CLINICAL RESEARCH

Value of measuring end tidal partial pressure of carbon dioxide as an adjunct to treadmill exercise testing

JOHN B CHAMBERS, PETER J KIFF, WILLIAM N GARDNER, GRAHAM JACKSON, CHRISTOPHER BASS

Abstract

The end tidal partial pressure of carbon dioxide (P_{CO_2}) was measured during treadmill exercise in 30 normal controls and 113 patients referred for assessment of chest pain. Among the 92 patients without significant ST depression hypocapnia occurred more often in those reporting "typical" than "atypical" chest pain (17 of 22 patients compared with 29 of 70; $p<0.01$). Hypocapnia was uncommon in patients with significant ST depression whether reporting typical or atypical chest pain (one of 10 patients and two of 11, respectively).

Hypocapnia at rest (P_{CO_2} <4 kPa) occurred in 16 (14%) patients but in only one control. Hypocapnia occurred during or after exercise in only one control and three of the 21 patients with significant ST depression on exercise (group 1). The remaining 92 patients were divided into those with a history suggestive of hyperventilation (group 2; n=30) and those without (group 3; n=62). Hypocapnia developed significantly more often in both these groups (21 and 25 patients respectively) than in controls or patients with significant ST depression.

An abnormal response of the P_{CO_2} to exercise provided objective data to support a clinical suspicion of chest pain induced by hyperventilation in 24 cases, suggested a cause for equivocal ST depression other than coronary stenosis in five patients, and led to the diagnosis of previously unsuspected respiratory disease in 14 patients.

Measurement of end tidal P_{CO_2} gives additional valuable diagnostic information during the conventional treadmill exercise test in patients with both typical and atypical chest pain.

King's College Hospital, London SE5 9RS
JOHN B CHAMBERS, MA, MRCP, research fellow, cardiac unit
PETER J KIFF, MA, MRCP, registrar, cardiac unit
WILLIAM N GARDNER, DPHIL, MRCP, senior lecturer, department of thoracic medicine
GRAHAM JACKSON, MB, FRCP, consultant, cardiac unit
CHRISTOPHER BASS, MD, MRCPSYCH, senior lecturer, academic department of psychological medicine

Correspondence to: Dr Chambers.

Introduction

Hyperventilation may mimic ischaemic heart disease by provoking chest pain[1 2] or ST segment changes in the electrocardiogram.[3 4] This may cause diagnostic uncertainty, and it is important to improve the power of non-invasive tests to avoid excessive reliance on diagnostic angiography.[5 6]

Voluntary overbreathing at rest reproduces chest pain in only 40-50% of patients thought to have symptoms induced by hyperventilation,[1 5 7] many of whom may be normocapnic at rest. Gardner *et al* found that hypocapnia may be precipitated or exacerbated by light exercise,[8] which prompted us to measure the end tidal partial pressure of carbon dioxide (P_{CO_2}) during standard electrocardiographic stress testing.

This paper aims at establishing the incidence of hypocapnia before and during routine treadmill exercise and examines the relation between the development of hypocapnia, symptoms suggestive of hyperventilation, and the reproduction of symptoms by voluntary overbreathing at rest.

Subjects and methods

Consecutive patients on routine exercise test lists between November 1985 and April 1986 were entered for the study. Patients were referred from all medical outpatient clinics, and there were no standardised criteria for requesting exercise tests nor standardised screening investigations. Patients were excluded from the study only if referral was for indications other than chest pain—for example, suspected cardiac arrhythmia—or if there was documented poor left ventricular function, valvular heart disease, or a resting electrocardiographic abnormality such as bundle branch block. Unmatched controls were recruited from "clinically naive" hospital paramedical and secretarial staff and their relatives. None complained of chest pain or other relevant symptoms.

Interview was conducted by one of us (CB) immediately before the exercise test. Demographic data and a description of complaints of chest pain and breathlessness were recorded by using a questionnaire modified from Master[9] and one designed by us. Chest pain was considered typically cardiac if it was precipitated on exercise more than seven times out of 10 by a particular stressor and relieved by rest within five minutes. The quality and location of the pain were not used as criteria, though 28 of the 32 patients with "typical" pain had aching, diffuse pain in a band across the chest. Pain was regarded as "atypical" if it was not precipitated by exertion or not relieved by rest. Significant breathlessness was defined by the presence of

five or more of the following 10 symptoms[10]: breathlessness at (*a*) rest or during (*b*) conversation or (*c*) trivial exertion; breathlessness precipitated by (*d*) emotion or (*e*) particular settings such as crowds or supermarkets; breathlessness of (*f*) sudden onset or (*g*) preceded or (*h*) followed by chest pain; (*i*) "air hunger" or (*j*) a feeling of suffocation. The questions were designed to detect patients with psychogenic breathlessness, possibly associated with hyperventilation, but were not intended to exclude patients with lung disease.

Treadmill test—Investigators conducting the treadmill test were unaware of the findings at interview but had the routine clinical summary written on the request form. Antianginal agents were stopped routinely 48 hours before the test. A standard, semiautomatic treadmill system was used, producing electrocardiograms at the end of every three minute stage, at peak exercise, and every two minutes throughout a 10 minute recovery period. A conventional Bruce protocol was used with a maximum of five three minute stages increasing in speed from 1·7 to 5·0 mph (2·7 to 8·0 kph) and in gradient from 10% to 18%.[11] Subjects were given a description of the test and asked to report the first appearance of pain or of any other symptom. During the test they were asked to describe any symptom at the time it occurred and to state whether it was similar to the symptoms discussed in the pretest interview. ST depression was measured 80 ms after the J point over at least three successive complexes. It was considered indicative of ischaemia if there was 1·5 mm or more depression of any morphology with or without chest pain or 1·0 mm planar or downsloping ST depression only if associated with typical cardiac pain. ST depression was measured relative to the resting traces, two of which had minor ST depression. All the electrocardiograms were reported by one of us (JC).

End tidal P_{CO_2}—An infrared capnograph (Gould mark 4) with a 0-95% response time of 0·1 s was calibrated with 5% carbon dioxide before and after each session. Tidal air was sampled by an Engstrom Aridus sampling line taped just inside one nostril after checking that the nasal passage was clear. A continuous record was made on a paper chart recorder running at 5 mm/s. Obvious plateaus on the recorded signal could not be obtained in one case, in which the trace was therefore rejected.[12] Recordings were made for at least one minute at rest, throughout exercise, and during a 10 minute recovery period. End tidal P_{CO_2} and respiratory rate were averaged over the 15 seconds before and after each minute marker. All measurements were performed by JC. In our laboratory the lower 95% limit for P_{CO_2} in normal people at rest is 4·3 kPa.[8] For this study we adopted a stricter definition of hypocapnia—namely, a P_{CO_2} below 4·0 kPa at rest before the start of the test, at any time during exertion, or for more than five minutes during the 10 minute recovery period. Figure 1 gives examples of normal and abnormal traces of P_{CO_2}.

Lung function testing—At the end of the 10 minute recovery phase the mean of three peak expiratory flow rate recordings was taken with a Wright peak flow meter whenever this was available. All patients who developed hypocapnia during exercise or complained of breathlessness on exertion[13] were given further lung function tests. These consisted of measurement of forced expiratory volume in one second, slow vital capacity, and single breath carbon monoxide diffusion coefficient. The normal range was taken as >80% of the predicted value.

Hyperventilation provocation test was performed at least one week after the exercise test. It was offered to all subjects, but some were unable to reattend or could not be contacted. The investigator (CB) was not aware of the result of the exercise test. The same capnograph as above and an electrocardiographic system using a single chest lead (usually V5) were attached. Each patient was seated in a comfortable armchair and asked to overbreathe to a P_{CO_2} <2·7 kPa for three minutes.[12] Afterwards a standard questionnaire was given assessing how many of the patient's usual symptoms, including chest pain, were reproduced by the test. The result of the test was considered positive only if chest pain recognised as the patient's usual pain was reproduced.

Statistical analysis—The data were analysed by using the statistical package for the social sciences program (SPSSX) of the University of London computer. Results were expressed as means and standard deviations. One way analysis of variance and a χ^2 test with Yates's correction were used.

Results

One hundred and twenty one patients were referred for routine exercise testing. Of these, five were excluded and data were missing in three. The remaining 113 patients had a mean age of 53 (SD 12) years, and 69 (61%) were male. Seventy three patients (65%) were employed, 19 (17%) had a history of myocardial infarction, and 11 (10%) had had coronary vein grafting. Two patients had histories suggestive of cervical spondylosis and five were thought to have symptoms of acid reflux. The 30 controls had a mean age of 45 (SD 10) years and 16 (53%) were male. All were in employment and none had cardiac or other disease.

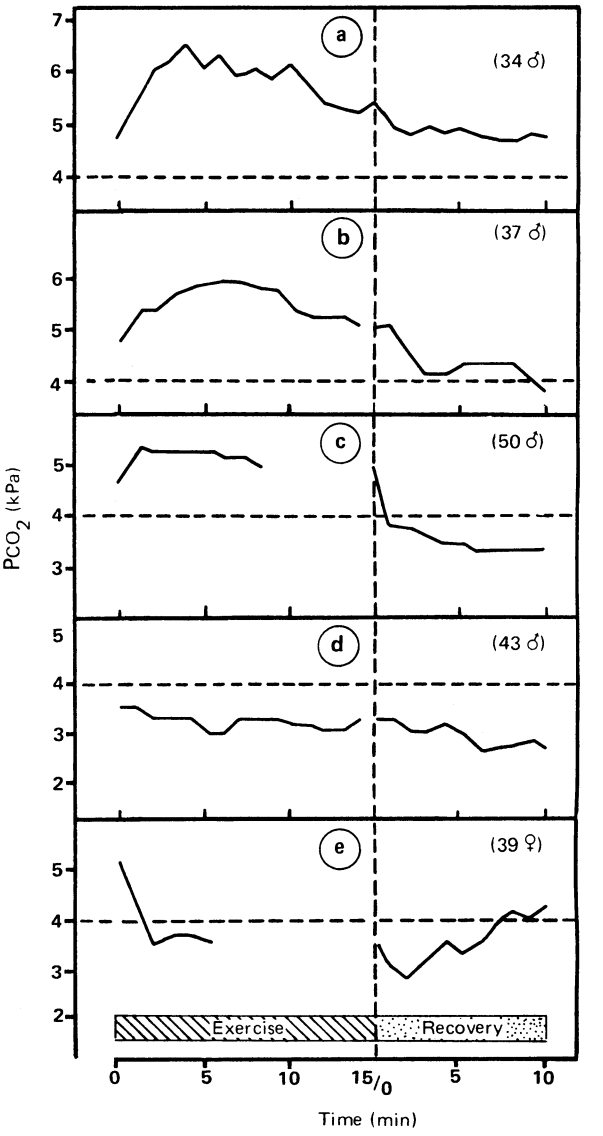

FIG 1—Examples of response of P_{CO_2} to exercise testing. (Numbers and sex of subjects on whom examples based given in parentheses.) (*a*) Normal response: P_{CO_2} above 4 kPa throughout test; this pattern found in 22 (73%) controls and 46 (41%) patients. (*b*) Normal response: P_{CO_2} below 4 kPa for five minutes or less during recovery; this pattern observed in 7 (23%) controls and 18 (16%) patients. (*c*) Abnormal response: P_{CO_2} below 4 kPa for more than five minutes during recovery; this pattern seen in only one control (3%): but 21 (19%) patients. (*d*) Abnormal response: P_{CO_2} below 4 kPa during exercise; this pattern not seen in controls but occurred in 28 (25%) patients. (*e*) Abnormal response: failure of P_{CO_2} to rise by end of first minute of exercise, found in 24 (21%) patients but in no control.

CLINICAL AND ELECTROCARDIOGRAPHIC FINDINGS

At the interview 32 patients reported "typical" and 81 "atypical" chest pain. These patients were divided into three mutually exclusive groups according to the possible mechanisms of pain production—namely, ischaemic heart disease, hyperventilation, and "uncertain" (table I). All 21 patients (19%) who developed significant ST depression during the study were assigned to group 1. The remaining 92 patients were further divided into 30 patients (27%; group 2) who admitted breathlessness suggestive of hyperventilation during the interview and 62 patients (55%; group 3) who did not. No patient in group 2 had significant ST depression, but two patients in group 1 and one control admitted breathlessness. Cardiac

TABLE I—*Clinical groups and incidence of hypocapnia in patients with typical and atypical pain. Results expressed as numbers (percentages) of patients*

	Group 1 (n=21)	Group 2 (n=30)	Group 3 (n=62)	Hypocapnia (n=49)
Typical pain (n=32)	10 (48)	11 (37)	11 (18)	18 (37)
Atypical pain (n=81)	11 (52)	19 (63)	51 (82)	31 (63)

catheterisation was performed in 18 patients in group 1, in all of whom coronary stenoses were confirmed. Coronary angiography was performed in 11 patients in groups 2 and 3, of whom six (55%) had hypocapnia. Normal coronary arteries were shown in all.

Hypocapnia occurred more commonly in patients without significant ST depression who reported typical (17 of 22) rather than atypical pain (29 of 70) ($p<0.01$). Hypocapnia was uncommon in patients with ischaemic exercise test results whether they reported typical (one of 10) or atypical pain (two of 11).

Minor ST depression occurred in 10 patients (33%) in group 2 and 10 (16%) in group 3. Chest pain developed during the test in 15 patients (50%) in group 2 and 22 (35%) in group 3. No control had electrocardiographic criteria of ischaemia or chest pain during the procedure.

Table II shows the haemodynamic responses to treadmill exercise. The higher peak pulse rate in controls was probably explained by their longer exercise time and because none had been treated with β blockers. Both peak and resting blood pressures were higher in groups 1 and 3 than in the other two groups.

TABLE II—*Exercise test data in patients and controls. Values are means (SD)*

	Controls (n=30)	Group 1 (n=21)	Group 2 (n=30)	Group 3 (n=62)	F Value
Age (years)	45 (10)	58 (7)	54 (15)	51 (15)	11·5 ($p<0.001$)
Exercise time (s)	704 (123)	437 (145)	387 (190)	593 (189)	21·5 ($p<0.001$)
Resting systolic blood pressure (mm Hg)	122 (19)	144 (34)	125 (18)	138 (21)	6·4 ($p<0.001$)
Peak systolic blood pressure (mm Hg)	173 (24)	188 (27)	156 (24)	177 (27)	7·1 ($p<0.001$)
Resting pulse rate (beats/min)	83 (15)	77 (15)	78 (18)	80 (19)	0·6
Peak pulse rate (beats/min)	165 (14)	147 (22)	144 (31)	160 (23)	5·7 ($p<0.001$)
Maximum ST depression (mm)	0·1 (0·4)	1·7 (1·0)	0·1 (0·4)	0·2 (0·4)	56·0 ($p<0.00001$)

TABLE III—*Numbers of patients and controls reaching each minute of exercise up to nine minutes and results of analysis of variance at each minute during exercise period*

	Time (minutes)									
	0	1	2	3	4	5	6	7	8	9
Controls	30	30	30	30	30	30	30	29	29	29
Group 1	21	21	21	20	18	17	15	12	9	8
Group 2	30	29	29	25	20	17	15	13	11	9
Group 3	62	62	61	61	59	59	59	52	49	44
F Value	4·9*	10·8†	14·4†	10·4†	8·4†	5·3‡	6·0‡	6·4‡	5·2*	4·7*

*$0.002<p<0.005$.
†$p<0.00001$.
‡$0.0005<p<0.002$.

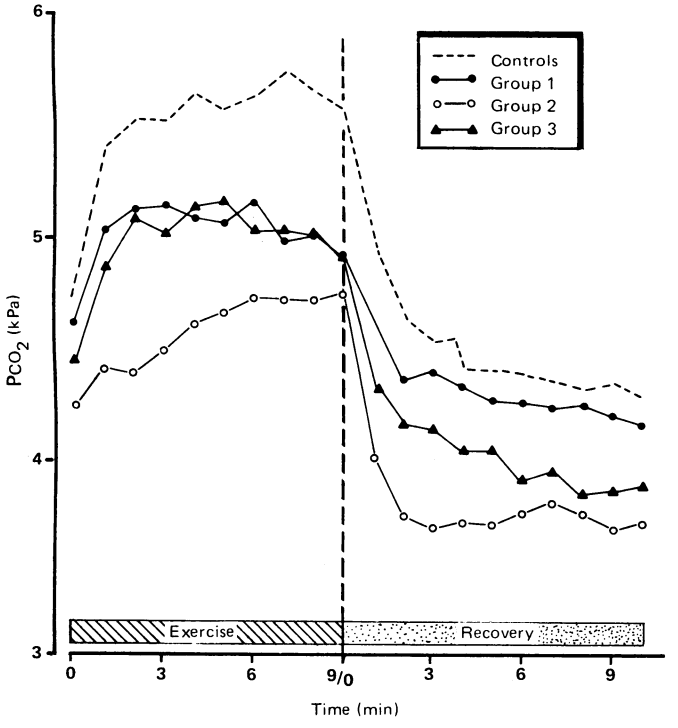

FIG 2—Mean responses of end tidal P_{CO_2} to exercise in controls (n=30) and three groups of patients—group 1 (significant ST depression on exercise; n=21), group 2 (breathlessness but no significant ST depression; n=30), group 3 (no significant ST depression and no breathlessness; n=62). (There was progressive reduction in numbers of patients reaching each minute of exercise, and no further calculations were made beyond nine minutes (see table III). Every patient was studied throughout the 10 minute recovery period, when analysis of variance showed significant group differences ($p<0.001$) at each minute.)

PATTERNS OF RESPONSE OF P_{CO_2} TO EXERCISE

Controls—In the 30 controls mean end tidal P_{CO_2} rose by 0·7 kPa in the first minute of exercise above a resting value of 4·8 kPa. It then rose more slowly to a maximum of 5·7 kPa before falling in the final minutes of exercise. It continued to fall throughout recovery to about 0·5 kPa below the resting value (fig 2). The pattern in individual controls was similar. In 22 the P_{CO_2} remained above 4·0 kPa throughout the study (fig 1 *a*), and in seven it fell below 4·0 kPa in the latter part of recovery but always for less than five minutes (fig 1 (*b*)). These response patterns were normal by the criteria used for this study. In one control the resting P_{CO_2} was below 4·0 kPa, rose normally during exercise, but fell below 4·0 kPa for longer than five minutes during recovery. This pattern fitted the criteria for abnormality.

Patients—Mean P_{CO_2} in the breathless patients (group 2) was lower throughout the study than in controls. There was a smaller rise in the first minute of exercise and a lower maximum. The minimum during recovery was reached three minutes earlier. Mean responses of P_{CO_2} in groups 1 and 3 were similar and lay in an intermediate position between the controls and group 2 (fig 2). Interpretation of the mean response, however, was made difficult by progressive attrition of patients during exercise (table III). Furthermore, the mean response obscured important differences in the pattern of behaviour of P_{CO_2} in individual patients. Normal patterns (fig 1 (*a*), (*b*)) occurred in 18 of the 21 patients in group 1 but in only nine patients in group 2 and 37 (60%) in group 3. In a total of 28 patients hypocapnia occurred during exercise (fig 1 (*d*)) and in 21 for more than five minutes during recovery (fig 1 (*c*)). The total incidence of hypocapnia during both recovery and exercise (table IV) was not significantly different in group 1 (three cases) from controls (one case), but was significantly greater in group 2 (21 cases; $p<0.001$) and group 3 (25 cases; $p<0.05$). Hypocapnia was present at rest before the start of the test in 16 (14%) of the 113 patients but in only one control. This difference did not attain statistical significance. In 10 subjects the P_{CO_2} began to rise normally at the start of exercise but always returned to below 4·0 kPa either during exercise (four cases) or during recovery (five patients and the control). In the remaining seven patients the P_{CO_2} stayed consistently below 4·0 kPa. Resting hypocapnia was not seen in group 1. A separate criterion of abnormality was defined by the absence of the normal rise in P_{CO_2} during the first minute of exercise ("failure to rise"; fig 1 (*e*)). In the 24 patients with this pattern chest pain was reported to be provoked more frequently by exercise (14 patients *v* 24; $p<0.01$) and by emotion (19 patients *v* 40; $p<0.01$) compared with the 89 patients with a normal rise. "Failure to rise" did not occur in controls and was observed

TABLE IV—*Patterns of response of P_{CO_2} to exercise by clinical group. Results expressed as numbers (percentages) of subjects*

	Controls (n=30)	Group 1 (n=21)	Group 2 (n=30)	Group 3 (n=62)
Normal (fig 1(*a*)(*b*))	29 (97)	18 (86)	9 (30)*	37 (60)
Hypocapnia during recovery (fig 1(*c*))	1 (3)	2 (10)	9 (30)	10 (16)
Hypocapnia on exercise (fig 1(*d*))	0	1 (5)	12 (40)†	15 (24)
Failure to rise (fig 1(*e*))	0	2 (10)	15 (50)‡	7 (11)

Compared with group 1 (χ^2 test): *$p<0.001$; †$0.01<p<0.02$; ‡$0.005<p<0.01$.

more commonly in group 2 (15 of 30 patients) than in either group 1 (2/21; $p<0.01$) or group 3 (7/62; $p<0.001$). Nineteen patients with this pattern also developed hypocapnia.

LUNG FUNCTION TESTS

Full lung function tests were performed in 34 patients. Ten patients, all in group 2, showed abnormalities. Two had reduced gas transfer consistent with interstitial lung disease, and both had resting hypocapnia. Three had definite and five possible airflow obstruction, all of whom developed hypocapnia on exercise. In a further 21 patients all test results were normal, but nine of them had minor reversibility after using bronchodilators, which would be consistent with asthma in remission. One patient could not hold the breath long enough to perform an adequate test, and two had borderline reductions in both expiratory volume in one second and vital capacity, making interpretation unreliable. A further 44 patients had measurement of peak expiratory flow rate. Of these, 33 had normal, seven low, and four borderline values. Four with abnormal and two with borderline values had developed hypocapnia. One control had a borderline result. These findings suggest that in at least 14 of 49 patients who developed hypocapnia the hyperventilation observed may have been secondary to mild lung disease not diagnosed at the initial outpatient assessment.

HYPERVENTILATION PROVOCATION

Overbreathing reproduced the patient's characteristic chest pain in 17 of a total of 46 provocation tests. The test gave a positive result in seven of 17 patients who developed hypocapnia on exercise, five of 13 patients who had hypocapnia only during recovery, and five of 16 patients who did not develop hypocapnia. Two patients in group 1 had provocation tests, both of which gave negative results. Test results were positive in 12 of 20 patients in group 2 compared with five of 24 in group 3 ($p<0.001$).

As a predictor of membership of group 2 a positive hyperventilation provocation test result had a sensitivity of 60% and a specificity of 79%. By comparison, the development of hypocapnia or failure of the P_{CO_2} to rise in the first minute of exercise gave a sensitivity of 80% and a specificity of 64%. Two patients in group 2 who had normal P_{CO_2} response patterns had positive provocation test results, whereas seven patients with negative results developed abnormal P_{CO_2} patterns.

These results suggest that development of hypocapnia during the exercise protocol does not reliably predict reproduction of chest pain provoked at rest by voluntary overbreathing. Despite this, group 2, which had the highest rate of hypocapnia during the exercise test, also had the highest incidence of positive hyperventilation provocation test results.

Discussion

This is the first study of the response of P_{CO_2} during exercise testing by the Bruce protocol, though the response to light exercise has been well described.[14-16] We have shown a significantly higher incidence of hypocapnia during exercise testing in patients with non-ischaemic chest pain (46/92) than in ischaemic patients (3/21) and controls (1/30).

The aim of the study was exploratory, and it was appropriate to adapt a routine conventional exercise test rather than construct a more focused study group. Further investigations were therefore undertaken only when indicated clinically. Our ischaemic group was defined by the ST response to exercise, and possibly some patients with no or minor ST changes were wrongly assigned. Nevertheless, it is unlikely that we included many patients with false positive results in our ischaemic group as we used 1·5 mm rather than 1·0 mm ST depression as a criterion of ischaemia. Furthermore, angiography, performed in 18 of the 21 patients, confirmed coronary stenoses in all. The true incidence of respiratory abnormalities in this study is not certain because we did not investigate every patient. Although it is unlikely that we underestimated the incidence to any great extent, future studies should define clinical groups with greater certainty by performing lung function tests and catheterisation in all patients.

The patterns of response of P_{CO_2} to exercise described here have not been reported before. We found a high incidence of transient hypocapnia during recovery, usually in the second half, and adopted five minutes as an arbitrary cut off between "normal" and "abnormal." We believe that this was a realistic distinction because it separated controls and ischaemic patients on the one hand from patients with symptoms suggestive of hyperventilation on the other. None the less, further validation of this threshold should be undertaken. We used a fall in P_{CO_2} below 4·0 kPa as a simple and convenient criterion of abnormality. In future studies it might be worth using additional criteria such as the rate of rise or fall of P_{CO_2}, the difference between resting and maximum values, or the absolute minimum P_{CO_2} attained during the test.

Arterial P_{CO_2} remains constant or increases slightly during light exercise but decreases during heavy exercise with the onset of anaerobic respiration.[14 16] End tidal P_{CO_2} is close to arterial P_{CO_2} at rest but is slightly higher during exercise,[14] and the difference depends on the rate of production of carbon dioxide and tidal volume.[17] This may explain some of the initial rise in end tidal P_{CO_2} shown by 89 patients in this study and the tendency for values to fall towards the end of exercise. There were 24 patients in whom the P_{CO_2} failed to rise during the first minute of exercise, and these reported pain that occurred significantly more often on exercise or with emotion than those with normal rises. Possibly either the anticipation of exercise or anxiety caused by the treadmill made them hyperventilate at the start of exercise.

Most respiratory disorders—particularly mild airflow obstruction—can cause hypocapnia, and in our population 21 of the 78 patients tested had abnormalities of lung function. Possibly in some of these the abnormality was spurious as a consequence of the patients' inability to perform the test adequately. In most cases a range of further tests such as histamine bronchial challenge or bronchoalveolar lavage would have been required to establish airflow obstruction. We believe that hyperventilation should prompt a search for possible underlying respiratory or psychiatric disorder and should not be regarded as a primary diagnosis until these have been excluded. It is also possible that patients with psychiatric morbidity may report disproportionate breathlessness in the presence of mild lung disease.[18]

Normocapnia at rest does not exclude the possibility of symptoms induced by hyperventilation, and hypocapnia may be precipitated by specific stressors.[12] In this study only 17% (16/92) of non-ischaemic patients had hypocapnia at rest but hypocapnia occurred during the exercise protocol in half. Exercise testing provided objective evidence to support the clinical suggestion of hyperventilation in 24 (80%) patients with breathlessness (group 2). The development of hypocapnia during the exercise protocol, however, did not reliably predict the reproduction of pain by voluntary overbreathing at rest. These results confirm that treadmill exercise and voluntary overbreathing are complementary stressors, both of which should be used to establish a diagnosis of symptoms induced by hyperventilation.[8] Possibly psychological stressors (anxiety provoking thoughts or images) may precipitate hypocapnia[19] in those patients with symptoms suggestive of hyperventilation but in whom exercise testing and voluntary overbreathing at rest give negative results.

Measurement of end tidal P_{CO_2} provided important additional information in 23 of 92 exercise tests that gave "equivocal" or negative results by electrocardiographic criteria. It showed hypocapnia in 17 and failure of the P_{CO_2} to rise normally in a further two patients with typical cardiac pain but no significant ST depression. In these hyperventilation may be an alternative cause of chest pain.[10] Four of six patients with equivocal ST depression (1 mm in the absence of chest pain) had definite hypocapnia at the onset of ST depression. The other two had no hypocapnia but had a history of unequivocal myocardial infarctions, and in these the ST changes were likely to have been ischaemic. There are, however, other causes of chest pain which we did not assess formally. One patient had pain associated with both hypocapnia and 1 mm ST depression, which might have been caused by coronary spasm. Other patients had symptoms suggestive of cervical spondylosis or oesophageal disorders.

Of our patients with no significant ST depression on exertion, 17 of 22 with "typical" pain and 29 of 70 with "atypical" pain developed hypocapnia. Similar figures were reported by de Caestecker *et al* for the incidence of oesophageal abnormalities in

patients with normal coronary arteries and typical (17 of 24) or atypical pain (eight of 19).[20] Possibly hyperventilation and oesophageal abnormalities are not mutually exclusive. Hypocapnia has been reported to induce disorders of oesophageal motility.[21] Non-cardiac chest pain is a heterogeneous disorder and is unlikely to be caused by a single aetiological factor. In some patients more than one pathophysiological mechanism may be implicated. A systematic study in individual patients that takes account of oesophageal abnormalities, hyperventilation, and psychiatric disorders should now be undertaken.

We thank Dr Derek Cooper for the computer analysis and Derek Lowe for statistical advice; Sally Green, Tracy Ford, and Penny Barton for the lung function tests; the Wellcome Trust for financial support to buy equipment; and Dr David Jewitt, Dr John Costello, and Len Smith for the use of their laboratory facilities. JBC was supported by a grant from the Peel Medical Trust.

References

1 Evans DW, Lum LC. Hyperventilation: an important cause of pseudoangina. *Lancet* 1977;i: 155-7.
2 Magarian GJ. Hyperventilation syndromes: infrequently recognised common expressions of anxiety and stress. *Medicine* 1982;**61**:219-36.
3 Lary D, Goldschlager N. Electrocardiographic changes during hyperventilation resembling myocardial ischemia in patients with normal coronary arteriograms. *Am Heart J* 1974;**87**: 383-90.
4 Joy M, Trump DW. Significance of minor ST segment and T wave changes in the resting electrocardiogram of asymptomatic subjects. *Br Heart J* 1981;**45**:48-55.
5 Bass C. Unexplained chest pain: psychosocial studies in presumptive angina. London: University of London, 1984. (MD thesis.)
6 Bass C, Cawley R, Wade C, *et al*. Unexplained breathlessness and psychiatric morbidity in patients with normal and abnormal coronary arteries. *Lancet* 1983;i:605-9.
7 Wood P. Da Costa's syndrome (or effort syndrome). *Br Med J* 1941;i:767-72, 805-11, 845-51.
8 Gardner WN, Meah MS, Bass C. Controlled study of respiratory responses during prolonged measurement in patients with chronic hyperventilation. *Lancet* 1986;ii:826-30.
9 Master AM. The spectrum of anginal and noncardiac chest pain. *JAMA* 1964;**187**:104-9.
10 Bass C, Wade C, Hand D, Jackson G. Patients with angina with normal and near normal coronary arteries: clinical and psychosocial state 12 months after angiography. *Br Med J* 1983;**283**: 1505-8.
11 Bruce RA. Exercise testing of patients with coronary heart disease: principles and normal standards for evaluation. *Ann Clin Res* 1971;**3**:323-32.
12 Bass C, Gardner WN. Respiratory and psychiatric abnormalities in chronic symptomatic hyperventilation. *Br Med J* 1985;**290**:1387-90.
13 Fletcher CM. The clinical diagnosis of pulmonary emphysema. An experimental study. *Proceedings of the Royal Society of Medicine* 1952;**45**:577-84.
14 Wasserman K, van Kessel AL, Burton GG. Interaction of physiological mechanisms during exercise. *J Appl Physiol* 1967;**22**:71-85.
15 Ferguson A, Addington WW, Gaensler EA. Dyspnea and bronchospasm from inappropriate postexercise hyperventilation. *Ann Intern Med* 1969;**71**:1063-72.
16 Dejours P. Control of respiration in muscular exercise. In: Fenn WO, Rahn H, eds. *Handbook of physiology. Vol 1: sec 3*. Washington: American Physiological Society, 1964-5:631-48.
17 Jones NL, Robertson DG, Kane JW. Difference between end-tidal and arterial pCO_2 on exercise. *J Appl Physiol* 1979;**47**:954-60.
18 Burns BH, Howell JBL. Disproportionately severe breathlessness in chronic bronchitis. *Q J Med* 1969;**38**:277-94.
19 Freeman LJ, Conway A, Nixon PGF. Physiological responses to psychological challenge under hypnosis in patients considered to have the hyperventilation syndrome: implication for diagnosis and therapy. *J R Soc Med* 1986;**79**:76-83.
20 de Caestecker JS, Blackwell JN, Brown J, Heading RC. The oesophagus as a cause of recurrent chest pain: which patients should be investigated and which tests should be used? *Lancet* 1985;ii:1143-6.
21 Rasmussen K, Ravnbaek J, Funch-Jensen P, Bagger JP. Oesophageal spasm in patients with coronary artery spasm. *Lancet* 1986;i:174-6.

(Accepted 2 February 1988)

Identifying people at high risk of cutaneous malignant melanoma: results from a case-control study in Western Australia

DALLAS R ENGLISH, BRUCE K ARMSTRONG

Abstract

To assess whether screening people at high risk of malignant melanoma would be effective in reducing the mortality from the disease data from 400 case-control pairs in a study of cutaneous malignant melanoma conducted in Western Australia during 1980-1 were used to predict the risk of melanoma in the remaining 111 pairs. All variables previously shown to be associated with a decrease or increase in the incidence of melanoma were considered for inclusion in a single conditional logistic regression model of the incidence of melanoma in the randomly chosen subset of 400 case-control pairs. Five of these variables—number of raised naevi on the arms, arrival in Australia before 10 years of age, history of non-melanocytic skin cancer, time spent outdoors in summer from the age of 10 to 24, and family history of melanoma—provided good discrimination between patients and controls in this sample and the 111 other case-control pairs. Among the 222 subjects in these other case-control pairs a group defined as being at high risk of melanoma by a risk score derived from these five variables contained 60 (54%) of the patients with melanoma but only 18 (16%) of the controls.

These data suggest that in Western Australia more than half of all new patients with melanoma arise in an identifiable subpopulation constituting less than one fifth of the whole population. Identifying this subpopulation and screening it regularly for cutaneous malignant melanoma could be cost effective in reducing mortality from this disease.

National Health and Medical Research Council Research Unit in Epidemiology and Preventive Medicine, University Department of Medicine, Queen Elizabeth II Medical Centre, Nedlands 6009, Western Australia

DALLAS R ENGLISH, PHD, senior research officer
BRUCE K ARMSTRONG, DPHIL, FRACP, director and professor of epidemiology and cancer research

Correspondence to: Dr English.

Introduction

Cutaneous malignant melanoma is an important public health problem in Australia. Queensland has the world's highest recorded incidence of the disease (39·6/100 000 person years[1]), and the incidences in other states, particularly Western Australia, are also high.[2] Mortality from melanoma in Australia has risen steadily since the 1930s,[3] and similar trends have been observed in other countries.[4] Although the relative survival after diagnosis of melanoma in Australia is 85-90% at five years,[5] about 600 people still die from malignant melanoma each year, and it ranks 10th among cancers as a cause of death.[2]

Provided that effective measures are available for treating patients whose melanoma has been diagnosed early, programmes for early detection should be effective in reducing morbidity and mortality from this disease. Screening the whole population, however, may not be cost effective because most people (98% even