

Patient with chest pain of obscure origin: can AMI be recognised early at AED? - a review of diagnostic methods and a suggested protocol for the local A&E department

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Chest pain is a common presentation to Accident and Emergency departments (AED). There are many causes ranging from the most trivial, an example of which is costochondritis to the life-threatening examples such as acute myocardial infarction (AMI). It is not uncommon for acute myocardial infarction to present as atypical chest pain or discomfort, or non-diagnostic electrocardiogram (ECG). The various common diagnostic methods for AMI in patients with atypical chest pain are reviewed and a suggested protocol for managing patient with chest pain of obscure origin at AED is presented. The recent introduction of rapid bedside troponin assay is likely to bring a major impact on the management of atypical chest pain in future. (*Hong Kong j.emerg.med.* 2000;7:148-156)

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Introduction

According to the World Health Organization's (WHO) definition, the diagnosis of myocardial infarction (MI) is based on the presence of at least two of the following three criteria: (1) a clinical history of ischaemic-type of chest discomfort, (2) electrocardiographic changes on serially obtained tracings, and (3) a rise and fall in serum cardiac markers.¹

There are numerous causes of chest pain ranging from benign conditions, such as costochondritis to life-threatening diseases such as acute myocardial infarction. Unfortunately, certain subgroups of patients are known to present with unusual symptoms of acute MI. Thus, women often experience atypical ischaemic-type chest discomfort,² while the elderly are more likely to present with the nonspecific symptoms like

dizziness or weakness, or dyspnoea with no pain at all unlike the younger patients.³ Physicians evaluating chest pain patients in the AED therefore not only face the challenge of having to avoid unnecessary admissions but also minimising the number of patients discharged home inappropriately. With the advent of reperfusion therapy in AMI, there is a desire to minimise the door-to-needle time for administration of thrombolytic agents. In some instances, a primary PTCA is needed and a rapid triage to the cardiac catheterisation laboratory is important. Therefore, there is a clear need for better methods of prompt identification of patients experiencing an acute MI as accurately and as quickly as possible.

There is great variability in reported symptoms among patients with acute myocardial ischaemia. The traditional diagnostic tools, history and physical examination, were shown to fail in providing adequate data to accurately distinguish patients with acute myocardial ischaemic syndromes from those with more benign causes.⁴ Studies have shown that 2 to 5% of A&E patients with AMI are inadvertently discharged home.⁵⁻⁸

In the following discussion, the diagnostic values of ECG, serum cardiac markers, and other tests

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(echocardiography, myocardial scintigraphy and exercise stress test) are reviewed, followed by a suggested protocol on early recognition of atypical AMI patients and management of patients with low risks of acute cardiac events.

It cannot be overemphasised that there are other serious causes of chest pain such as aortic dissection and acute pulmonary embolism, which have to be considered and excluded on clinical grounds with reasonable confidence before this protocol can be applied.

The value of ECG

It is important to remember that the ECG and a history of ischaemic-type chest discomfort remain the primary methods for screening patients for myocardial ischaemia and infarction.⁹ Unfortunately, in patients with ischaemic-type chest discomfort, ST-segment elevation on the ECG has a specificity of 91% but a sensitivity of only 46% for diagnosing acute MI.¹⁰ Another study also showed that ECG is initially non-diagnostic in up to 50% of AMI patients presenting to the A&E.¹¹

In a study by McGarthy et al¹² of 1050 patients with AMI, 1.9% were missed and discharged home. Of this group of patient, 25% had ST elevation on the ECG (and were missed), 35% were discharged with diagnosis of ischaemic heart disease. 25% of missed AMI patients were dead or suffered potentially lethal complications. These missed AMI cases were less likely than admitted AMI patients to have a history of AMI or nitroglycerine use. In fact, only 30% of missed AMI had normal or non-specific ECG changes, and this suggests that either the ECG changes were misread, leading to erroneous discharge, or perhaps in the context of a negative past history, the impact of the ECG changes was minimised. The authors concluded that 25% of missed AMI patients might have been prevented by correctly interpreting the ECG. An additional 25% of missed AMI patients might have been prevented by not discharging patients with symptoms believed to be due to ischaemic heart disease.

Initial errors in ECG interpretation can result in up to 12% of patients being categorised

inappropriately (ST elevation versus no elevation).⁹ Thus, the computer interpretation should be read with respect and senior or expert advice should be sought in uncertain cases.

On the other hand, serial ECG, obtained at least every 20 minutes during ED evaluation, was found in a study to be more sensitive than the initial ECG for detection of AMI (68% versus 55.4%; $P < 0.0001$).¹³ In this study, serial ECG detected injury in an additional 16.2% of AMI patients whose initial ECG were non-diagnostic. Therefore, in patients with chest pain where AMI cannot be excluded, another ECG should be repeated every 20 minutes. On the other hand, since the mean time from the onset of monitoring until diagnostic serial ECG was 28.9 ± 35.9 minutes, at least four 12 lead ECG tracings should be done within the first hour of presentation: 0 minute, 20 minutes, 40 minutes, and 60 minutes.

However, it should be noted that 20.1% of AMI still occurred in patients who had no changes even on serial ECG.¹³ Therefore, the serial ECG is only of value if it is positive. The absence of changes on serial ECG does not preclude life-threatening acute coronary syndromes and other clinical data and tests must be considered in order to determine the need for hospital admission and treatment. In this regard, decision aids such as high-risk clinical indicators,^{14,15} rapid determination of cardiac serum markers,^{16,17} two-dimensional echocardiogram screening for regional wall motion abnormalities,¹⁸ myocardial perfusion imaging,¹⁹ and computer-based diagnostic aids^{20,21} have been proposed in patients in whom the ECG is non-diagnostic. However, in the local emergency departments (ED) setting, only serum cardiac markers are available easily.

The role of serum cardiac markers

The most common ones are CK, CK-MB, cardiac troponin T (cTnT), cardiac troponin I (cTnI), and serum myoglobin.

Although ST-segment elevation and/or Q waves on the ECG are highly indicative of MI, about 50% of patients with MI do not exhibit ST elevation^{11,22} but display other or non-diagnostic ECG changes.²³

Thus, for the majority of patients, serum cardiac markers are useful for confirming the diagnosis of MI when patients present without ST elevation, when the diagnosis may be unclear, and when the doctor must distinguish patients with unstable angina from those with a non-Q-wave MI.⁹ The laboratory therefore plays an essential role in establishing the diagnosis of MI.

For patients presenting within the first two or three hours of symptom onset, the two markers most appropriate for the early diagnosis of AMI are myoglobin and CK-MB subforms. However, these two tests are not available in the local hospital laboratories as urgent tests.

The CK-MB

It has been documented that normal total CK levels may mask the diagnosis of MI among patients with elevated CK-MB isoenzyme levels.²⁴⁻²⁶ On the other hand, AED measurement of the CK-MB concentration has been shown to be able to identify AMI in low-risk patients in whom the diagnosis would otherwise have been missed.^{27,28} Other studies have also shown that CK-MB measurements performed on presentation at the Emergency departments and at 2 hours were predictive of 'potentially life-threatening cardiovascular complications'.²⁹ Unfortunately, in most hospitals in Hong Kong, the CK-MB is not done unless the total CK is raised and it takes one hour for urgent CK level and up to 24 hours for CK-MB result to be available. This inevitably makes the CK-MB not readily available for early detection of AMI in patients with non-diagnostic ECG findings. Notwithstanding these limitations, and in the absence of a better alternative until now, total CK level still retain its role as a baseline initial screening test and should therefore be checked first.

Bearing in mind the kinetic properties of CK inside the body, the timing of checking CK in relation to the onset of chest pain is important in the interpretation of the results. In a study of 616 patients with chest pain by Gibler and his colleagues,³⁰ CK-MB levels were checked on presentation at Emergency departments and hourly for three hours for chest pain with non-diagnostic ECG. When the sensitivity of hourly CK-MB is represented as a function of the duration of chest

pain for AMI patients with non-diagnostic ECG tracings, they found that after three hours of symptoms (i.e. during the fourth hour of chest pain), around 50% had a positive CK-MB levels. By sixth hour, more than 80%; by ninth hour, more than 90%; and 100% during 11th and 12th hour of symptoms. Using serial cardiac enzyme sampling during the first three hours after ED presentation, they were able to detect nearly 80% of AMI patients with non-diagnostic ECG tracings (sensitivity 79.1%) with a specificity of 93.7% and a negative predictive value of 97.1%. They found that 80% had a raised enzyme level within three hours of presentation. The negative predictive value for no AMI was 96.2% within 3 hours in A&E.

CK-MB isoforms are another new serum cardiac marker that may be useful for evaluating patients with an acute coronary syndrome. CK-MB exists in only 1 form in myocardial tissue but in different isoforms (or subforms) in the plasma. An absolute level of CK-MB2 >1 U/L or a ratio of CK-MB2 to CK-MB1 of 1.5 has improved sensitivity and specificity for diagnosis of MI within the first 6 hours compared with conventional assays for CK-MB.³¹ Unfortunately the isoforms are not available in most hospitals in Hong Kong.

The troponins

Because the conventional serum cardiac marker, creatine kinase (CK) and its MB isoenzyme (CK-MB) lack sufficient sensitivity and specificity, there is a need for more sensitive and cardiac-specific markers of myocardial necrosis.³²⁻³⁴

The troponin complex consists of 3 subunits: troponin T, troponin I, and troponin C. The complex is a calcium-sensitive molecular apparatus that regulates the interaction of actin and myosin. Isoforms of troponins exist in both cardiac and skeletal muscles, but they are so different that the current immunoassay methods can detect (and differentiate) cardiac-specific troponin T (cTnT) and cardiac specific troponin I (cTnI) from their skeletal counterparts.

Using the current immunoassay methods, the cut-off value for elevated cTnI and cTnT levels are set only slightly above the upper reference range. As a result, they permit doctors to diagnose less degree

of myocardial necrosis than CK-MB. In fact, there have been case reports of myocardial necrosis with elevated cardiac troponin levels but normal CK values.³⁵

Another study has shown that elevated cTnI or cTnT levels, even in the presence of normal CK-MB levels, identify patients without ST-segment elevation who have increase risk of death.⁹ Further study has also demonstrated that among patients with a non-diagnostic ECG, a positive troponin T result was found to be almost six times as predictive of adverse events as negative test result, whereas the CK-MB markers was not found to be significantly predictive.⁴ Doing both troponin T and CK-MB did not perform better than either test alone in terms of diagnostic and prognostic value.⁴

It is important to remember that, like creatine kinase, cardiac-specific troponins may not be detectable for up to 6 hours after onset of chest pain. However, serum levels of cTnT and cTnI may be present for several days after MI (up to 7 days for cTnI and up to 10 to 14 days for cTnT), whereas CK and CK-MB will return to normal levels within the first 24 to 36 hours. The former is therefore useful in diagnosing recurrent myocardial infarction.

Myoglobin

It is a low molecular weight heme protein found in both cardiac and skeletal muscles, and is therefore not cardiac specific. However, it is released more rapidly from infarcted myocardium than CK-MB and may be detected as early as 2 hours after AMI. Unfortunately, being non-cardiac specific, a raised level of serum myoglobin alone has limited value in early detection of AMI.

Comparing various serum cardiac markers

The diagnostic sensitivity and specificity for MI were compared for total CK-MB (activity and mass), CK-MB subforms, myoglobin, cTnI, and cTnT in the Diagnostic Marker Cooperative Study (DMCS).³⁶ The DMCS was a large, prospective, multicentre, double-blind study of patients presenting to the Emergency departments with chest pain. It had been shown that CK-MB subforms were most efficient for early diagnosis (within 6 hours) of MI, whereas cTnI and cTnT were highly cardiac specific and particularly efficient for late diagnosis

of MI. The DMCS investigators concluded that CK-MB subforms were most sensitive and specific (91% and 89%) within 6 hours of onset. For late diagnosis, total CK-MB activity (derived from subforms) was the most sensitive and specific (96% and 98%) at 10 hours from onset. They suggest that either a single assay (CK-MB subforms) or a select combination (CK-MB subforms and a cardiac-specific troponin) reliably triages patients with chest pain and could potentially lead to improved therapy and reduced cost of care for patients with acute coronary syndromes. Unfortunately, as mentioned previously, assay of CK-MB subforms are not available in most local hospitals. However, the cardiac-specific troponins are now available in Hong Kong.

Elevated concentrations of both troponin T or CK-MB begin to appear in serum 4 to 6 hours after the onset of myocardial injury. One study has shown that the association between a positive troponin T or CK-MB assay and the occurrence of serious adverse events held only for those patients whose blood was obtained 6 hours or more after symptom onset.⁴ The authors suggest that serial myocardial marker measurements are necessary to accurately stratify the risk of patients presenting very early after symptom onset.⁴

It cannot be overemphasised that the timing of checking CK, CK-MB or troponins in relation to the onset of chest pain must be considered when interpreting the results. Even more importantly, a normal CK, if checked at the wrong time, may result in missing the diagnosis of an AMI.

The role of echocardiography, myocardial scintigraphy and exercise stress test

Echocardiography,³⁷ stress echocardiography,³⁸ and myocardial scintigraphy³⁹⁻⁴¹ have been advocated as rapid and accurate means of recognising unstable coronary events in AED patients. These techniques may reduce the risk of failing to recognise an unstable coronary event and avoid a prolonged period of observation. In addition, using immediate exercise treadmill testing in low-risk patients (as indicated by clinical and ECG criteria) has also been suggested. One study has demonstrated the safety

and utility of such a test in low-risk patients presenting to the AED.⁴¹ In this study, all patients with negative test results and 93% with non-diagnostic test results were discharged directly from the AED. Thirty-day follow-up revealed no mortality in these patients. However, the imaging examinations provide sensitivity and specificity superior to exercise ECG and its routine use has been challenged to contribute little to the accuracy of the triage process. A further discussion is beyond the scope of this guideline.

Bedside testing for serum cardiac markers

To be useful in the evaluation of chest pain for patients presenting to the ED, the results of various cardiac markers must be available within a relatively short time. In most hospital laboratories in Hong Kong, serum total CK results may be available in one hour, while the cardiac troponins assay are rarely, if at all, available as an urgent service. Fortunately, rapid bedside assays for the serum cardiac markers are now clinically available in Hong Kong for measuring cTnI, cTnT, myoglobin, and CK-MB. The results can be available in as little as 15 minutes. Both handheld kits and small desktop rapid analysers are available for the same purpose, and both qualitative results (i.e. positive or negative) and quantitative results can be obtained. When using a handheld rapid bedside assay for a serum cardiac marker, the doctor places a small aliquot of the patient's blood or serum in the specimen well and observes the development of a colour line in the read zone of the device. It should be noted that the time to development of the colour line and the intensity of the colour are related to the concentration of the serum cardiac marker in the specimen. For example, when a handheld bedside immunoassay is used to test the blood of patients with high cTnT levels, a red line quickly appears; such patients are at increased mortality risk.⁴² Careful attention to the timing of the appearance of a positive bedside assay result may provide clinicians with a tool for a semi-quantitative estimate of a serum cardiac marker level at the patient's bedside. A positive bedside test however should be confirmed by a conventional quantitative test.

In a recent study by Hamm and his colleagues⁴³

using bedside rapid diagnostic kits for cTnT and cTnI, for those patients with AMI but no ST-elevation, 94% had a positive cardiac troponin T test and 100% had a positive cardiac troponin I test when tested at least 6 hours after onset of chest pain. Equally important is the finding that at this time, the negative predictive value was 98.9% for troponin T and 99.7% for troponin I. An emergency department protocol for chest pain using troponin T or I instead of the usual creatine kinase has appeared in a recent article by Kllotwijk and Hamm.⁴⁴

A suggested chest pain protocol

In the setting of non-diagnostic ECG findings (non-ST elevation), acute coronary syndrome represents a continuum between chronic stable angina and AMI. Although the prognosis of the patient with chronic stable angina can be stratified and the emergency situation engendered by ST-elevation MI is readily evident, patients with acute symptoms but non-diagnostic ECG findings can range from those with non-cardiac chest pain to very high-risk MI with multi-vessel disease. It is therefore highly desirable to have a chest pain protocol available in the ED setting to facilitate evaluation of patients with chest pain and non-diagnostic ECG changes. (Figures 1 & 2)

This protocol takes into account the current evidence of the usefulness and limitations of various methods in evaluating the chest pain patient for the possibility of AMI, the characteristics of local Emergency department settings and the availability of various serum markers as an urgent or rapid test.

When the rapid cardiac troponins assay are not available (Figure 1)

The usual practice of performing urgent serial total CK should be employed for patient with chest pain of obscure origin, in addition to serial ECG. The CK result should be available in approximately 1 hour in most local hospitals. When the total CK is raised in any serial tests and the source cannot be explained by any extra-cardiac origin, for example, recent intramuscular injection or muscular trauma one should admit the patient or to confirm the cardiac origin of CK by checking CK-MB. When

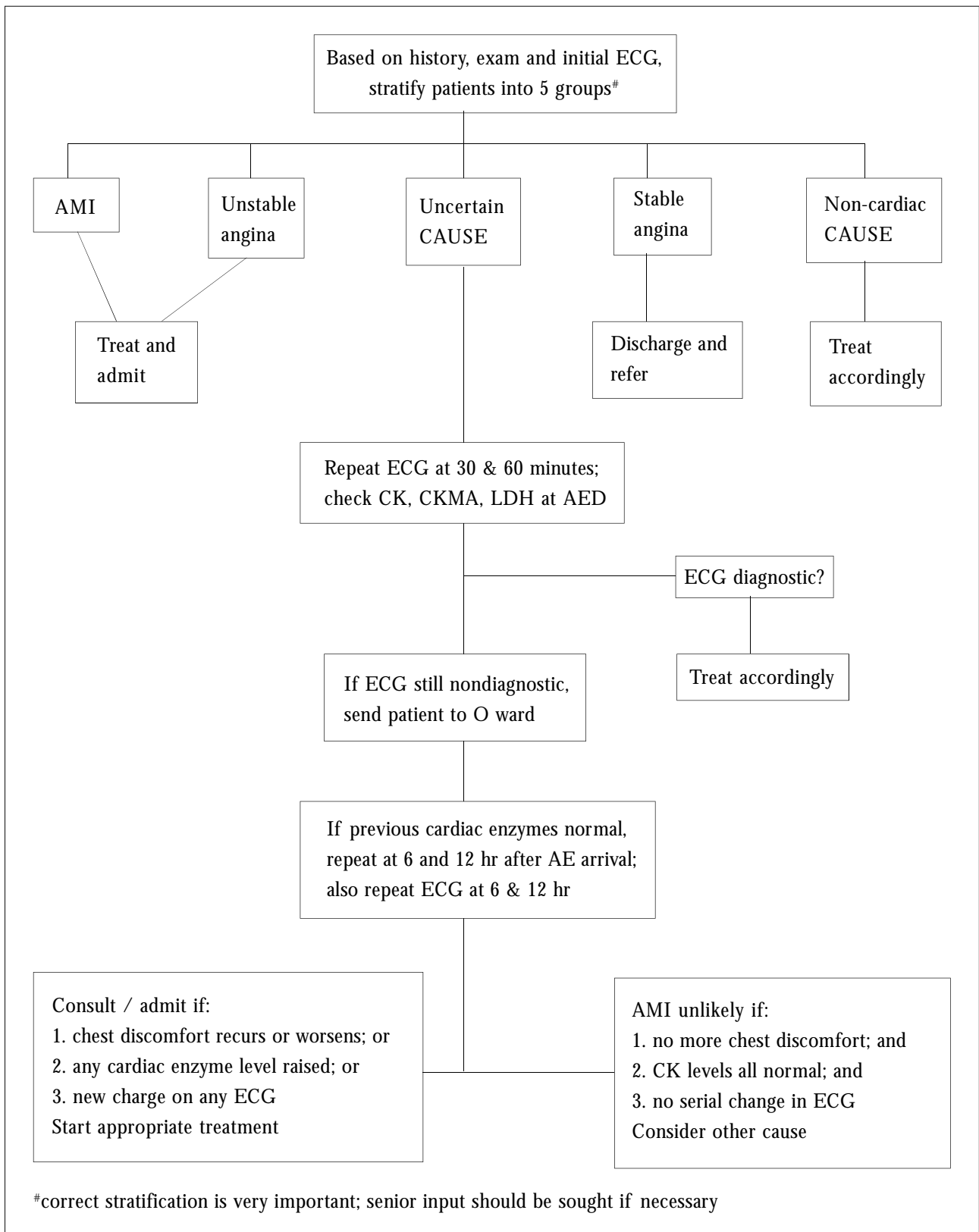


Figure 1. A&E chest pain protocol (when pulmonary embolism and aortic dissection are unlikely) & when troponin T test is not available.

the relative index (CKMB/total CK x 100%) is greater than 5, it is considered positive for cardiac origin. However, checking CK-MB requires prior discussion and approval with the laboratory and it may take up to 24 hours before the result is available, rendering it useless in confirming the cardiac origin of a raised total CK. In essence, the protocol relies on a good clinical judgement for initial stratification of chest pain into various groups, and the checking of serial ECG and serial CK for those with obscure cause.

When the rapid cardiac troponins assay are available (Figure 2)

The many advantages of using cardiac troponins have been mentioned in the aforesaid discussion,

and patients can be observed for a shorter period of time compared with those using total CK, CK-MB and LDH as serum cardiac markers. However, it is worthwhile mentioning that performing bed-side troponin tests are expensive (HK\$100 per test). The cost of the troponin assay is likely a major limiting factor in its adoption in our practice in the Emergency departments in Hong Kong. Hopefully, that the cost can be dramatically reduced to benefit more patients.

Conclusion

Not all patients with acute myocardial infarction present with typical characteristics of chest pain and

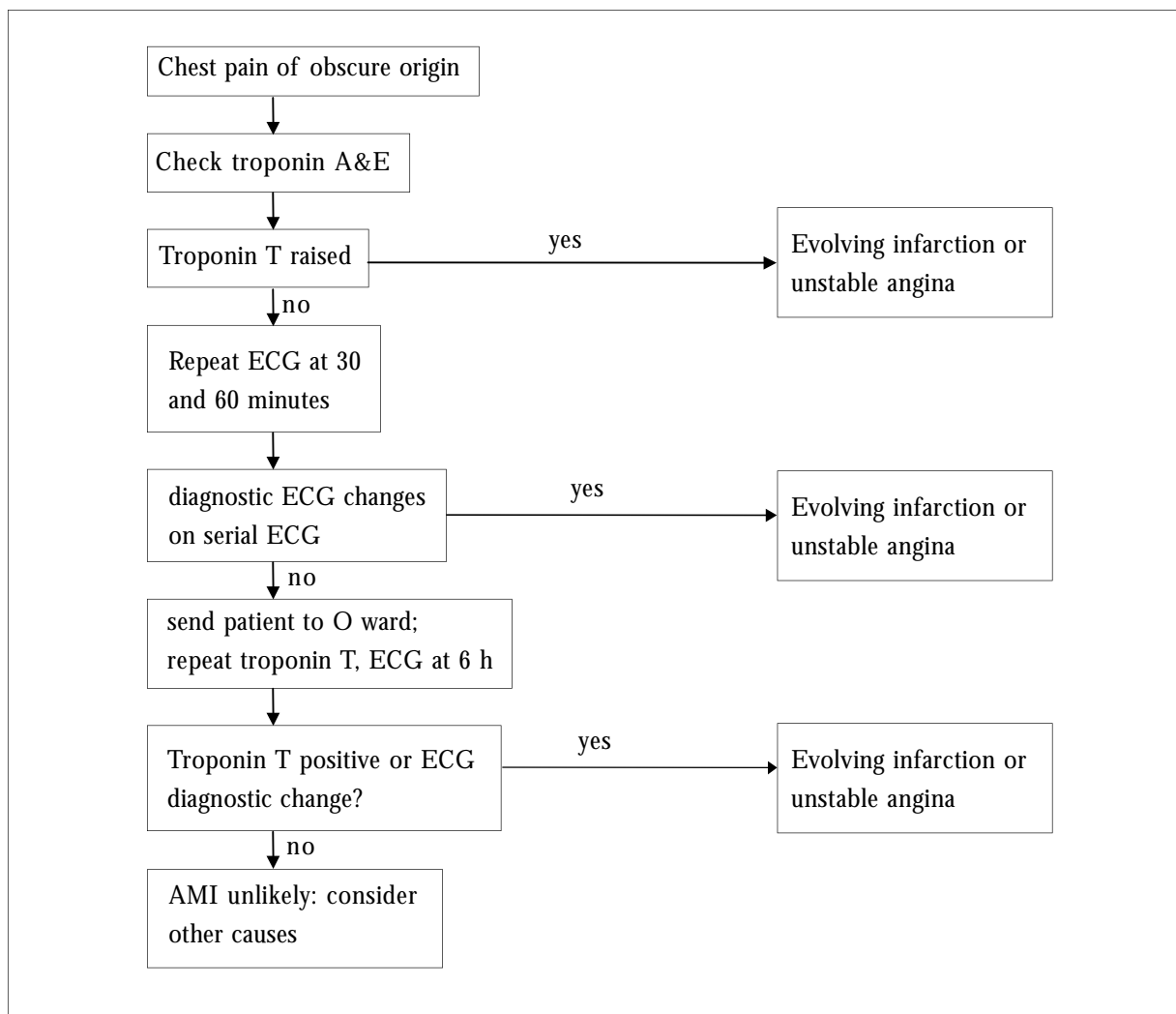


Figure 2. A&E chest pain protocol (when aortic dissection and pulmonary embolism unlikely) & when troponin T test is available.

the associated symptoms. Not all patients with acute myocardial infarction have typical diagnostic features in either the initial or even serial ECG tracing. Missing acute myocardial infarction in patients with atypical presentation may have disastrous consequence. After the initial clinical assessment and ECG, for those patients with chest pain of obscure origin, there are various common diagnostic methods available, each with its roles and limitations. There is a need to develop a chest pain protocol, making use of the currently available facilities in Hong Kong for patients with chest pain so as to enable recognition or exclusion of AMI as early as possible. The introduction of the rapid bedside assay of cardiac specific troponins is likely to have a great impact on the management of patients with chest pain of obscure origin in local emergency departments.

References

1. Tunstall-Pedoe H, Kuulasmaa K, Amouyel P, et al. Myocardial infarction and coronary deaths in the World Health Organisation MONICA Project. *Circulation* 1994;90(1):583-612.
2. Maynard C, Litwin PE, Martin JS, et al. Gender differences in the treatment and outcome of acute myocardial infarction: results from the Myocardial Infarction Triage and Intervention Registry. *Arch Intern Med* 1992;152(5):972-6.
3. Young GP, Stapczynski JS. Myocardial ischaemia and infarction. In: Tintinalli JE, Ruiz E, Krome RL (ed). *Emergency Medicine- a comprehensive study guide*. 4th ed. McGraw Hill 1996:328-36.
4. Green GB, Beaudreau RW, Chan DW, et al. Use of troponin T and creatine kinase-MB subunit levels for risk stratification of emergency department patients with possible myocardial ischemia. *Ann Emerg Med* 1998;31(1):19-29.
5. Wolff L, Wolff R, Samartzis MD, et al. Vectorcardiographic diagnosis: a correlation with autopsy findings in 167 cases. *Circulation* 1961;23: 861-80.
6. Schor S, Behar S, Modan B, et al. Dispositions of presumed coronary patients from an emergency room: a follow-up study. *JAMA* 1976;236(8):941-3.
7. Zarling EJ, Sexton H, Minor P. Failure to diagnose acute myocardial infarction: The clinicopathologic experience at a large community hospital. *JAMA* 1983;250(9):1177-81.
8. Lee TH, Rouan GW, Weisbery MC, et al. Clinical characteristics and natural history of patients with acute myocardial infarction sent home from the emergency room. *Am J Cardiol* 1987;60(4):219-24.
9. The American College of Cardiology and the American Heart Association. ACC/AHA guidelines for the management of patients with acute myocardial infarction 1999.
10. Rude RE, Poole WK, Muller JE, et al. Electrocardiographic and clinical criteria for recognition of acute myocardial infarction based on analysis of 3,697 patients. *Am J Cardiol* 1983;52(4): 936-42.
11. Goldman L, Cook EF, Brand DA, et al. A computer protocol to predict myocardial infarction in emergency department patients with chest pain. *N Engl J Med* 1988;318(13):797-803.
12. McGarthy BD, Beshansky JR, D'Agostino RB, et al. Missed diagnoses of acute myocardial infarction in the emergency department: results from a multicenter study. *Ann Emerg Med* 1993;22(3):579-82.
13. Fesmire FM, Percy RF, Bardoner JB, et al. Usefulness of automated serial 12-lead ECG monitoring during the initial emergency department evaluation of patients with chest pain. *Ann Emerg Med* 1998;31 (1):3-11.
14. Fuchs R, Scheidt S. Improved criteria for admission to cardiac care units. *JAMA* 1985;246(18):2037-41.
15. Nattel S, Warnica JW, Ogilvie RI. Indications for admission to a coronary care unit in patients with unstable angina. *Can Med Assoc J* 1980;122(2):180-4.
16. Eisenberg JM, Horowitz LN, Busch R, et al. Diagnosis of acute myocardial infarction in the emergency room: a prospective assessment of clinical decision making and the usefulness of immediate cardiac enzyme determination. *J Community Health* 1979;4(3):190-8.
17. Seager SB. Cardiac enzymes in the evaluation of chest pain. *Ann Emerg Med* 1980;9(7):346-9.
18. Horowitz RS, Morganroth J. Immediate detection of early high risk patients with an acute myocardial infarction using two-dimensional echocardiographic evaluation of left ventricular regional wall abnormalities. *Am Heart J* 1982;103(5):814-22.
19. Wackers FJ, Kie KI, Liem KI, et al. Potential value of thallium-201 scintigraphy as a means of selecting patients for the coronary care unit. *Br Heart J* 1979; 41(1):111-7.
20. Pozen MW, D'Agostino RB, Selker HP, et al. A predictive instrument to improve coronary care unit admission practices in acute ischemic heart disease. *N Engl J Med* 1984;310(20):1273-8.
21. Goldman L, Cook EF, Brand DA, et al. A computer protocol to predict myocardial infarction in emergency department patients with chest pain. *N Engl J Med* 1988;318(13):797-803.
22. Goldberg RJ, Gore JM, Alpert JS, et al. Incidence and case fatality rates of acute myocardial infarction (1975-1984): the Worcester Heart Attack Study. *Am Heart J* 1988;115(4):761-7.
23. Gibler WB, Lewis LM, Erb RE, et al. Early detection

- of acute myocardial infarction in patients presenting with chest pain and nondiagnostic ECGs: serial CK-MB sampling in the emergency department. *Ann Emerg Med* 1990;19(12):1359-66.
24. McQueen MJ, Strickland RD, Mori L. Detection of ischaemic myocardial injury in patients with normal, or moderately elevated, serum CK and AST activities. *Clin Biochem* 1982;15(3):138-40.
 25. Heller GV, Blaustein AS, Wei JY. Implications of increased myocardial isoenzyme level in the presence of normal serum creatine kinase activity. *Am J Cardiol* 1983;51(1):24-7.
 26. Dillon MC, Calbreath DF, Dixon AM, et al. Diagnostic problem in acute myocardial infarction: CK-MB in the absence of abnormally elevated total creatine kinase levels. *Arch Intern Med* 1982;142(1):33-8.
 27. Hedges JR, Rouan GW, Toltzis R, et al. Use of cardiac enzymes identifies patients with acute MI otherwise unrecognized in the emergency department. *Ann Emerg Med* 1987;16(3):248-52.
 28. Green GB, Hansen KN, Chan DW, et al. The potential utility of a rapid CK-MB assay in evaluating emergency department patients with possible myocardial infarction. *Ann Emerg Med* 1991;20(9):954-60.
 29. Hoekstra JW, Hedges JR, Gibler WB, et al. Emergency department CK-MB: a predictor of ischemic complications. *Acad Emerg Med* 1994;1(1):17-27.
 30. Gibler WB, Young GP, Hedges JR, et al. Acute myocardial infarction in chest pain patients with nondiagnostic ECGs: serial CK-MB sampling in the emergency department. *Ann Emerg Med* 1992;21(5):504-12.
 31. Puleo PR, Meyer D, Wathen C, et al. Use of a rapid assay of subforms of creatine kinase MB to diagnose or rule out acute myocardial infarction. *N Engl J Med* 1994;331(9):561-6.
 32. Tsung SH. Several conditions causing elevation of serum CK-MB and CK-BB. *Am J Clin Pathol* 1981;75(5):711-5.
 33. Tsung JS, Tsung SS. Creatine kinase isoenzymes in extracts of various human skeletal muscles. *Clin Chem* 1986;32(8):1568-70.
 34. Adams JE 3d, Bodor GS, Davila-Roman VG, et al. Cardiac troponin I: a marker with high specificity for cardiac injury. *Circulation* 1993;88(1):101-6.
 35. Antman EM, Grudzien C, Mitchell RN, et al. Detection of unsuspected myocardial necrosis by rapid bedside assay for cardiac troponin T. *Am Heart J* 1997;133(5):596-8.
 36. Zimmerman J, Fromm R, Meyer D, et al. Diagnostic Marker Cooperative Study for the diagnosis of myocardial infarction. *Circulation* 1999;99(13):1671-7.
 37. Sabia P, Afrooktch A, Touchstone DA, et al. Value of regional wall motion abnormality in the emergency room diagnosis of acute myocardial infarction. A prospective study using two-dimensional echocardiography. *Circulation* 1991;84(3 Suppl):I85-92.
 38. Trippi JA, Lee KS, Kopp G, et al. Dobutamine stress tele-echocardiography for evaluation of emergency department patients with chest pain. *J Am Coll Cardiol* 1997;30(3):627-32.
 39. Varetto T, Cantalupi D, Altieri A, et al. Emergency room technetium-99m sestamibi myocardial perfusion imaging in the emergency room evaluation of chest pain. *J Am Coll Cardiol* 1994;23:1016-22.
 40. Kontos MC, Jesse RL, Schmidt KL, et al. Value of acute rest sestamibi perfusion imaging for evaluation of patients admitted to the emergency department with chest pain. *J Am Coll Cardiol* 1997;30(4):976-82.
 41. Kirk JD, Turnipseed S, Lewis WR, et al. Evaluation of chest pain in low-risk patients presenting to the emergency department: the role of immediate exercise testing. *Ann Emerg Med* 1998;32(1):1-7.
 42. Antman EM, Sacks DB, Rifai N, et al. Time to positivity of a rapid bedside assay for cardiac troponin-T predicts prognosis in acute coronary syndromes: a Thrombolysis in Myocardial Infarction (TIMI) 11A substudy. *J Am Coll Cardiol* 1998;31(2):326-30.
 43. Hamm CW, Goldmann BU, Heeschen C, et al. Emergency room triage of patients with acute chest pain by means of rapid testing for cardiac troponin T or troponin I. *N Engl J Med* 1997;337(23):1648-53.
 44. Klootwijk P, Hamm C. Acute coronary syndromes: diagnosis. *Lancet* 1999;353(suppl 2):SII 10-5.