Atypical Chest Pain in a Patient with Multiple Cardiovascular Risk Factors: Stress Testing should be the 1st Step

Kostas Zacharias, MBBS, MRCP, Roxy Senior MD, DM, FRCP; *London, UK*

Coronary artery disease is the number one cause of death in the world. Its prevalence in India has increased dramatically from 3.5% in the 1960s to 11% in late 1990s. The spectrum of initial presentation of coronary artery disease (CAD) in an individual patient can vary greatly from that of stable angina on effort to the extremes of acute coronary syndrome (ACS) or even of sudden cardiac death. The optimal risk stratification of patients who present with symptoms suggestive of coronary artery disease remains a challenge. This is both in patients who present to their primary care physician with suspected angina and in patients who present as an emergency with suspected ACS in a hospital setting. These two populations will be addressed separately in this review as the challenges are somewhat different. However one could argue that stress testing, and in particular stress echocardiography, could be used as the first step in both of these settings.

Acute Coronary Syndromes

The clinical and financial impact of ACS to healthcare systems across the world is significant. In England and Wales, approximately 700,000 patients per year present with acute chest pain to the Accident and Emergency departments. This accounts for around 6% of all adult emergency attendances. Two thirds of these patients

From: Royal Brompton Hospital, London, UK (K.Z., R.S.).

Corresponding Author: Roxy Senior MD, DM, FRCP, FESC, FACC
Professor of Clinical Cardiology
National, Heart and Lung Institute, Imperial College, London
Consultant Cardiologist and Director of Echocardiography
Royal Brompton Hospital, London
Consultant Cardiologist and Director of Cardiac Research,
Northwick Park Hospital, Harrow, UK
Tel: +44 208 869 2547, 44 207 349 7740
Mb: +44 789 999 0306

E mail: roxysenior@cardiac-research.org, R.Senior@rbht.nhs.uk

end being admitted to hospital but only a minority have diagnostic changes on their ECG. Approximately one third of attendances and half of patients admitted have a clinical diagnosis of ACS without clear ECG changes (1).

Although there seems to be a clear international consensus in the management of patients presenting with an ST elevation myocardial infarction on their ECG, the management of patients who present with non-diagnostic ECG changes and normal myocardial enzyme assays such as Troponin (a marker of myocardial necrosis), remains controversial. A previous study in the US, reported that up to 60% of patients who present with a presumed ACS have a non-diagnostic ECG (2). The same study illustrated that the diagnosis of ACS was more likely to be missed if the patients were female, non-caucasian, or presented with atypical symptoms. A similar study in the UK, showed that up to 6% of patients with prognostically important ACS, were inadvertently discharged from emergency departments (3).

Various risk scoring systems have been created in an effort to aid with the risk stratification of such patients. A meta-analysis of 40 relevant studies on 216,552 patients concluded that the two scores most extensively investigated were the Thrombolysis in Myocardial Infarction (TIMI) and Global Registry of Acute Coronary Events (GRACE) scores, with GRACE performing slightly better (4).

However, even in patients with normal cardiac enzymes and admission ECG, the rate of subsequent cardiac events in one year has been quoted as high as 6.7% (5). European Society of Cardiology guidelines therefore recommend pre-discharge stress testing to provide additional prognostic information (6).

The most widely used stress testing modality is the exercise ECG. For years, this has been considered a relatively cheap and accurate way of risk-stratifying patients. However, a prospective randomised study performed in our centre in 2006 demonstrated that stress echocardiography, in patients with suspected ACS is superior to exercise ECG in terms of risk stratification. Moreover, the mean cost to diagnosis, in patients undergoing stress echocardiogram as first line investigation, was significantly lower to that of patients undergoing exercise ECG, due to the much lower number of patients requiring further investigations when an inconclusive test resulted in persistent diagnostic uncertainty (7). Our experience in running an acute stress echocardiography service suggests that such a service is feasible, and can significantly reduce the time interval from admission to discharge of such patients with excellent outcome(8).

The relatively recent development of coronary computed tomography (CT) has led to some controversy as to whether a rapid rule-out protocol involving the use of CT in such patients would be feasible at the point of admission. The known disadvantages of CT, include the use of ionising radiation which may be unsuitable for some patients (for example younger patients or women of childbearing age), the need for contrast agents that may be contra-indicated in certain groups of patients (for example patients with deranged renal function), requirement of beta blocker therapy to achieve heart rate of less than 70bpm, which may be contra-indicated or insufficient, and the need for dedicated infrastructure that may not exist in many district general or rural hospitals. There are also practical limitations with performing coronary CT in acute patients who may require continuous cardiac monitoring, may have signs of cardiac failure or may have persistent tachycardias. In a recent study, even after patients with known history of CAD had been excluded, a further 33% of patients could not undergo CT due to contraindications (9).

Moreover, a decision analytic model comparing diagnostic strategies for chest pain in patients with low risk ACS implied that CT angiography may be associated with a higher event rate in negative patients (more false negative results) compared to functional tests such as SPECT studies. The authors suggested that large, comparative randomised trials are needed, but that no such studies have yet taken place (10).

Stable Angina

Data extrapolated from the 2006 Health Survey for England estimate that there are about 1,132,000 men and 849,000 women over the age of 35 living in the UK who have had angina (11). Various mathematical models have been created to help with the risk stratification of patients who present with suspected cardiac chest pain, on the basis of the typicality of symptoms and the presence of established cardiovascular risk factors. One of these models (12) has formed the basis for the UK's National Institute for Health and Clinical Excellence (NICE) guideline for the investigation and management of chest pain of recent onset (13). This stated that any patient presenting with chest pain with intermediate likelihood of CAD needs further non-invasive testing.

In patients presenting with chest pain, it is important to exclude myocardial ischaemia as the cause. Myocardial Ischaemia may occur even in the absence of flow limiting epicardial CAD, for example in cases of underlying cardiomyopathy, left ventricular hypertrophy or microcirculatory disorders. The morbidity and mortality of such patients may be equivalent to that of patients with epicardial CAD (14).

Various stress testing techniques have shown that a negative test portends an excellent outcome (mortality <1%/year) and that mortality increases with presence and severity of abnormalities (15,16). This risk stratification by stress testing was even beyond that predicted by coronary angiography (17). Identification of myocardial ischaemia as a cause of chest pain may help to target appropriate symptom relieving therapy. Even in patients with demonstrated CAD, the outcome is dictated by the extent of ischaemia rather than by the extent of CAD on angiography (18). Anatomical testing for CAD, while important in establishing the diagnosis of CAD, may only therefore be necessary in high risk patients when medical therapy has failed to relieve symptoms (13).

This line of management is suggested by the results of the COURAGE study (19). This study revealed a lack of revascularisation benefit in terms of major cardiovascular events compared to optimal medical therapy alone in patients with mild-moderate angina. A revascularisation strategy based on the burden of ischaemia showed improved outcome compared with medical therapy alone.

What remains open to question, is whether optimal medical therapy even in the presence of large amounts of ischaemia may be equivalent to a revascularisation strategy. This will be addressed in the ISCHEMIA trial where patients with significant ischaemia on non-invasive testing will be randomised to optimal therapy alone versus revascularisation (20). Patients in this trial will be randomised prior to undergoing coronary angiography.

The use of coronary CT in patients presenting with chest pain and risk factors has several limitations. As it is an anatomical test, it cannot establish directly whether myocardial ischaemia is the cause of chest pain, as outlined above. A significant number of patients may have intermediate coronary stenosis that would require a subsequent stress test to look for ischaemia. The negative predictive value of coronary CT for predicting CAD in this population has not yet been tested prospectively. The positive predictive value is in the region of 60% (21). The use of CT as first line investigation therefore, may result in a large amount of unnecessary invasive angiograms. In a large US registry study, the cost-effectiveness of CT was inferior to stress testing for the detection of CAD (22). The practical limitations in the use of CT in this population are similar to the ones described above in the context of ACS. In a large multicentre study, the feasibility of CT in this population was only 66% (23).

Finally, the main question that needs to be addressed in patients presenting with chest pain is whether the chest pain is due to functional myocardial ischaemia. This is best answered by a functional test, such as stress echocardiogram which assesses ischaemia. Inducible ischaemia detected by stress echocardiogram in our centre, resulted in 75% of patients undergoing revascularisation whereas the absence of ischaemia showed excellent prognosis (24).

Summary

The timely assessment and correct risk stratification of patients presenting with chest pain remains challenging even in the presence of typical symptoms. This becomes even more difficult in patients who present with atypical symptoms, who form the majority of all patients and in particular of patients who are female or of non-caucasian ethnic background.

The development of various imaging modalities in the last 20 years has led to the development of a range of sometimes conflicting guidelines. We feel however that in terms of feasibility, diagnostic and prognostic value, cost-effectiveness and lack of significant contra-indications, there is a strong argument to be made for the use of a functional test such as stress echocardiogram as first line assessment in patients presenting with chest pain and cardiovascular risk factors.

References

1. Goodacre S, Cross E, Arnold J, Angelini K, Capewell S, Nicholl J. The health care burden of acute chest pain. Heart 2005; 91:229-30.Goodacre S, Cross E, Arnold J, Angelini K, Capewell S, Nicholl J. The health care burden of acute chest pain. *Heart* 2005; 91:229-30.

2. Pope JH, Aufderheide TP, Ruthazer R, Woolard RH, Feldman JA, Beshansky JR, et al. Missed diagnoses of acute cardiac ischemia in the emergency department. *N Engl J Med* 2000; 342: 1163-70.

3. Collinson P O, Premachandram S, Hasehmi K. Prospective audit of incidence of prognostically important myocardial damage in patients discharged from emergency department. *BMJ* 2000; 320:1702–5.

4. D'Ascenzo F, Biondi-Zoccai G, Moretti C, Bollati M, Omedè P, Sciuto F, Presutti DG, Modena MG, Gasparini M, Reed MJ, Sheiban I, Gaita F. TIMI, GRACE and alternative risk scores in Acute Coronary Syndromes: A meta-analysis of 40 derivation studies on 216,552 patients and of 42 validation studies on 31,625 patients Contemporary Clinical Trials 2012; 33(3):507-14.

5. Sanchis J, Bodí V, Núñez J, Bertomeu-González V, Gómez C, Bosch MJ, Consuegra L, Bosch X, Chorro FJ, Llàcer A. New risk score for patients with acute chest pain, non-ST-segment deviation, and normal troponin concentrations: a comparison with the TIMI risk score. *J Am Coll Cardiol.* 2005; 46(3):443-9.

6. ESC Clinical Practice Guidelines: Acute Coronary Syndromes in patients presenting without persistent ST-segment elevation. Available From: www.escardio.org/guidelines-survey/esc-guidelines/Pages/ACS-non-ST-segment-elevation.aspx.

7. Jeetley P, Burden L, Stoykova B, Senior R. Clinical and economic impact of stress echocardiography compared with exercise electrocardiography in patients with suspected acute coronary syndrome but negative troponin: a prospective randomized controlled study. *Eur Heart J* 2007; 28(2): 204-11.

8. Shah B, Balaji G, Hajiri A, Ramzy I, Ahmadvazir S. Stress echocardiography incorporated into an acute chest pain service provides excellent feasibility, rapid assessment with early triaging and accurate risk stratification of patients with suspected acute coronary syndrome but non-diagnostic ecg and negative 12-hr troponin. *J Am Coll Cardiol.* 2012;59(13s1):E1274-E1274. doi:10.1016/S0735-1097(12)61275-3.

9. Hoffmann U, Bamberg F, Chae CU, Nichols JH, Rogers IS, Seneviratne SK, Truong QA, Cury RC, Abbara S, Shapiro MD, Moloo J, Butler J, Ferencik M, Lee H, Jang IK, Parry BA, Brown DF, Udelson JE, Achenbach S, Brady TJ, Nagurney JT. Coronary computed tomography angiography for early triage of patients with acute chest pain: the ROMICAT (Rule Out Myocardial Infarction using Computer Assisted Tomography) trial. *J Am Coll Cardiol.* 2009; 53(18):1642-50.

10. Priest VL, Scuffham PA, Hachamovitch R, Marwick TH. Cost-effectiveness of coronary computed tomography and cardiac stress imaging in the emergency department: a decision analytic model comparing diagnostic strategies for chest pain in patients at low risk of acute coronary syndromes. *JACC Cardiovasc Imaging.* 2011; 4(5):549-56.

11. Coronary Heart Disease Statistics Available From: http://www.heartstats.org.

12. Pryor DB, Shaw L, McCants CB, Lee KL, Mark DB, Harrell FE Jr, Muhlbaier LH, Califf RM. Value of the history and physical in identifying patients at increased risk for coronary artery disease. *Ann Intern Med.* 1993; 118(2):81-90.

13. National Institute for Health and Clinical Excellence. Chest Pain of Recent Onset March 2010. Available From: http://www.NICE.org.uk.

14. From AM, Kane G, Bruce C, Pellikka PA, Scott C, McCully RB. Characteristics and outcomes of patients with abnormal stress echocardiograms and angiographically mild coronary artery disease (<50% stenoses) or normal coronary arteries. *J Am Soc Echocardiogr.* 2010; 23(2):207-14.

15. Marwick TH, Case C, Sawada S, Rimmerman C, Brenneman P, Kovacs R, Short L, Lauer M. Prediction of mortality using dobutamine echocardiography. *J Am Coll Cardiol.* 2001; 37(3):754-60.

16. Metz LD, Beattie M, Hom R, Redberg RF, Grady D, Fleischmann KE. The prognostic value of normal exercise myocardial perfusion imaging and exercise echocardiographya meta-analysis. *J Am Coll Cardiol.* 2007; 49(2):227-37.

17. Sicari R, Pasanisi E, Venneri L, Landi P, Cortigiani L, Picano E. Echo Persantine International Cooperative (EPIC) Study Group; Echo Dobutamine International Cooperative (EDIC) Study Group. Stress echo results predict mortality: a large-scale multicenter prospective international study. *J Am Coll Cardiol.* 2003; 41(4):589-95.

18. Shaw LJ, Berman DS, Maron DJ, Mancini GB, Hayes SW, Hartigan PM, Weintraub WS, O'Rourke RA, Dada M, Spertus JA, Chaitman BR, Friedman J, Slomka P, Heller GV, Germano G, Gosselin G, Berger P, Kostuk WJ, Schwartz RG, Knudtson M, Veledar E, Bates ER, McCallister B, Teo KK, Boden WE; COURAGE Investigators. Optimal medical therapy with or without percutaneous coronary intervention to reduce ischemic burden: results from the Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) trial nuclear substudy. *Circulation.* 2008; 117(10):1283-91.

19. Boden WE, O'Rourke RA, Teo KK, Hartigan PM, Maron DJ, Kostuk WJ, Knudtson M, Dada M, Casperson P, Harris CL, Chaitman BR, Shaw L, Gosselin G, Nawaz S, Title LM, Gau G, Blaustein AS, Booth DC, Bates ER, Spertus JA, Berman DS, Mancini GB, Weintraub WS; COURAGE Trial Research Group. Optimal medical therapy with or without PCI for stable coronary disease. *N Engl J Med.* 2007; 356(15):1503-16.

20. The ISCHEMIA Study. Available at: www.ischemiatrial.org

21. Budoff MJ, Dowe D, Jollis JG, Gitter M, Sutherland J, Halamert E, Scherer M, Bellinger R, Martin A, Benton R, Delago A, Min JK. Diagnostic performance of 64-multidetector row coronary computed tomographic angiography for evaluation of coronary artery stenosis in individuals without known coronary artery disease: results from the prospective multicenter ACCURACY (Assessment by Coronary Computed Tomographic Angiography of Individuals Undergoing Invasive Coronary Angiography) trial. *J Am Coll Cardiol.* 2008; 52(21):1724-32.

22. Shreibati JB, Baker LC, Hlatky MA. Association of coronary CT angiography or stress testing with subsequent utilization and spending among Medicare beneficiaries. *JAMA.* 2011; 306(19):2128-36.

23. Cheng V, Berman DS, Dunning AL, Achenbach S, Al-Mallah, M, Budoff, MJ, Cademartiri F, Callister TQ, Chang H, Chinnaiyan KM, Chow BJW, Delago AJ, Hadamitzky M, Hausleiter J, Kaufmann P, Lin FY, Nasir K, Raff G, Shaw LJ, Villines TC, Min JK. Cigarette smoking, proximal coronary arterial plaque composition, an risk of myocardial infarction and death: a study of nondiabetic men and women in the multinational confirm registry (coronary ct angiography evaluation for clinical outcomes: an international multicenter registry). *J Am Coll Cardiol.* 2011;57(14s1):E641-E641. doi:10.1016/S0735-1097(11)60641-4.

24. Chelliah R, Anantharam B, Burden L, Alhajiri A, Senior R. Independent and incremental value of stress echocardiography over clinical and stress electrocardiographic parameters for the prediction of hard cardiac events in new-onset suspected angina with no history of coronary artery disease. *Eur J Echocardiogr.* 2010; 11(10):875-82.