Atypical Chest Pain: The Modern Dilemma of Chest Pain Despite Normal Coronary Anatomy

EUGENE B WU, CHU-PAK LAU*

From Cardiology Division, Department of Medicine and Therapeutics, Prince of Wales Hospital, The Chinese University of Hong Kong, *Cardiology Division, University Department of Medicine, Queen Mary Hospital, Hong Kong

WU AND LAU: ***Atypical Chest Pain: The Modern Dilemma of Chest Pain Despite Normal Coronary Anatomy.*** *Atypical chest pain is a common problem with substantial morbidity and an increasing prevalence, partially driven by our anxiety over legal peril. A normal coronary angiogram is a suboptimal outcome for the patient as it entrenches the idea of disease and often fails to reassure the patient. There is an urgent need to readjust our clinical practice to prevent normal coronary angiography by careful clinical history taking and selective non-invasive investigations of patients with chest pain. The chest pain score provides an excellent way to achieve the above aims. Once we have documented normal coronary angiography, we must strongly reassure the patient as well as offer an alternative diagnosis and treatment as appropriate and not leave these patients to fend for themselves, as many of them face unemployment and continuing pain if left untreated. Hypertension, postmenopausal pain, panic attacks, oesophageal reflux, and anxiety neurosis should be identified and dealt with to minimize the morbidity of these patients. (J HK Coll Cardiol 2002;10:88-93)*

Atypical pain, chest pain, defensive medicine, normal coronary, syndrome X

摘要

不典型胸痛是一種越來越常見的症狀，部分由焦慮引起。若患者滿腦的疾病心態，且不能消除這些顧慮，正常的冠脈造影結果也是一個不佳的預後。這很有必要對胸痛患者進行仔細的臨床病史詢問及選擇無創性檢查方法來調整臨床實踐以防止常規的冠脈造影。胸痛評分是達到這一目的有效辦法。一旦我們確定了冠脈造影正常，則需說服患者消除顧慮、提供一些可能的診斷與治療，並不讓患者自己照顧他們自己，因他們許多會面臨失業以及不治療者還會有胸痛發作。高血壓、月經後疼痛、驚恐發作、食管返流和神經焦慮應明確診斷和治療以減少患者的病態發生。

關鍵詞：不典型胸痛　胸痛　防禦性醫療　正常冠脈　X綜合征

Background

Almost everyone experiences chest pain once in a while. Self reported chest pain is extremely common in the community, but has a benign aetiology in the majority of patients.[1] With the increasing availability of coronary angiography and a shift towards a legally defensive ethos in medical practice, physicians increasingly refer patients for coronary angiography "just in case" of coronary artery disease. The overestimation of both the risk of coronary artery disease and the risk of legal peril exposes patients to costly and ethically suspect investigation.[2] Not only does a normal coronary angiogram expose the patient to a small but inherently real morbidity and mortality, it often fails to reassure the patient[3] and may even entrench the idea of disease.[4] Besides the obvious economic cost of the normal coronary angiogram, the patient also endures

Address for reprints: Dr. Eugene B Wu
Department of Medicine and Therapeutics, Prince of Wales Hospital, 30-32 Ngan Shing Street, Shatin, N.T., Hong Kong

Tel: (852) 2632 3133, Fax: (852) 2713 3302

Received December 10, 2001; revision accepted February 21, 2002

the physical and emotional costs of the procedure too. Although the prognosis in terms of mortality after the demonstration of normal coronary anatomy is good, the morbidity is substantial. 50% of patients continue to have worsening chest pain and results in job loss or job change in 50% of patients.[5-9] Therefore, the finding of a normal coronary angiogram is not a reason to celebrate but rather a motive to review our diagnostic paradigm. How then can we better select patients for further investigation?

The History

Traditionally, chest pain has been subjectively divided into "typical" and "atypical" pain. However, different people mean different things by "typical" pain. For example, Detry et al[10] considered pain "atypical" if there were no features of angina or some features suggesting angina but not definitely so or if it was unclassifiable. On the other hand, Proudfit[11] classified pain as normal, probably normal, atypical (pain thought to be angina but with unusual or inconsistent precipitating factors) and definite angina. Even if we defined "typical" chest pain as exertional, the degree of reproducibility varies considerably within patients with exertional chest pain. Day and Sowton[12] showed that 60% of patients with normal coronary anatomy had pain that was sometimes related to exercise while in only 16% was it consistently and reproducibly related. Despite this variation and unsatisfactory definition of "typical" chest pain, there are very few studies that look at whether chest pain characteristics correlate with the findings on coronary angiography.

Cooke et al[13] examined 50 chest pain characteristic variables and demonstrated that only three chest pain characteristics differentiated between 65 patients with normal coronary anatomy and 65 controls with coronary artery disease. These were reproducibility, duration and presence of rest pain. For reproducibility, typical is defined as chest pain being reproducible in 10 out of 10 episodes of strenuous exertion. For rest pain, typical is defined as pain occurring at rest once or fewer of 10 episodes. For duration, typical is defined as less than or equal to 5 minutes. The reproducibility score, the rest pain score and the duration score can be added together to give a score between 0-3, where 0 is very atypical chest pain, and three typical angina pain. We took Cooke's work further and prospectively demonstrated the validity of this chest pain score in 250 patients attending day case coronary angiography.[14] Applying the chest pain score, in conjuncture with Duke's[15] and Framingham score,[16] to 363 consecutive patients presenting to a tertiary cardiology centre, we demonstrated the possibility of preventing 17 (11% of 155 angiograms performed in this group) normal coronary angiograms at the risk of missing 2 patients with significant coronary artery disease.[17] We also showed that the site, quality and radiation of the pain had no predictive power for coronary artery disease on angiography by multivariate analysis. Therefore, we should move away from subjective terminology in describing chest pain, but instead focus on the duration, reproducibility and the proportion of rest pain, as this is helpful in risk stratification for coronary artery disease. Further investigations should be focused upon those patients with typical chest pain: reproducible every time on exertion, rarely occurring at rest and lasting less than 5 minutes.

Investigations

Exercise testing is a safe and noninvasive method to risk stratify patients with chest pain. However, the notoriously high rate of false positive exercise test in women[18-20] make it a poor tool in these patients who have a low pretest risk of coronary artery disease. Traditional ST segment changes have little predictive power in women. Pratt et al[18] found on multivariate analysis that persistent ST depression for longer than 6 minutes and total exercise time are good predictors of coronary artery disease demonstrated on coronary angiography in women. The low pretest risk of coronary artery disease in young women and the high false positive rate means that exercise testing should rarely be used as an investigation. Hung et al[20] have already demonstrated the superiority of thallium scintigraphy in female patients. Therefore, for low risk patients (females under 55 years of age) we recommend thallium scintigraphy only in those with typical pain (chest pain score of 3).

The combination of the chest pain score and Framingham risk profiles allow us to carefully select those in whom exercise testing is worthwhile. Together

with the exercise test we can avoid some unnecessary coronary angiography and reduce the cost and mortality associated with normal coronary angiography. However, there will inevitably be a few patients who end up having coronary angiography demonstrating normal anatomy. How should we manage these patients who have low mortality but considerable morbidity?

Management

To Discharge or Not to Discharge

Most patients with normal coronary anatomy are promptly discharged from a busy cardiology clinic with the diagnosis of non-cardiac chest pain. With normal coronary anatomy accounting for 30-40% of diagnostic coronary angiography in most centers, continued indefinite follow up of these patients poses a considerable burden upon already full cardiology clinics. Besides, one can argue that less exposure to cardiology clinic may reduce the entrenching of the idea of cardiac disease in patients. However, more than half of these patients will continue to worsen and visit doctors in primary care with emergency departments bearing the brunt of their continuing chest pains. Non cardiac chest pain is not a single diagnostic entity and a few causes of non-cardiac chest pain may be amenable to effective therapy and reduce the morbidity for the patient as well as the burden for primary care physicians. Our practice is to see the patient once in clinic after coronary angiography. This serves as an opportunity to repeat the all-important message of reassurance to the patient. At this clinic visit we also attempt to formulate a working diagnosis of the aetiology of non-cardiac chest pain and apply appropriate therapy based on this diagnosis. This method seems to maximize the reassurance while minimizing entrenching the idea of disease. Yet offering an alternative diagnosis for the patient and future physicians they may consult.

Oesophageal Pain

Several large studies in the late 80s and early 90s demonstrated abnormalities of manometry and acid reflux in 50-70% of patients with chest pain despite normal coronary anatomy.[21-24] This lead to the belief that most patients with chest pain despite normal coronary anatomy had oesophageal disorders. However, motility disorder or reflux alone is not a chest pain causing disease and should only be considered causative if it is tightly and temporally associated with chest pain episodes. This tight relationship is found only in about 30% of patients.[25] Therefore, only about a third of the patients with chest pain despite normal coronary anatomy have oesophageal reflux as a cause of their pain. This high prevalence has prompted some authors to recommend a trial of proton pump inhibitor in all patients with chest pain despite normal coronary anatomy, which has been demonstrated to be cost effective.[26] However, the rate of oesophageal reflux may be lower in Hong Kong due to differences in body weight and diet. Therefore we recommend a trial of proton pump inhibitors only in those with some clinical indicators of oesophageal reflux or those with persisting chest pain. In those with symptoms suggestive of oesophageal reflux who have not responded to an initial trial of proton pump inhibitors, we suggest 24 hours pH and manometric studies for definitive diagnosis of oesophageal reflux.

Psychological

Soon after Kemp and Likoff[27,28] described the cases of normal coronary anatomy associated with "unmistakable coronary artery disease" in 1967, Waxler[29] found that 40% of their sample of 86 women with normal coronary anatomy and chest pain had neurotic or hypochondriacal behaviour. Since Waxler, many larger and more systematic studies with control groups have demonstrated that psychological abnormalities exists in 40-60% of those with normal coronary anatomy as oppose to 20% of controls.[30-32] These differences are not solely due to the sex and age differences between those with coronary artery disease and those with normal anatomy as two studies with age sex matched controls also demonstrated significant differences in psychological abnormalities.[33,34] Nor are these psychological abnormalities transient, induced perhaps by the anxiety of attending coronary angiography. Long term follow up studies clearly demonstrate that these abnormalities both preceded before and persisted after coronary angiography.[35-37] The degree of psychological abnormalities also correlates well to the prognostic morbidity of the patients.[38]

Panic disorder is the most common psychological abnormality found in patients with chest pain despite

normal coronary anatomy.[31,39] Although both depression and anxiety neurosis have also been reported.[31,32] Cognitive behavioural therapy has been shown to be beneficial to patients with chest pain despite normal coronary anatomy.[40] In our practice we aim to refer 40% of our patients with normal coronary anatomy to cognitive behavioural therapy, although the acceptance is low and the resource often scarce.

Treatment with imipramine has been demonstrated to be effective in patients with chest pain despite normal coronary anatomy.[41,42] However, there is still a stigma associated with antidepressant therapy, which is occasionally a barrier to the patient's acceptance of the treatment. In our practice we often use a course of antidepressant in patients with chest pain despite normal coronary anatomy especially if our clinical intuition inclines us towards a psychological bases for their pain.

Oestrogen Deficiency

There is some evidence that the onset of chest pain in normal coronary anatomy patients correlates with the onset of menopause.[43,44] Based upon this, several investigators have conducted placebo control trials of hormone replacement therapy in postmenopausal women with chest pain despite normal coronary anatomy. Albertsson et al[45] in a placebo controlled, double blind, cross over trial found that 1 week of oestrogen replacement therapy improved exercise time, time to 1 mm ST depression and anginal pain in 15 postmenopausal syndrome X patients but not in 8 healthy postmenopausal age sex matched controls. Rosano et al[46] demonstrated a significant reduction from 7.3 to 3.7 episodes per 10 days of diary recorded chest pain in a double blind placebo controlled randomized cross over trial of 25 postmenopausal syndrome X patients with 2 months of oestrogen replacement therapy. However, they found no difference in exercise duration between placebo and replacement therapy. However, due to persisting controversies on hormonal replacement therapy, we balance our recommendation for hormone replacement therapy with caution.

Hypertension

Hypertension is common among those who have normal coronary angiography. This may be due to the selection bias inherent in the physician's choice of whom to investigate with angiography. Whether hypertension in itself causes chest pain is debated. However, even without causing chest pain, hypertension should be treated in order to prevent complications. Therefore we recommend aggressive antihypertensive therapy, particularly in those with left ventricular hypertrophy.

Microvascular Angina

Whether a small group of patients within the syndrome X patient group have microvascular angina is as yet unproven. Positron emission tomography studies have on the whole failed to demonstrate ischaemia[47] and so have dobutamine stress transoesophageal echocardiography.[48] The recent demonstration of Magnetic resonance spectroscopy abnormalities in 7 out of 35 women with normal coronary anatomy by Buchthal et al[49] has met with considerable and just criticism of their technique.[50] This includes vague inclusion criteria, inadequate stress, and possible movement with handgrip exercise. Even Cannon, who first coined the term microvascular angina, assigns this study into mass graveyard of controversial studies in syndrome X.[51] Therefore, to this day, the mystery of microvascular angina within syndrome X remains unsolved. However, these patient seem to have pain disproportionately to the evidence of ischaemia and have prognosis inconsistent with ischaemic heart disease. Although academically we might investigate and ponder hard at the possibility of microvascular angina, in our clinical practice we treat patients as if this entity did not exist. We do this in order to minimize the confusion for patients as many of them will continue to have the notion that they have heart disease and our reassurance will be less effective if we spin some unproven tale of microvascular angina to them.

Conclusions

Once the patient has had a normal coronary angiogram, it is important to review the patient in order to diagnose and treat the problem. Patients with predominantly oesophageal pain should be given a trial of proton pump inhibitor. Postmenopausal women should be given hormone replacement therapy. Patients with panic attacks or an anxious disposition should be persuaded into a short course of cognitive behavioural

therapy or a trial of imipramine. All patients should receive a confident reassurance. Since about two thirds of patients have a reasonable prognosis if we follow the above protocol, they can be discharged after the initial clinical visit. Chronic non-cardiac chest pain patients gain little benefit in staying in cardiology clinics. However, we must remember that patients with normal coronary anatomy may well develop coronary artery disease later on, although this is most unlikely within the first five years of normal coronary anatomy demonstrated on angiography. Therefore we must be open to reassessment of patients after 5 years but must be particularly careful not to repeat our mistake and perform a second normal coronary angiogram.

Clinical practice has changed considerably in the last 10 years in Hong Kong. Defensive medicine is practiced more and more due to pressures from the press and the public. Consequently, atypical chest pain has become more difficult to manage and each year we produce more patients with "chest pain despite normal coronary anatomy". In this article, we have outlined some methods to refine our diagnostic paradigm and reduce our "normal coronary anatomy" rate. We have also suggested some evidence based practical guidelines on how to manage the patient after the demonstration of normal coronary anatomy.

References

1. Kroenke K, Mangelsdorff AD. Common symptoms in ambulatory care: incidence, evaluation, therapy, and outcome. Am J Med 1989;86:262-6.
2. De Ville K. Act first and look up the law afterward?: medical malpractice and the ethics of defensive medicine. Theor Med Bioeth 1998;19:569-89.
3. Warwick HM, Salkovskis PM. Reassurance. Br Med J (Clin Res Ed) 1985;290:1028.
4. Fitzpatrick R. Telling patients there is nothing wrong. BMJ 1996; 313:311-2.
5. Proudfit WL, Bruschke VG, Sones FM Jr. Clinical course of patients with normal or slightly or moderately abnormal coronary arteriograms: 10-year follow up of 521 patients. Circulation 1980;62:712-7.
6. Pasternak RC, Thibault GE, Savoia M, et al. Chest pain with angiographically insignificant coronary arterial obstruction. Clinical presentation and long-term follow-up. Am J Med 1980; 68:813-7.
7. Wielgosz AT, Fletcher RH, McCants CB, et al. Unimproved chest pain in patients with minimal or no coronary artery disease: a behavioral phenomenon. Am Heart J 1984;108:67-72.
8. Papanicolaou MN, Califf RM, Hlatky MA, et al. Prognostic implications of angiographically normal and insignificantly narrowed coronary arteries. Am J Cardiol 1986;58:1181-7.
9. De Caestecker JS, Bruce GM, Heading RC. Follow up of patients with chest pain and normal coronary angiography: the impact of oesophageal investigations. Eur J Gastroenterol Hepatol 1991; 3:899-905.
10. Detry JM, Kapita BM, Cosyns J, et al. Diagnostic value of history and maximal exercise electrocardiography in men and women suspected of coronary artery disease. Circulation 1977;56:756-61.
11. Proudfit WL, Shirey EK, Sones FM Jr. Selective cine coronary arteriography: correlation with clinical findings in 1,000 patients. Circulation 1966;33:901-10.
12. Day LJ, Sowton E. Clinical features and follow-up of patients with angina and normal coronary arteries. Lancet 1976;2:334-7.
13. Cooke RA, Smeeton N, Chambers JB. Comparative study of chest pain characteristics in patients with normal and abnormal coronary angiograms. Heart 1997;78:142-6.
14. Wu EB, Smeeton N, Chambers JB. A chest pain score for stratifying the risk of coronary artery disease in patients having day case coronary angiography. Int J Cardiol 2001;78:257-64.
15. Mark DB, Shaw L, Harrell FE Jr, et al. Prognostic value of a treadmill exercise score in outpatients with suspected coronary artery disease. N Engl J Med 1991;325:849-53.
16. Murabito JM, Anderson KM, Kannel WB, et al. Risk of coronary heart disease in subjects with chest discomfort: the Framingham heart study. Am J Med 1990;89:297-302.
17. Wu EB, Smeeton N, Hodson F, Chambers JB. A prospective study to test the predictive value of an objective chest pain score with exercise test for stratifying the risk of coronary artery disease in patients presenting with chest pain Unpublished data.
18. Pratt CM, Francis MJ, Divine GW, et al. Exercise testing in women with chest pain. Are there additional exercise characteristics that predict true positive test results? Chest 1989; 95:139-44.
19. Ellestad MH, Savitz S, Bergdall D, et al. The false positive stress test. Multivariate analysis of 215 subjects with hemodynamic angiographic and clinical data. Am J Cardiol 1977;40:681-5.
20. Hung J, Chaitman BR, Lam J, et al. Noninvasive diagnostic test choices for the evaluation of coronary artery disease in women: a multivariate comparison of cardiac fluoroscopy exercise electrocardiography and exercise thallium myocardial perfusion scintigraphy. J Am Coll Cardiol 1984;4:8-16.
21. Chobanian SJ, Benjamin SB, Curtis DJ, et al. Systematic esophageal evalutation of patients with noncardiac chest pain Arch Int Med 1986;146:1505-8.
22. Ghillebert G, Janssens J, Vantrappen G, et al. Ambulatory 24 hour intraoesophageal pH and pressure recordings v provocation tests in the diagnosis of chest pain of oesophageal origin. Gut 1990;31:738-44.
23. Stein HJ, DeMeester TR, Eypasch EP, et al. Ambulatory 24-hour esophageal manometry in the evaluation of esophageal motor disorders and noncardiac chest pain. Surgery 1991;110: 753-61.

24. Rokkas T, Anggiansah A, McCullagh M, et al. Acid perfusion and edrophonium provocation tests in patients with chest pain of undetermined etiology. Dig Dis Sci 1992;37:1212-6.
25. Wu EB, Cooke R, Anggiansah A, et al. Are oesophageal disorders a common cause of chest pain despite normal coronary anatomy? QJM 2000;93:543-50.
26. Ofman JJ, Gralnek IM, Udani J, et al. The cost-effectiveness of the omeprazole test in patients with non-cardiac chest pain. Am J Med 1999;107:219-27.
27. Likoff W, Segal BL, Kasparian H. Paradox of normal selective coronary arteriograms in patients considered to have unmistakable coronary heart disease. N Engl J Med 1967;276: 1063-6.
28. Kemp HG, Elliot WC, Gorlin R. The anginal syndrome with normal coronary arteriography. Trans Assoc Am Physicians 1967;80:59-70.
29. Waxler EB, Kimbiris D, Dreifus LS. The fate of women with normal coronary arteriograms and chest pain resembling angina pectoris. Am J Cardiol 1971;28:25-32.
30. Bass CM, Wade C. Chest pain with normal coronary arteries: a comparative study of psychiatric and social morbidity. Psychol Med 1984;14:51-61.
31. Katon W, Hall ML, Russo J, et al. Chest pain: relationship of psychiatric illness to coronary arteriographic results. Am J Med 1988;84:1-9.
32. Carney RM, Freedland KE, Ludbrook PA, et al. Major depression, panic disorder, and mitral valve prolaspe in patients who complain of chest pain. Am J Med 1990;89:757-60.
33. Colgan SM, Schofield PM, Whorwell PJ, et al. Angina-like chest pain: a joint medical and psychiatric investigation. Postgrad Med J 1988;64:743-6.
34. Ho KY, Yang JY, Yeo B, et al. Non-cardiac, non-oesophageal chest pain: the relevance of psychological factors. Gut 1998;43: 105-10.
35. Lantinga LJ, Sprafkin RP, McCroskery JH, et al. One-year psychosocial follow-up of patients with chest pain and angiographically normal coronary arteries. Am J Cardiol 1988; 62:209-13.
36. Beitman BD, Kushner MG, Basha I, et al. Follow-up status of patients with angiographically normal coronary arteries and panic disorder. JAMA 1991;265:1545-9.
37. Costa PT, Fleg JL, McCrae RR, et al. Neuroticism, coronary artery disease, and chest pain omplaints: cross-sectional and longitudinal studies. Exp Aging Res 1982;8:37-44.
38. Bass C, Wade C, Hand D, et al. Patients with angina with normal or near normal coronary arteries: clinical and psychosocial state 12 months after angiography. Br Med J 1983;287:1505-8.
39. Beitman BD, Mukerji V, Lamberti JW, et al. Panic disorder in patients with chest pain and angiographically normal coronary arteries. Am J Cardiol 1989;63:1399-403.
40. Klimes I, Mayou RA, Pearce MJ, et al. Psychological treatment for atypical non-cardiac chest pain: a controlled evaluation. Psychol Med 1990;20:605-11.
41. Cox ID, Hann CM, Kaski JC. Low dose imipramine improves chest pain but not quality of life in patients with angina and normal coronary angiograms. Eur Heart J 1998;19:250-4.
42. Cannon RO 3rd, Quyyumi AA, Mincemoyer R, et al. Imipramine in patients with chest pain despite normal coronary angiograms. N Engl J Med 1994;330:1411-7.
43. Sarrel PM, Lindsay D, Rosano GM, et al. Angina and normal coronary arteries in women: gynecologic findings. Am J Obstet Gynecol 1992;167:467-71.
44. Rosano GM, Collins P, Kaski JC, et al. Syndrome X in women is associated with oestrogen deficiency. Eur Heart J 1995;16: 610-4.
45. Albertsson PA, Emanuelsson H, Milsom I. Beneficial effect of treatment with transdermal estradiol-17-beta on exercise-induced angina and ST segment depression in syndrome X. Int J Cardiol 1996;54:13-20.
46. Rosano GM, Peters NS, Lefroy D, et al. 17-beta-Estradiol therapy lessens angina in postmenopausal women with syndrome X. J Am Coll Cardiol 1996;28:1500-5.
47. Meeder JG, Blanksma PK, van der Wall EE, et al. Coronary vasomotion in patients with syndrome X: evaluation with positron emission tomography and parametric myocardial perfusion imaging. Eur J Nucl Med 1997;24:530-7.
48. Cannon RO 3rd, Curiel RV, Prasad A, et al. Comparison of coronary endothelial dynamics with electrocardiographic and left ventricular contractile responses to stress in the absence of coronary artery disease. Am J Cardiol 1998;82:710-4.
49. Buchthal SD, den Hollander JA, Merz CN, et al. Abnormal myocardial phosphorus-31 nuclear magnetic resonance spectroscopy in women with chest pain but normal coronary angiograms. N Engl J Med 2000;342:829-35.
50. Maseri A. Chest pain and Normal coronary arteries. N Engl J Med 2000;343:511-2.
51. Cannon RO 3rd, Balaban RS. Chest pain in women with normal coronary angiograms. N Engl J Med 2000;342:885-7.