Mechanism of disease: Update

Chest pain and the hyperventilation syndrome – some aetiological considerations

Leisa J. Freeman and P.G.F. Nixon

Cardiac Department, Charing Cross Hospital (Fulham), Fulham Palace Road, Hammersmith, London W6 8RF, UK.

Chest pain is reported in 50–100% of patients with the hyperventilation syndrome (Lewis, 1953; Yu *et al.*, 1959). The association was first recognized by Da Costa (1871) ‘... the affected soldier, got out of breath, could not keep up with his comrades, was annoyed by dizziness and palpitation and with pain in his chest ... chest pain was an almost constant symptom ... and often it was the first sign of the disorder noticed by the patient’. The association of hyperventilation and chest pain with extreme effort and disorders of the heart and circulation was acknowledged in the names subsequently ascribed to it, such as vasomotor ataxia (Colbeck, 1903); soldier’s heart (Mackenzie, 1916 and effort syndrome (Lewis, 1918).

In 1941, Paul Wood declared that hyperventilation played a minor and subsidiary role in the production of chest pain in this syndrome and he considered the basic disorder to be psychiatric. This view has continued, with a few notable exceptions, in English cardiological circles (Evans & Lum, 1977; Nixon, 1982). Friedman (1945) was the first to describe two distinct types of chest pain. A dull, aching and predominantly left sided pain in 42% of patients was considered to be due to fatigue of the intercostal muscles. In the remainder, the pain was sharp, piercing and less sustained, and was associated with forceful heart beatings, considered to reflect undamped autonomic nervous discharge. A third type of pain was added by Wheatley (1975) and Margarian (1982). They described a heavy substernal pain radiating to the neck and arms whose characteristics were sufficiently similar to Heberden’s angina so as to cause diagnostic confusion in some cases.

The extent of this difficulty is highlighted by a recent study of patients whose history of chest pain had convinced cardiologists that investigation with coronary arteriography was essential (Bass *et al.*, 1983). The hyperventilation syndrome was found in 62% of patients with normal/near normal coronary arteriograms and 7% of patients with abnormal

coronary arteriograms. Hyperventilation and ischaemic heart disease clearly were not mutually exclusive. This is a vital point. It is time for clinicians to accept that dynamic factors associated with hyperventilation are commonplace in the clinical syndromes of angina pectoris and coronary insufficiency. The production of chest pain in these cases may be better understood if the direct consequences of hyperventilation on circulatory and myocardial dynamics are considered.

The mechanical work of hyperventilation increases the cardiac output by a small amount (up to 1.3 l/min) irrespective of the effect of the blood carbon dioxide level and can be accounted for by the increased oxygen consumption that is caused by the overbreathing. When hyperventilation is performed with a gas mixture that ensures hypercapnia other circulatory responses are due to the elevated PaCO_2 such as peripheral venous dilatation, increased venous pressure, and a higher rate of ventilation. Hyperventilation with a gas mixture that induces the usual hypocapnia produces a fall of central venous pressure, a small fall of pulmonary artery pressure and a reduction of up to 40% in coronary blood flow. There is also a rise in arterial blood lactate. The left ventricular end diastolic pressure is unchanged (Richards, 1965), or increased (Al-Abassi *et al.*, 1984).

Neil & Hattenhauer (1975) have shown that hyperventilation interferes with myocardial oxygen supply in man by a combination of coronary vasoconstriction which decreases coronary blood flow, and an increase in the oxygen affinity of the blood in the coronary capillaries (Bohr shift to the left). Confusion about the effect of hyperventilation on coronary blood flow has resulted from experiments on dogs which, unlike man, hyperventilate naturally in order to lose heat.

In recent years the contribution of coronary spasm to the pathogenesis of cardiac pain has been increasingly recognized and the provocation of spasm has become a routine test in some laboratories. Ergonovine, tris buffer and hyperventilation, and more recently hyperventilation alone have been employed effectively. Girotti *et al.* (1982) have found that

Correspondence: L.J. Freeman, M.B., M.R.C.P.

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Figure 1 The mechanisms by which hyperventilation, causing a fluctuating reduction of the blood CO_2 tension, induces vasomotor instability and disturbances of function (courtesy of Abbasi personal communication). $[\]_o$ = extracellular concentration, e.g. $[\text{K}^+]_o \downarrow$ decreased concentration of extracellular ionized potassium. $[\]_i$ = intracellular concentration, e.g. $[\text{Ca}^{2+}]_i \uparrow$ increased intracellular concentration of ionized calcium. LVDP = Left ventricular end-diastolic pressure.

hyperventilation alone had a 70% sensitivity and 100% specificity for the production of spasm in such patients.

The falling carbon dioxide tension of the blood (PaCO_2) associated with hyperventilation causes a rapid migration of carbon dioxide from the cells and so the intracellular pH rises (Yasue *et al.*, 1981) (Figure 1). As a result the intracellular ionized calcium also rises, principally by two mechanisms which are both pH dependent (a more alkaline medium increases the amplitude of the response). There is an initial phase where tightly bound intracellular calcium ions are released from sites such as the sarcoplasmic reticulum and mitochondria which accounts for up to 70% of the maximum tension generated by the smooth muscle contraction. The slower and more tonic phase

occurs mainly due to the influx of freely exchangeable extracellular calcium ions into the cell through the 'slow calcium' channels, thus depleting the concentration of extracellular calcium ions. (It is only this phase that can be blocked by the calcium blocking agents such as verapamil and nifedipine) (Ginsberg *et al.*, 1980). This effect is probably not limited to the coronary arteries since spasm in forearm vessels and other arteries has occurred during provocation by hyperventilation, which suggests that these patients may have a generally higher degree of vasoconstrictor reactivity (Rasmussen *et al.*, 1984). The potent effect of hyperventilation on cerebral blood flow is also well documented. The earlier title of vasomotor ataxia applied to the hyperventilation syndrome is still apt.

Hyperventilation has also been known for some

time to produce 'pseudoischaemic' changes in the electrocardiogram. T wave flattening and QT prolongation occur as a result of a respiratory alkalosis but the cause for the more marked ST segment depression is still not clear. The autonomic nervous system is considered to play the major contributing role (Lary & Goldschlager, 1974). An initial fall in the PaCO_2 produces a greater selective suppression of parasympathetic activity, leading to sympathetic dominance. In addition, analysis of urinary catecholamine excretion in patients who hyperventilate has shown that adrenaline output can be increased by up to three times that of normals (Folgering & Cox, 1981). A combination of autonomic imbalance and high adrenaline drive may contribute to asynchronous myocardial repolarization with electrocardiographic abnormalities (Gardin *et al.*, 1980). Furthermore, the catecholamine surge (both from the adrenal medulla – adrenaline – and from the sympathetic nerve endings in the heart – noradrenaline) boosts the heart's 'need' for oxygen and in certain circumstances, has an acutely hypoxiating action. For example, the injection of adrenaline into a normal subject can produce true anginal pain (Raab, 1962) and similarly high catecholamine concentrations have been found under everyday circumstances of environmental stress (Kagan & Levi, 1974; Nestell *et al.*, 1967). Under these

circumstances the ST segment depression may indeed be hypoxic.

The second feature of the electrocardiogram which we have noticed in patients who hyperventilate is the markedly increased incidence of ectopics. These are commonly of a right ventricular type, described by Rosenbaum (1969) as benign (Figure 2). At Charing Cross Hospital the random observation of such an ectopic has frequently yielded a diagnostic history and positive provocation testing. We are not yet in a position to comment on the pathogenesis of the right ventricular ectopy. What is certain is that the subjective sensation of a single ectopic is uncomfortable in hyperventilators and recurrent ectopy is commonly reported as painful.

In order to accommodate the foregoing we would like to present a revised classification of five causes of chest pain in patients who hyperventilate.

The first type of pain has a truly mechanical cause either from aerophagia producing gastric distension or discomfort from persistently hyperinflated lungs, which becomes a pain when the patient attempts the deep breathing required by exercise or emotional strain.

Secondly, it is reasonable to postulate a muscular cause for the pain, associated with overuse of the intercostal muscles and subsequent fatigue. In addi-

Figure 2 PC 445425. An electrocardiogram showing frequent right ventricular ectopy. A history consistent with a diagnosis of hyperventilation was subsequently obtained and provocation testing was positive. The characteristics of the ectopic beat to note are: (1) LBBB pattern in the chest leads and a QRS interval of at least 0.12 s. The LBBB pattern in the chest leads can be distinguished from the typical LBBB electrocardiographic pattern by the fact that the initial forces are directed anteriorly and are very slowly inscribed. (2) The main QRS force is directed inferiorly and to the right. (3) The R wave from V1 to V3 is relatively tall and wide. (4) The horizontal vectorcardiogram rotates counter-clockwise.

tion, extracellular alkalosis increases the tendency of skeletal muscle to spasm, probably because the increased membrane permeability to sodium produces the 'oedematous' cells described by Newnham & Edwards (1979). In view of public awareness of the linkage between chest pain and heart disease it is not surprising that this group of patients, with increased sensitivity to somatic functions, should report these pains more frequently with a bias of reference to the left side of the chest ('wherein lies the heart').

A third type of pain is reported in the left submammary area and occurs when there is high sympathetic tone and the resultant tachycardia is perceived as heavy and uncomfortable, much like the patient with true supraventricular tachycardia or fast atrial fibrillation. The forceful adrenergic slap against the chest wall frequently produces a tender area at the apex, which is more prominent when a mechanical restraint in the form of a bra, has pressed over the area. Increased ectopy experienced by these patients who hyperventilate also produces a definite apical thud as the left ventricle empties an increased diastolic load.

The fourth variety of pain we have called 'catecholamine myopathy'. Elevated catecholamine levels which have been documented in hyperventilators, not only produce pain in normal hearts (Raab, 1962) but can more easily provoke ischaemia and pain where there is an underlying vascular handicap. There is further evidence which suggests that chronic intermittent hypercatecholaminaemia may induce small areas of focal necrosis (with subsequent scarring) of the subendocardium (Raab, 1971). This increases left ventricular stiffness, reduces compliance and predisposes to pain and even infarction (Eliot & Buell, 1983). The associated clinical signs may include evidence of left ventricular distension with a palpable and audible atrial gallop rhythm, both of which frequently resolve with rest, but the atrial sound may persist as evidence of the left ventricular disturbance (Nixon 1974). The coronary arteries are often normal.

The fifth type of chest pain is true myocardial pain. Ischaemic discomfort can be produced in some hyperventilators by the combination of the Bohr shift to the left (which increases the oxygen affinity of the blood in the coronary capillaries), and coronary vasoconstriction which decreases coronary blood flow. This vasoconstriction may be a contributing factor in those patients with angina and normal coronary arteriograms, as in Bass's study, in Prinzmetal angina and possibly in those cases of myocardial infarction and documented normal coronary arteries (Legrand *et al.*, 1982). Marzilli *et al.* (1980) have even suggested that the organic atheromatous stenotic lesion might be caused by spasm damaging the intima; the role of hyperventilation should then perhaps be regarded more seriously (Freeman & Nixon, 1985).

The first three types of pain will be the more

commonly encountered in younger patients with the hyperventilation syndrome. However, the middle aged patient who may have all five varieties of chest pain is at risk for uncomfortable, costly or invasive investigation unless the diagnosis of hyperventilation is considered. Treatment of the hyperventilation then will allow pain produced from types 1–3 to be screened out. However, it is also pertinent to consider the diagnosis of hyperventilation when the pain more closely mimicks that of coronary insufficiency, as in types 4 and 5. Furthermore, since the mechanisms that we have described may play an important role in the production of pain by emotion and cold in Heberden's angina, alleviation of the hyperventilation must now be regarded as an essential part of the management. It may reduce the weight of drug therapy and the need for open heart surgery. For all practical purposes, and until proved otherwise, hyperventilation should be regarded as the usual cause of coronary artery spasm. No other cause has been so clearly incriminated nor any other linkage as plausible as that of the carbon dioxide/alkalosis-calcium chain. One of the unsolved, untackled problems of hyperventilation is to explain why the hyperventilator has periods when the disordered breathing causes no symptoms and periods when it causes devastating and catastrophic symptoms. We believe the symptoms come when the individual is put to effort which carries him beyond the limits of endurance and physiological competence. Unable to cope and to 'keep up with his comrades' the hyperventilation now causes him to be withdrawn from the struggle. This aspect of the clinical illness has not yet been investigated to the best of our knowledge.

Conclusions

The hyperventilation syndrome often presents with pains in the chest. There has been little agreement about the nature and variety of these pains in the past, as this review shows, but recent physiological studies of the haemodynamic and autonomic effects of hyperventilation make it possible now to offer a rational classification for clinical purposes.

- (1) Mechanical – from aerophagy and/or hyperinflated lungs.
- (2) Muscular – from overuse of the chest wall muscles and increased tendency to skeletal muscle tensions.
- (3) High sympathetic tone associated with forceful adrenergic heart beat and Rosenbaum's right ventricular ectopy causing tenderness at the apex beat.
- (4) 'Catecholamine myopathy' associated with hypoxia and loss of left ventricular compliance.
- (5) Myocardial pain from a combination of coronary vasoconstriction and the Bohr effect which makes oxygen less available to the myocardium.

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