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Polycythemia Vera and Acute Coronary Syndromes: Pathogenesis, Risk Factors and Treatment

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Abstract

Polycythemia vera is a chronic myeloproliferative disorder marked by significant thrombotic complications. Myocardial infarction and heart failure is the most common cause of death. Mechanisms involved in the pathogenesis of these complications are not yet well elucidate; erythrocytosis and quantitative platelet abnormalities may play a major role in the development of thrombosis and ischemia. Age older than 60 years and prior history of thrombosis are the two main risk factors. Evidence for the prevention and treatment of specific cardiovascular complications in PV is too scarce. However, current evidence supports the use of hydroxyurea as the initial choice of cytoreductive agent in PV patients with acute coronary syndrome.

Keywords: Myocardial infarction; Polycythemia vera; Pathogenesis; Risk factors; Prevention; Treatment

Introduction

Polycythemia Vera (PV) is a chronic myeloproliferative disorder, involving a multipotent hematopoietic progenitor cell, which causes in general an increased production of red cells, granulocytes and platelets, but most significantly in erythrocytes, which leads to hyperviscosity and an increased risk of thrombosis.

Bleeding, thrombotic, and vascular complications are the major causes of morbidity and mortality in PV, occurring in 40 to 60% of the patients [1,2]. Myocardial infarction (MI) and heart failure is the most common cause of death [3].

The pathophysiology of thromboembolic events in polycythemia Vera has not been elucidated, but many factors are involved: increases in hematocrit and blood hyperviscosity, stimulation of platelet aggregation and thrombogenesis, the presence of leukocytosis, rigidity of the membrane and intimal proliferation [4-6].

Advanced age and a prior history of thrombosis are the two most important risk factors for vascular complications; hypercholesterolemia, hypertension, smoking, and diabetes have been recognized as predictors of thrombosis [7-10]. Furthermore, thrombosis often complicates treatment in patients with PV and modest hematocrit elevations (50-60%) [11].

Myocardial infarction and sudden death are complications of newly diagnosed or untreated PV; they occur most often in elderly people (≥ 65 years) with underlying coronary artery disease [12]. However, younger patients with PV who are free from coronary artery disease can also be affected, and sometimes the outcome is death [12,13].

Cytoreductive treatment of blood hyperviscosity by phlebotomy or chemotherapy and antiplatelet therapy with low-dose aspirin have dramatically reduced the number of thrombotic complications and substantially improved survival [14].

This review highlights recent breakthroughs in the pathogenesis, risk factors, prevention, and treatment of myocardial infarction in PV.

Pathogenesis

Thrombotic occlusion of large arterial vessels is also a frequent finding in PV and generally involves cerebral and coronary vessels. Acute coronary syndromes have been often reported to occur in patients without risk factors and with normal coronary arteries [13,15-17].

Several mechanisms are implicated:

Erythrocytosis

The hematocrit is the major determinant of whole blood viscosity, increased hematocrit level is associated with decreased cerebral blood flow rate and contribute to the thrombotic tendency in PV. In addition to increased blood viscosity, the axial migration of red cells occurs with displacement of platelets to the mural plasmatic zone, exposing them to maximal vessel wall shearing forces; erythrocytosis enhances platelet-vascular interactions, especially at the high shear rates found in arterioles and capillaries [18]. The increased mass of red cells in PV may also contribute to heightened platelet activation [19].

Nevertheless, the hemorrheologic effects of erythrocytosis cannot be the only explanation for the thrombotic tendency in PV; comparable or even greater degrees of secondary erythrocytosis are not associated with thrombosis, and even normalization of the hematocrit in PV does not fully protect against the risk of thrombosis [4].

Quantitative platelet abnormalities

Thrombocytosis may contribute to the pathogenesis of myocardial infarction in PV, particularly because platelet cytoreduction reduces the risk of recurrent thrombosis in high-risk patients. However, the degree of platelet count has not been significantly correlated with thrombosis risk in PV [20,21].

Qualitative platelet abnormalities

A variety of structural and functional abnormalities of platelets have

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been reported in patients with myeloproliferative diseases, including abnormal expression of platelet membrane glycoproteins, spontaneous platelet aggregation and circulating platelet aggregates; increased platelet microparticles; acquired storage pool disease and other structural and biochemical abnormalities [1,5]. Unfortunately, none of these qualitative platelet defects has been convincingly demonstrated to be causally associated with either thrombotic or bleeding complications in PV.

Leucocytes

The role of leukocytes in the pathogenesis of vascular events is increasingly recognized.

In addition, in patients with atherosclerotic vascular disease, leukocytosis has been associated with an increased thrombotic risk. Because leukocytosis characterizes many PV subjects, it has been hypothesized to be a potential determinant of their thrombotic risk [1,5].

In PV these cells have an increased tendency to activate and to form platelet-leukocyte aggregates, particularly in subjects with a thrombotic history thus suggesting that leukocytes and platelets, which share the same clonal origin, might have similar functional abnormalities that might also give raise to a complex interplay [22,23].

However, further research is needed to explore the possible role of qualitative leukocyte defects in the vascular ischemic complications of this disorder.

Other possible mechanisms

Recently, it have been reported that bone marrow hematopoietic stem cell–derived endothelial progenitors can migrate to areas of vascular injury or ischemia and repopulate the initial surfaces of the vessel wall as differentiated endothelial cells [24,25].

It is possible, that hemostatically defective endothelial cells, derived from abnormal hematopoietic stem cell clones in PV might also play a role in the clinical bleeding and thrombotic complications.

Erythropoïetine (Epo) levels are persistently decreased in PV, and this hormone is now recognized to have non-erythroid functions that are mediated by expression of Epo and its receptor in many other tissues, including the cardiovascular system [26,27]. Therefore, Chronic "Epo deficiency" that occurs in PV patients might enhance cerebral and cardiac infarction.

Recently, the influence of the JAK2 V617F mutational load on the thrombotic risk has been evaluated in patients with PV. This analysis indicated that the JAK2 V617F/JAK2 wild-type ratio behaved as an independent risk factor for major vascular events (p=0.027) [28].

Risk Factors

The evaluation of the vascular ischemic risk in PV subjects is based on a combination of established criteria, widely used in these patients [5,7]. Tentative stratifications of thrombotic risks of PV are reported in table 1.

Age

Age is a general risk factor for thrombosis under any circumstance [29]. Barbui et al. have reported in a large PV epidemiologic study (n=1638), a hazard ratio of vascular complications of 8:6 for patients older than 60 years than in younger patients (p<0.0001) [30]. More recent, In the ECLAP (European Collaboration on Low dose Aspirin in Polycythemia) study, the incidence of cardiovascular complications was higher in patients aged more than 65 years (5.0% per patient-year, hazard ratio 2.0, 95% confidence interval [CI] 1.22–3.29, p<0.006) [9].

History of thrombosis

A prior history of thrombosis has been indicated as a factor significantly contributing to the overall risk of thrombosis in PV. In the ECLAP study, the incidence of cardiovascular complications was higher in patients with a history of thrombosis (4.93% per patient-year, hazard ratio 1.96, 95% CI 1.29–2.97, p<0.0017) than in younger subjects with no history of thrombosis (2.5% per patient-year, reference category). Patients with a history of thrombosis and who were aged over 60 years had the highest risk of cardiovascular events during follow-up (10.9% per patient-year, hazard ratio 4.35, 95% CI 2.95–6.41, p<0.0001) [9]. These data confirm previous findings that increasing age and a history of thrombosis are the two most important prognostic factors for the development of vascular complications [8,31].

Cardiovascular risk factors

Smoking, hypertension, congestive heart failure, hypercholesterolaemia, diabetes mellitus were other significant risk factors for thrombosis that have been assessed in multiple studies. The role of these minor factors is partially derived from the ECLAP observational study.

This analysis indicates that hypertension and smoke play an important role as risk factors for myocardial infarction and stroke; the role of other risk factors could not be determined because of the very large number of patients and events required for these analyses [30-32]. When present in a young patient without prior thrombosis ('low-risk' patient), these factors define an 'intermediate risk' category. This classification forms the rationale for the indication of therapy [9].

Prevention and Treatment

Evidence for the prevention and treatment of specific cardiovascular complications in PV is too scarce. In general, the treatment of acute coronary syndromes secondary to chronic myeloproliferative disorders require special attention in maintaining the delicate balance between the risk of bleeding and clotting tendency.

Correction of cardiovascular risk factors

The identification and appropriate management of cardiovascular risk factors and the promotion of a healthy lifestyle in PV, as in the general population, should be considered a cornerstone of vascular prevention. However, a definitive causative/contributory role for CV risk factors on the incidence of vascular events in PV is not yet defined, except for smoking [5]. Therefore, particular attention has to be given to smoking habit which has an important effect on vascular risk and

Risk level	Factors	
High	Age ≥ 60 years or previous thrombosis or diabetes	* Risk factors: smoking, hypertension, hypercholesterolemia. Diabetes is considered a major risk factor, equivalent to a previous thrombosis or to advanced age.
Intermediate	Age> 40 to <60 years plus one risk factor* or age < 40 years plus two risk factors*	
Low	None of the above	

Table 1: Thrombotic risk level in PV patients.

which was found to be surprisingly common among PV patients recruited in the ECLAP observational study [30].

Antiplatelet therapy

The prevention of vascular risk is the foremost objective thrombotic treatment of PV. In the ECLAP study, the efficacy and safety of Low-dose aspirin to prevent thrombotic complications in patients with PV was assessed, data analysis showed a significant reduction of a primary combined end-point including cardiovascular death, non-fatal myocardial infarction, non fatal stroke and major venous thromboembolism (relative risk: 0.4; [95% CI: 0.18–0.91], p=0.0277) [33]. However, it is important to underline that the ECLAP trial was conducted in a relatively low risk population.

In a review from 86 studies, Willoughby et al. found that prophylactic aspirin use in patients with polycythemia vera reduced the occurrence of major vascular events by 22% and nonfatal myocardial infarction by 30% [34].

Based on these data, it can be inferred that initiating therapy with aspirin up to a maximum dose of 300 mg in PV patients who present with an acute coronary syndrome and then quickly reducing the dose to 100 mg by discharge for long-term prophylactic use would provide the greatest benefit in mortality reduction with a minimal risk for bleeding.

Cytoreductive therapy

The purpose of prophylactic cytoreduction in managing patients with PV is to reduce the risk of thrombosis, which accounts for the morbidity and mortality associated with the disease. Phlebotomy and myelosuppression are the treatment options most often utilized, either alone or in combination. Phlebotomy to maintain hematocrit at <45% in males and <42% females remains the cornerstone of therapy for all patients with PV. In addition to treatment with phlebotomy in PV, myelosuppressive agents such as hydroxyurea should be considered in patients who are considered at high risk for thrombosis [30].

Recently, Marchioli et al. showed that maintaining a hematocrit target of 45 to 50% in patients receiving conventional treatment (including phlebotomy, hydroxyurea, or both) was associated with four times the rate of death from cardiovascular causes or major thrombosis, as was maintaining a hematocrit target of less than 45%. The incidence of the primary end point was 1.1 events per 100 patient-years in the low-hematocrit group, as compared with 4.4 events per 100 patient-years in the high hematocrit group [35].

Appropriate cytoreduction with the goal to optimize the control of the blood cell counts is recommended in all patients with acute vascular events [36,37].

Anticoagulation

Treatment with Oral Anticoagulants (OA) may be promising as an antithrombotic strategy in patients with PV. However, no clinical studies have been carried out to evaluate the efficacy of OA in prevention and treatment of vascular complications of patients with PV.

Anti-vitamin K agents was found to be independently effective in preventing recurrent thrombosis in PV. De Stefano et al. have reported that long-term treatments with antiplatelet or anti-vitamin K agents prevent independently recurrence, with reductions of re-thrombosis of 58% and 68%, respectively. In contrast, the association of antiplatelet agents plus vitamin K antagonists resulted in a higher incidence of major bleeding (2.8% patient-years) [38]. Recent guidelines therefore recommend oral anticoagulation in venous thrombosis for 3–6 months in PV and essentiel thrombocythemia (ET) patients [39].

New oral anticoagulants

New oral anticoagulants may replace warfarin (anti-vitamin K) in prophylaxis of thrombosis in PV. Apixaban and rivaroxaban are selective factor Xa inhibitors while dabigatran is a direct thrombin inhibitor. Compared to warfarin, the newer oral anticoagulants are associated with several advantages. These new agents do not require anticoagulation monitoring and they have limited food- and drug-drug interactions due to their minimal metabolism through the CYP450 system. Of special interest in the setting of PV is the fact that the bleeding complications seem to be lower compared with vitamin-K antagonist [39].

Anagrelide

It is a nonleukemogenic drug that relatively selectively inhibits megakaryocyte proliferation and differentiation. However, in a head-to-head study between HU and anagrelide plus low-dose aspirin in both arms, anagrelide was inferior to HU in terms of response and safety.

Patients in the anagrelide arm showed an increased rate of arterial thrombosis, major bleeding and myelofibrotic transformation but a decreased incidence of venous thrombosis compared to HU. In addition, anagrelide was more poorly tolerated than HU and presented significantly greater rates of cardiovascular, gastrointestinal, neurological and constitutional complications [30].

Pipobroman

Patients with PV may also be treated with pipobroman, a bromide derivative of piperazine. Recents reports demonstrates, in a large series of patients homogeneously treated and observed for a long period, that pipobroman is an effective and well tolerated agent for the control of PV, with a relatively low risk of early thrombotic complications (6% at 3 years) [40]. Hematologic evolution to myelofibrosis was found to be higher in patients treated predominantly with HU (32% at 20 years) compared with those treated with pipobroman. (32% at 20 years) [41].

Interferon alpha (IFN-αlpha)

IFN-alpha was considered for the treatment of patients with myeloproliferative disorders since this agent suppresses the proliferation of hematopoietic progenitors. It is now well established that IFN-α can control erythrocytosis or thrombocytosis in the majority patients with PV or ET. Its widespread use was offset by its parenteral administration, cost, and toxicity although, and the largest study of IFN- with long-term follow-up reported to date [42] the frequency of treatment discontinuation resulting from toxicity was only 15% when low doses were used. Furthermore, no vascular event was recorded with the use of IFN.

Tyrosine Kinase Inhibitors (TKIs)

Many recent reports have showed that therapy with TKIS (Imatinib, dasatinib, nilotinib) was generally well tolerated in PV patients. Neverthless, Ribeiro et al. have found that even if Imatinib was not related to systematic deterioration of cardiac function, there is still a possibility of isolated cases of cardiotoxicity [43]. There is scarce information about cardiotoxicity of dasatinib and nilotinib. Being aware of the risk of using these drugs and a close relationship between haematologists/oncologists and cardiologists is particularly important to early detect and institute the appropriate treatment to prevent irreversible myocardial injury [44].

New drugs

The JAK2V617F mutation, a point mutation in the tyrosine kinase

gene JAK2 (Janus Kinase 2), has emerged as a central feature in the pathogenesis of PV. The diagnostic criteria of PV have been revised in 2008 and include the JAK2V617F mutation as one of the two major criteria of the disease. Thus, a significant number of new drugs with JAK 2 target are currently at varying stages of clinical evaluation, especially in patients with PV/ET refractory or intolerant to conventional therapy. Recently Ruxolitinib (a JAK1 and JAK2 inhibitor) became the first-in-class JAK inhibitor to receive approval by the Food and Drug Administration for use in intermediate-2 and high-risk myelofibrosis [30].

Coronary reperfusion

The safety and efficacy of fibrinolytic therapy as the exclusive treatment of an acute coronary syndrome in patients with polycythemia vera is unknown. Furthermore, effective fibrinolytic therapy may be undermined by residual coronary thrombus, which potentially may be seen in polycythemia vera patients who have high platelet counts [45].

However, Ruggeri et al. demonstrated that controlling blood counts in PV patients undergoing coronary artery bypass grafting reduced but did not eliminate the risk for postoperative thrombosis and hemorrhage [46].

Treatment Strategy

In a patient with myeloporliferative disease, an acute venous thrombosis is managed in the standard fashion (heparin followed by oral anticoagulant therapy). However, systemic anticoagulation alone in PV may not be sufficient and concomitant myelosuppressive therapy with hydroxyurea is highly recommended [3,30]. Moreover, one of the principal factors to consider in choosing a therapy for myocardial infarction in patients with PV is the increased risk of bleeding associated with the use of thrombolytic therapy. Although, there are no current guidelines that address stent restenosis risk reduction or treatment of acute MI in PV patients, current evidence supports, in addition to the standard antiplatelet therapy, the use of hydroxyurea as the initial choice of cytoreductive agent in PV patients with acute coronary syndrome [47-54].

Conclusion

PV is a chronic myeloproliferative disorder characterized by a high risk of developing arterial and venous thromboembolic complications. In recent years, great insight has been gained into the understanding of the pathogenesis of thrombosis in PV. Nevertheless, the search for new strategies for management the cardiovascular events in PV patients has undoubtedly become a priority for future research.

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