Smoking - a major cause of polycythaemia

R Aitchison MRCP **N Russell** MRCP MRCPath *Haematology Department, City Hospital, Nottingham*

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Summary

The importance of smoking in the aetiology of polycythaemia has been assessed in a group of patients referred to a general haematology clinic. All patients with true and relative polycythaemia (excluding those with polycythaemia rubra vera) were studied. Of the 21 such patients evaluated, 14 were smokers and had raised carboxyhaemoglobin levels and had no other demonstrable cause for their polycythaemia. The commonest physiological abnormality in these patients was a raised red cell mass combined with a low plasma volume. Six of the 14 patients were able to reduce their smoking with subsequent improvement in their haematocrits. These results suggest that smoking is a major cause of polycythaemia in an unselected series of referrals to a general haematology clinic. The early identification of these patients may be useful in planning therapy.

Introduction

The investigation of a raised haemoglobin or haematocrit is a fairly common cause for referral to a haematology clinic. Normally the first step in the investigation of these patients is the measurement of red cell mass (RCM) and plasma volume (PV). Patients who have a significantly raised RCM require further investigation for evidence of polycythaemia rubra vera (PRV) and for causes of secondary polycythaemia, but some patients ultimately have no features suggestive of either of these. Patients who do not have a significantly raised RCM can be arbitrarily classified into relative polycythaemia (plasma volume $<87\%$ of predicted) and apparent polycythaemia (marginal abnormalities of both variables, RCM $<125\%$ of predicted, PV $>87\%$ of predicted).

The causes, significance and management of these types of non-PRV polycythaemia are controversial. Relative polycythaemia is usually idiopathic, although the Polycythaemia Vera Study Group (PVSG) found a strong association with hypertension and also markedly impaired survival, worse even than that of adequately treated PRV[1]. These findings were supported by another study on relative polycythaemia which showed a death rate six times greater than expected[2]. The main aim of treatment in these patients is the control of other risk factors for vascular disease, especially hypertension. In contrast, the PVSG in following up a group of patients with apparent polycythaemia, found normal survival. They therefore suggested that this group may be simply at one extreme of the normal population. The current Royal College of Physicians Research Unit study should throw more light on the natural history of these groups.

The evidence that smoking causes polycythaemia comes from two main sources. First, a study on a population of blood donors in Denmark showed a significant correlation between cigarette consumption and haematocrit[3]. Secondly, small series of smokers who had polycythaemia without other evident cause have been described[4,5]. In these cases the polycythaemia was due to either a raised RCM or a low PV or a combination of both abnormalities. It was observed that stopping smoking reversed the changes which are probably due to carbon monoxide inhalation leading to carboxyhaemoglobin formation. Non-smoking urban dwellers may have 1-2% of their haemoglobin converted to carboxyhaemoglobin but smokers have levels in the range of 3-20%, the highest levels being seen in cigar smokers.

It is not clear, however, how common smokers' polycythaemia is in unselected patients undergoing investigation for polycythaemia. The aim of this study was to assess its importance in all the patients with polycythaemia not fulfilling the PVSG criteria for PRV[6] who were attending a general haematology clinic.

Methods

The study was approved by the local Hospital Ethical Committee. All patients attending the haematology clinic at Nottingham City Hospital because of a raised haemoglobin or haematocrit between May 1985 and July 1986 were identified. Those thought to have PRV and those whose polycythaemia was due to chronic hypoxia (2 patients) were excluded. The remaining 21 patients, none of whom met the PVSG criteria for PRV, were studied. They were assessed by a detailed history of their smoking habits, alcohol consumption and drug therapy, and note was made of coexistent hypertension.

All patients had RCM/PV measurements by a standard radioisotope technique[7] and their results were compared with the predicted value[8]. Plasma gammaglutamyl-transpeptidase (GTP) and the capillary partial pressure of oxygen (P_{O_2}) were also measured. Patients with a raised red cell mass were investigated for causes of secondary polycythaemia. The smokers had random venous carboxyhaemoglobin levels measured in the early afternoon by a spectrophotometric method[9]: they were then repeatedly counselled to stop smoking or at least substantially reduce their cigarette consumption. Those who managed this had their carboxyhaemoglobin levels remeasured. One patient had a repeat RCM/PV done after reducing cigarette consumption.

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Table 1. Smokers with polycythaemia

Patient	Hb g/dl	Hct	COHb %	Red cell mass ml/kg (% of predicted)	Plasma volume ml/kg (% of predicted)
Group 1 (raised RCM, low PV)					
1	19.1	0.56	4.2	37 (132)	38 (84)
2	20.5	0.60	5.0	35 (130)	30 (73)
3	19.1	0.58	3.0	35 (134)	31 (81)
4	20.9	0.67	2.6	43 (122)	30 (73)
5	19.1	0.55	3.0	38 (131)	35 (76)
6	19.2	0.56	5.9	32 (114)	36 (83)
7	19.4	0.57	7.0	41 (145)	34 (77)
8	20.3	0.58	9.4	41 (136)	30 (75)
9	20.3	0.59	4.8	32 (118)	31 (74)
Group 2 (Low PV, RCM in normal range)					
10	19.0	0.57	4.1	33	37 (80)
11	19.0	0.56	2.4	29	32 (88)
12	18.6	0.54	7.5	25	34 (77)
13	18.3	0.56	2.4	29	39 (86)
14	19.5	0.56	4.7	28	33 (72)

Table 2. Effects of stopping smoking

Patient	Age	Initial cigarette consumption per day	Hb (g/dl)	Hct	Reduced cigarette consumption per day	On reduced cigarettes Hb (g/dl)	Hct	Time since last venesection
1	20	25	19.1	0.56	5	15.1	0.44	Never
5	46	49	19.1	0.55	5	14.8	0.43	3 months
9	26	15-20	20.3	0.59	5	17.9	0.50	Never
10	22	25	19.0	0.57	3	15.4	0.47	Never
11	34	15	19.0	0.56	3	15.8	0.45	7 months
12	41	20	18.6	0.54	5	15.8	0.48	3 months

Results

Twenty-one patients were identified with high haemoglobin and/or haematocrit, 18 males (mean Hb 19.4 g/dl, range 18.1-20.6; mean haematocrit 0.565, range 0.54-0.62) and 3 females (mean Hb 19.6, range 18.3-20.6; mean haematocrit 0.60, range 0.56-0.67). Fourteen of the patients smoked (Table 1), 12 males and 2 females, 12 of them smoking cigarettes (mean 18/day, range 3-40), one cigars, and one a pipe. The smokers all had raised carboxyhaemoglobin levels (mean 4.9%, range 2.4-9.4%). Nine of the 14 had a raised RCM (mean 37.1 ml/kg, expected 28.5 ml/kg). All patients with a raised RCM also had a reduced PV, all <87% of expected (mean 32.7 ml/kg, expected 42.5 ml/kg). The remaining 5 patients had a normal RCM but a reduced PV (mean 35.0 ml/kg, expected 43.4 ml/kg) and 4 of these had PV <87% of expected. Seven of the smokers had evidence of hypertension (diastolic BP >95 mmHg) but only one was receiving treatment with a diuretic. None of the patients with a raised RCM was found to have any other cause for their polycythaemia, in particular Po_2 was normal in all cases. Most of the patients had been previously treated by venesection, but 3 patients newly referred during this study received no treatment for their polycythaemia apart from encouragement to stop smoking.

Ten of the 14 patients managed to reduce their cigarette consumption significantly (to less than half of the initial value). All had a concurrent improvement in their haematocrits, but in 4 the improvement could have been due to other treatments. However, in 6 patients the improvement can be reasonably attributed to reducing smoking (Table 2). Three of these patients received no other form of treatment, and 3 had had previous venesections but reduced smoking had resulted in a sustained reduction in haematocrit at a time when they would normally have needed further venesection. A RCM/PV measurement done on one patient after he had reduced his smoking showed that the parameters had returned to the normal range (RCM 31 ml/kg, PV 42 ml/kg, compared with 37 ml/kg and 38 ml/kg respectively on presentation).

Discussion

The present study has clearly identified cigarette smoking as the major identifiable cause of polycythaemia in this group of patients. Six of 21 patients had an improvement in Hb/Hct values when cigarette consumption was reduced (mean Hb 19.2, Hct 0.56 on presentation, falling to mean Hb 15.8, Hct 0.46). Unfortunately, some subsequently increased their consumption and their haematocrits then deteriorated.

In addition, most of the 8 other smokers managed to reduce their consumption but some only marginally, and in other patients the haematocrit improved but this could have been due to other treatments. Thus smoking could be implicated as the main cause of polycythaemia in at least 6 (26%) and possibly 14 (61%) of the patients studied.

The pattern of RCM/PV changes in the smokers was also of interest. The commonest abnormality was a reduced PV, present in all 14 patients, and in 9 of these this was associated with a raised RCM. This combination of a low PV and a high RCM has previously been reported to be typical of smokers' polycythaemia[4] and our study confirms this finding. Therefore this RCM/PV pattern may be useful in distinguishing smokers' polycythaemia from other causes of secondary polycythaemia and from PRV where the plasma volume is usually normal.

In conclusion, we have demonstrated that smoking is a major cause of polycythaemia in an unselected group of patients attending a general haematology clinic. The identification of smoking as the cause is important both to avoid inappropriate treatment for the polycythaemia and possibly also to motivate the patient to stop. Smoking should be considered at an early stage in the differential diagnosis of unexplained polycythaemia.

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