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Acute coronary disease in essential thrombocythemia and polycythemia vera

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Abstract. Rossi C, Randi ML, Zerbinati P, Rinaldi V, Girolami A (University of Padua Medical School, Padua, Italy). Acute coronary disease in essential thrombocythemia and polycythemia vera. *J Intern Med* 1998; **244**:49–53.

Objectives. The aim of this study is to report our experience on myocardial infarction (MI) in patients with essential thrombocythemia (ET) and polycythemia vera (PV).
Design. Patients with PV and ET consecutively diagnosed and followed in authors' Department between 1 July 1986 and 30 June 1996.
Subjects. Over the past 10 years we have followed 170 patients with ET and 149 with PV, diagnosed according to the Polycythemia Vera Study Group (PVSG) criteria. The patients were divided into 3 groups on the basis of the age at diagnosis (group A < 40, B 41–65, C > 65 years).
Interventions. In all patients with PV phlebotomies and/or myelosuppressive therapy were used to keep haematocrit level lower than 45%. Hydroxyurea was given to patients with ET with a positive history for major vascular complications or with an extreme thrombocytosis. Aspirin therapy (ASA) (100 mg per day) was administered in patients with microvascular disturbances or previous thrombosis (in patients with PV also in the presence of atherosclerotic risk factors).
Main outcome measures. Frequency of MI in patients with ET and PV with and without ASA therapy.
Results. 9.4% of patients with ET and 11.4% of those with PV had MI. 17.6% of patients with PV were younger than 40 years at the moment of MI in contrast to 0% of those with ET. 75% of patients with ET and 70.6% of those with PV with MI had atherosclerotic risk factors such as smoking, hypertension, diabetes, dyslipidaemia. All patients with MI received ASA 100 mg daily after thrombosis and four of the ET group developed a transient ischaemic attack (TIA) afterwards. Four subjects with PV during the follow-up had TIAs and two peripheral arteriopathy in spite of ASA treatment.
Conclusions. MI is less common in patients with ET younger than 40 years than in older patients. Association of MI and cardiovascular risk factors is frequent in patients with ET and PV. A low dose of ASA could be able to reduce the number of coronary thrombosis without increasing bleeding complications in patients with elevated platelet count and common atherosclerotic risk factors. However, a larger population must be evaluated to confirm our hypothesis.

Keywords: essential thrombocythemia, myocardial infarction, polycythemia vera.

Introduction

Bleeding and thrombosis are major causes of morbidity and mortality in patients with myeloproliferative disorders (MPD); these complications occur in 40–60% of patients with polycythemia vera (PV) or essential thrombocythemia (ET) [1–3].

In the past, ET was described as haemorrhagic thrombocytosis [4] because bleeding complications were more frequent than thrombosis [5, 6]. However, the more recent studies report that thromboembolic complications are more frequent than haemorrhages, particularly at lower degrees of thrombocytosis [3, 7].

PV and ET are disorders of the middle age but they have also been observed in young adults [8–10]. At the moment, only old age and a previous thrombotic event are considered as negative prognostic factors for thrombotic complications in ET [11]. Neither the

absolute level of platelet count nor their functional alterations have been correlated with thrombotic complications [1, 3, 12–14].

Although thrombocytosis may be associated with vascular thrombosis and consequent ischaemia, coronary artery occlusion and myocardial infarction (MI) have been rarely described in patients with ET [15, 16] whilst they are particularly frequent in those with PV [1, 17]. Only a few authors [18] included ET in the rare causes of myocardial infarction without atherosclerosis.

Because the studies concerning the incidence of acute coronary disease in ET are very old, the aims of this study were (i) to report our experience on coronary thrombosis and myocardial infarction in patients affected by ET and PV, (ii) to clarify the significance of age in the development of these complications and (iii) to evaluate the efficacy of aspirin (ASA) in the prevention of myocardial infarction (MI).

Patients and methods

Over the past 10 years we have studied 170 patients with ET and 149 patients with PV diagnosed according to the Polycythemia Vera Study Group (PVSG) criteria [2, 19].

The subjects were divided into three groups according to age: patients younger than 40 years (group A: 58 with ET, mean age 26.8 ± 9.67 years and 28 with PV, mean age 31.27 ± 9.05 years), patients from 41–65 years (group B: 77 with ET, mean age 53.14 ± 7.53 years and 81 with PV, mean age 54.94 ± 7.50 years) and patients older than 65 years (group C: 35 with ET, mean age 71.11 ± 4.81 years and 40 with PV, mean age 71.71 ± 4.62 years).

No bleeding complications were observed in these patients. 43 patients with ET and 31 with PV were excluded from this study because previous haemorrhagic complications suggested ASA was not advisable. Moreover, none of the patients included in the study had a MI either before or after the diagnosis of ET or PV.

Our patients with ET were treated with hydroxyurea (HU) at a dose of 15 mg per kg body weight until the platelet count was below $600 \times 10^9\ L^{-1}$, and thereafter at a dose able to maintain this situation. In all cases HU was stopped if platelet count fell to below $350 \times 10^9\ L^{-1}$ [11]. This treatment was confined to subjects with: (i) platelets higher than $1000 \times 10^9\ L^{-1}$ in patients of group A or higher than $750 \times 10^9\ L^{-1}$ in patients of group B and C and (ii) positive history for thrombotic complications.

ASA therapy (Aspirinetta, Bayer, Basel, Switzerland, 100 mg per day) was confined to patients with microvascular disturbances (erythromelalgia, dizziness, blurred vision, headache), previous thrombosis, regardless of myelosuppressive treatment.

All the patients with PV were treated with cytostatic drugs and/or phlebotomies to keep haematocrit (Ht) value lower than 45%: the subjects older than 65 year were treated with radiophosphorus (32P), whilst the younger patients were treated with busulphan (2 mg per day) and, since 1985, with HU at the same dose as described above. Antiaggregating therapy was confined to patients with previous thrombosis, microcircular disease and/or cardiovascular risk factors.

Myocardial transmural infarction was diagnosed in the presence of a prolonged chest pain often accompanied by weakness, sweating, nausea, vomiting, giddiness, anxiety and/or electrocardiographic manifestations such as abnormal deep Q-waves and elevated ST-segment in leads subtending the area of damage. Non-transmural infarction was considered to be present if the electrocardiogram showed only transient ST-segment and sustained T-wave change.

An increase of serum creatine-phosphokinase (CK) within 8–24 h, with muscle-brain isoenzymes at least 10% was considered diagnostic.

In all subjects with MI the most important risk factors for vascular disease, namely increased serum cholesterol and triglycerides, hyperglycemia, smoke and hypertension, were determined. Blood cells counts were evaluated using a Technicon H-1-System automated cell counter (Technicon Terrytown, NY, USA).

Intraplatelet serotonin content (5HT) was evaluated with a fluorimetric method as previously described [20].

The nonparametric Mann–Whitney test was used for statistical difference evaluations of blood cells counts. The χ^2 test was used to ascertain differences in proportions.

Results

Of the 170 patients with ET, 56 patients (33%) and 64 out of 149 patients with PV (43%) developed a

Table 1 Circumstances of diagnosis of our patients with essential thrombocythemia (ET) and polycythemia vera (PV)

	ET	PV
Total patients	170	149
Fortuitous	140 (*5)	116 (*6)
Other thrombosis	19	22
MI	11	11

*, patients with myocardial infarction in whom diagnosis of ET was fortuitous and not related to MI.

thrombotic complication (stroke, transient ischaemic attack, peripheral arterial thrombosis, myocardial infarction, deep vein thrombosis with or without pulmonary emboli, abdominal vein thrombosis, Budd Chiari syndrome).

The circumstances of the diagnosis in our patients are reported in Table 1.

Sixteen patients with ET from group A (27.5%), 26 from group B (33.7%) and 14 from group C (40%) had a thrombotic complication both at diagnosis or during the follow-up. Seven patients with PV from group A (25%), 34 from group B (41.9%) and 23 from group C (57.5%) had a similar complication. The frequency of thrombotic complications was similar in patients with ET and PV of group A whilst it was statistically higher ($P < 0.001$) in patients with PV than in those with ET over 40 years of age (groups B and C) (Fig. 1).

The total incidence of acute coronary disease in patients with ET was 9.4% (eight males and eight females, mean age 55.5 ± 11.8 , range 41–79 years) whilst in PV was 11.4% (14 males and three females,

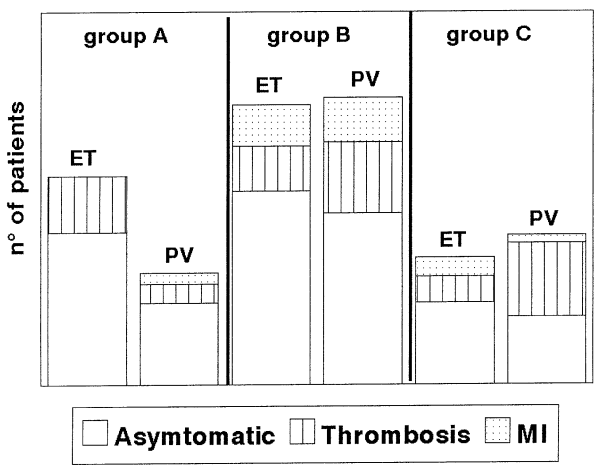

Fig. 1 Rate of thrombosis, with particular attention to coronary thrombosis with myocardial infarction (MI) in our essential thrombocythemia (ET) and polycythemia vera patients (PV).

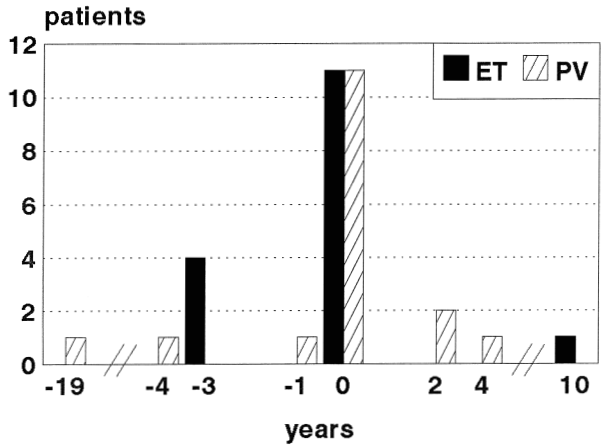

Fig. 2 Time of diagnosis of essential thrombocythemia (ET) or polycythemia vera (PV) related to time of myocardial infarction.

mean age 52.1 ± 13, range 28–74 years). In most patients, the diagnosis of ET (69%) and PV (64.8%) was contemporary to MI. In one patient with ET and three with PV MI complicated the follow-up of the disease (Fig. 2).

No statistical difference was observed comparing the frequency of MI between all thrombotic complications in different groups with the exception of group C ($P = 0.03$): no ET (0%) but three patients with PV (37.5%) of group A, 11 ET (42.3%) and 12 PV (35.2%) of group B, and five ET (35.5%) and two PV (8.6%) of group C had an MI.

The haemogram data at the moment of the MI are summarised in Table 2. No statistical difference was evident in platelet count between patients with ET and PV. On the contrary, haematocrit was statistically higher in PV than in ET at the moment of the MI.

The presence or absence of atherosclerotic risk factors was similar in both patients with ET and PV with myocardial infarction (Table 3).

All the patients with ET began ASA treatment after MI and no more MIs were observed, whilst four patients had a transient ischaemic attack (TIA) in

Table 2 Haemogram data of our patients at the time of myocardial infarction

	ET	PV	*P*
plts ($\times 10^9$ L^{-1})	757.81 ± 230.7	625.11 ± 180.16	n.s.
Ht (%)	40.88 ± 5.2	53.06 ± 7.66	0.0001
WBC ($\times 10^9$ L^{-1})	11.4 ± 5.4	11.1 ± 4.3	n.s.

ET, essential thrombocythemia; PV, polycythemia vera; plts, platelets number; Ht, haematocrit, WBC, white blood cells.

Table 3 Presence and absence of common atherosclerotic risk factors in our patients with essential thrombocythemia (ET) or polycythemia vera (PV) and myocardial infarction

	ET (n = 16)	PV (n = 17)
none	4 (25%)	5 (29.4%)
smoke	3 (18.7%)	7 (41.2%)
alone	2	3
diabetes	1	
dyslipidemia		1
hypertension		3
hypertension	7 (43.7%)	8 (47%)
alone	4	2
diabetes	1	
dyslipidemia	2	3
dyslipidemia	4 (25%)	4 (23.5%)
alone	2	

spite of treatment. In contrast, no thrombosis occurred in these patients before MI. No haemorrhagic complications were observed with this therapy. The follow-up of patients with PV after MI was complicated in four cases by TIAs and in two by peripheral artheriopathy. Moreover, three patients with PV had MI during ASA treatment begun because of microvascular disturbances (median follow-up before MI 6.67 years).

Discussion

Patients with MPD are known to be prone to thrombotic complications involving both the arterial and the venous system [3, 7, 21]. Some authors [1, 8, 15] consider these complications strictly related to the high platelet count. Arterial, including coronary, thrombi are composed largely of platelets and form at sites of vascular injury and high blood flow, unlike venous thrombi that contain few platelets, abundant fibrin and many trapped red cells and form in areas of stasis. Cardiologists have concluded that myocardial infarction is caused by platelet-rich thrombi that form at sites of rupture or fissure of atherosclerotic plaque [22]. Surprisingly despite this, few patients have been described in whom the evidence was convincing that thrombosis was produced by thrombocytosis. In fact, thrombotic complications are more frequent in polycythemia vera [1, 2, 11, 13] than in essential thrombocythemia [23] and the increase of red blood cell mass and hyperviscosity are considered more important than an increased platelet number in the formation of thrombus [1, 17]. Our data confirm that patients with PV present more thrombotic accidents than ET but the frequency of acute coronary disease is only slightly higher in PV than in ET, with a similar frequency with regard to all thrombotic complications in both instance. In the present study, no relation seems to exist between MI, history of previous thrombosis and duration of disease, in contrast to the findings in other studies [24]. On the contrary, a strong relation has been observed between arterial ischaemic complications including MI, smoking and hypertension in patients with ET and PV [25]. In PV, thrombosis is a major cause of morbidity and mortality: early studies in untreated patients with PV found a high incidence of thrombotic events and a low life expectancy [26]. Our results confirm this data; around half of untreated patients with PV developed thrombotic complications. A low rate of patients with PV, treated with ASA during the follow-up after MI, developed thrombotic accidents. Some authors [1, 17, 27] have reported a strong relation between Ht and vascular occlusive episodes in these subjects; in the majority of our MI patients, Ht value was higher than 50%. In our patients with ET, Ht was obviously normal whilst thrombocytosis was slightly higher than in those with PV. Instead, the white blood cell counts were similar in the two groups of patients. A history of prior thrombosis and advanced age are important factors that contribute significantly to the overall risk of thrombosis in ET [11]. It is interesting to note that our patients with ET younger than 40 years had no MI. Moreover ET subjects treated with ASA after MI did not develop any other coronary ischaemia during the follow-up but only TIAs in a low rate. In the past, the PVSG found that antiplatelet agents did not reduce the incidence of thrombosis, but significantly increased the incidence of serious gastrointestinal haemorrhage, and were therefore not recommended for patients with PV [28]. In contrast, cytoreductive treatment with phlebotomy or chemoterapy, has been shown to dramatically reduce the number of thrombotic events and substantially improve survival [12, 26]. Our patients did not develop haemorrhagic complications during aspirin treatment, probably because of the low dosage adopted. Furthermore, a good prevention of new thrombotic complications has been achieved.

In conclusion our data demonstrate that (i) the frequency of MI is lower in patients with ET younger

than 40 years than in older patients with ET and in patients with PV, (ii) low doses of ASA seem to be effective in patients with PV or ET in the prevention of coronary re-thrombosis but a larger population and a specific statistical analysis is needed to achieve clear indications in this field and (iii) the frequency of MI increases with age in patients with PV and ET. However, smoking and hypertension represent important risk factors for MI in these patients. An antiaggregating treatment should probably be recommended, particularly in subjects with increased platelet number and common atherosclerotic risk factors.

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