were admitted during the observation period, only 7% of all the patients evaluated in our CPC was admitted to the hospital, the remaining patients were discharged.

The institution of CPCs proved to be an effective means for triaging patients with chest pain in our hospital. Compared to the era before the opening of the CPC, the number of inappropriate hospitalizations decreased by 40%.¹³

LOW-RISK PATIENTS

CPC patients are typically *low-risk* patients. They have *low prevalence of ACS* and *low prevalence of inducible ischemia*. Thus, any diagnostic test proposed in this population for detecting CAD must face the reality of a small number of positive results: >90% of the tests can be predicted to be normal. Therefore, only the cheapest and simplest diagnostic approach may be justified.

Such a test is the exercise ECG.⁷ Admittedly the exercise ECG has suboptimal sensitivity and specificity. However, in CPC patients (with low-likelihood for CAD) the practical problem is not sensitivity, but specificity. If the exercise ECG is normal at adequate workload, one has effectively excluded significant CAD and these patients have a favorable outcome.¹⁴ However, if the exercise ECG is abnormal (which occurs only in a small number of patients) there is still a fair chance that this is a false-positive result. However, this can be elucidated by follow-up exercise MPI because of its higher specificity. Because about one-quarter of CPC patients may not be capable of performing adequate physical exercise, one has to resort to pharmacological stress MPI with loss of information on physical exercise capacity.

This CPC strategy, i.e., observation and stress testing, has been shown to be effective in many medical centers. After complete evaluation, only a small number of patients who were identified as high-risk was admitted and a large number of low-risk patients were sent home and costly hospital admission was avoided (Figure 1). It was generally assumed that the patients sent home had a favorable outcome, but in reality this was not known. Follow-up in ED patients is problematic if not impossible. In one study it was found that as many as 50% of patients seen in an ED had provided unreliable contact data.¹⁵

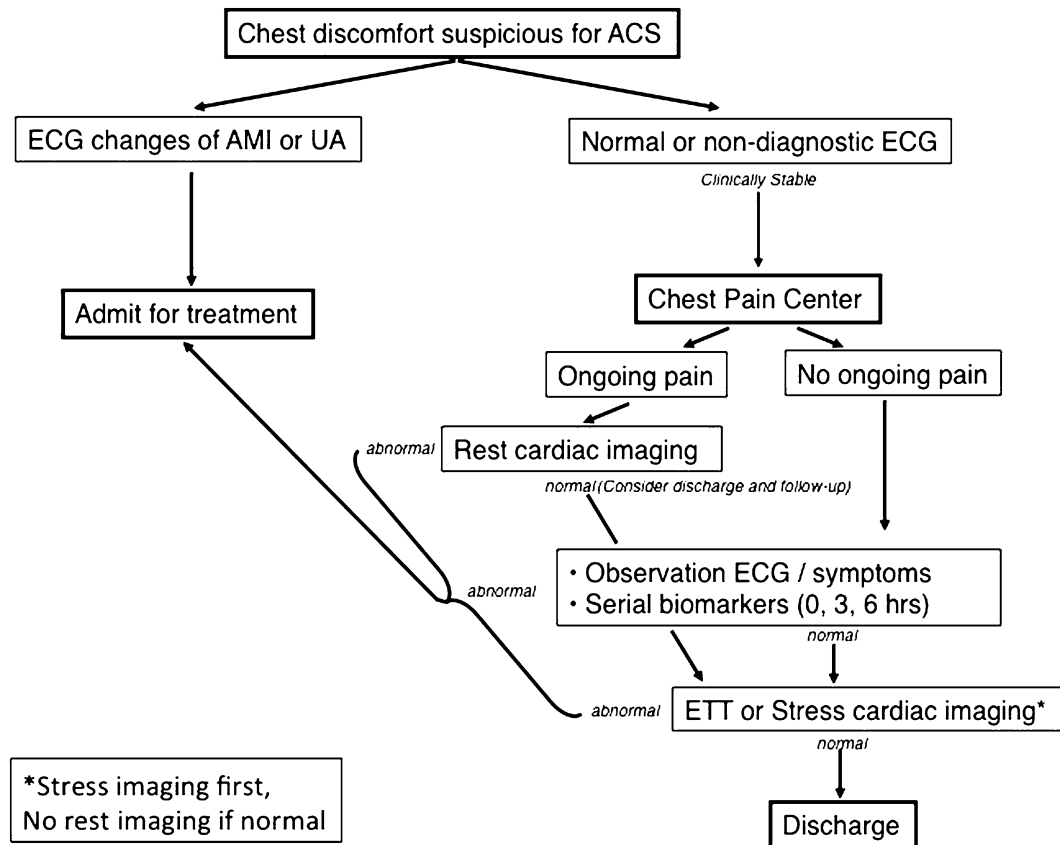


Figure 1. Evaluation diagram of patients in a CPC. Patients with ischemic ECG changes should not to be evaluated in a CPC but immediately admitted for treatment. Patients with a normal or non-diagnostic ECG and potentially ischemic chest discomfort may be evaluated in a CPC. Patients who have ongoing pain may have MPI at rest. Patients who have no longer chest pain are observed for recurrence of symptoms and have serial ECGs and serum markers of cardiac injury. Patients who remain stable for 4-8 hours after presentation may undergo subsequent ETT or stress cardiac imaging. If stress MPI is normal, no rest imaging is needed. Patients with abnormal stress test results are admitted. Patients with normal stress test results can be discharged. ACS, Acute coronary syndrome; AMI, acute myocardial infarction; ETT, ECG treadmill testing; MPI, radionuclide myocardial perfusion imaging; UA, unstable angina.

In this issue of the Journal, Nabi et al¹⁶ provide, for the first time, medium-term follow-up in a relatively large number of patients with equivocal chest pain, non-diagnostic rest ECG, and normal initial biomarkers. The 99% complete follow-up of ED patients is a remarkable accomplishment.

This study confirms once again the high negative-predictive value of stress SPECT MPI for diagnosing initial ACS and predicting subsequent cardiac events.

Consistent with the notion that CPC patients are by and large low-risk patients, 91.4% of patients had normal stress MPI. They also had very low in-hospital (0.5%) and follow-up (0.8%) cardiac event rates.

Of note, no cardiac death occurred in any of the patients with normal stress MPI.

Only 8.6% of patients had abnormal stress MPI. This occurred more often in patients with known CAD (37.6%)

than in patients without known CAD (4.6%). Patients with known CAD also had larger MPI abnormalities and more inducible ischemia. Total cardiac event rate was also significantly higher (40%) in patients with abnormal stress MPI than in patients with normal stress MPI (1.6%).

It is of interest that almost three-quarter of cardiac events occurred during the index admission. The single cardiac death (0.06% of all the patients) in this study occurred in a patient with abnormal index stress MPI and happened during follow-up.

The authors emphasize that stress MPI was an effective gatekeeper for coronary angiography: only 3.3% of patients with normal SPECT compared to 54% of patients with abnormal SPECT went on to have cardiac catheterization.

The investigators included patients with known CAD in their study. These patients often were excluded

in previous studies. As the authors remark, their observational study reflects real-world ED practice. They demonstrate that patients without known CAD in a CPC constitute indeed a very low-risk group, whereas *patients with known CAD* should be considered at higher risk and deserve close scrutiny.

All the patients in this study had, by design of protocol, low-dose/high-dose rest-stress MPI. The evaluation could have been more time- and cost-efficient if the basic protocol had consisted of low-dose stress MPI first, followed by high-dose rest MPI *only* if the stress MPI was abnormal. Since >90% of patients had normal stress MPI, this would have saved much time, cost, and importantly reduced patient radiation exposure.

Selective use of rest MPI and stress testing with or without imaging are effective approaches for identifying patients with acute chest pain who are at low risk who can be discharged safely. The work by Nabi et al provides further evidence that this is a responsible strategy.

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