SCIENTIFIC LETTER

Progenitor cell mobilisation in patients with acute and chronic coronary artery disease

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Tissue ischaemia is considered to be a major trigger for progenitor cell mobilisation because of the massive release of reactive molecules caused by myocardial necrosis and tissue inflammation.^{1,2} Surprisingly, despite the growing number of clinical investigations of the effects of stem cell administration to patients with acute myocardial infarction (AMI), very little is known about the spontaneous mobilisation of progenitor cells in patients with different clinical manifestations of ischaemic heart disease.^{3,4} To understand better the biology of progenitor cell mobilisation in the clinical setting, we measured the concentration of circulating haematopoietic progenitor cell associated antigen CD34+ in patients with AMI or chronic stable angina (CSA) and in healthy controls. Furthermore, we correlated the magnitude of progenitor cell mobilisation with a variety of demographic, clinical, and biochemical variables.

METHODS

Forty five consecutive patients with AMI (25 with ST segment elevation and 20 with non-ST elevation AMI), 33 patients with CSA and significant coronary artery disease, and 30 healthy controls were enrolled in the present study. Patients with ST elevation AMI were thrombolysed with recombinant tissue plasminogen activator according to the GUSTO (global utilisation of streptokinase and t-PA for occluded coronary arteries) protocol. Patients with CSA had evidence of inducible ischaemia at non-invasive stress test and significant stenoses at coronary angiography but no history of AMI or acute coronary syndromes in the preceding 24 months. We selected a control group of 30 healthy subjects (mean age 52 (18) years, 21 men) without overt heart disease and major cardiovascular risk factors. A single sample was obtained from patients with CSA and from healthy controls. Blood samples to measure CD34+ cells were collected from patients with AMI at baseline, 90 minutes after thrombolysis, 6–9 hours after hospital admission, and on days 1, 2, and 3 after the acute event. CD34+ cells were evaluated according to published methods.⁵ The concentration of CD34+ cells in the peripheral blood was expressed as the percentage of CD34+ cells and as the absolute number of CD34+ cells, calculated by multiplying the percentage of CD34+ cells by the total number of leucocytes (cells/ μ l) and expressed as CD34+/ μ l. The simultaneous influence of demographic, clinical, and instrumental variables and of coronary risk factors and biochemical markers on circulating CD34+ cells was assessed by using logistic regression analysis.

RESULTS

Peak total white cell count was higher in patients with AMI than in patients with CSA and in controls (12292 v 7513 v 7111 cells/ μ l, $p < 0.001$). The peak percentage of circulating CD34+ cells was similar in patients with AMI and with CSA. The peak percentage of CD34+ cells was higher in patients with AMI or CSA than in healthy controls. The peak absolute number of CD34+ cells was higher in patients with AMI

Figure 1 Peak absolute number of circulating CD34+ cells in healthy controls and in patients with chronic stable angina (CSA) and acute myocardial infarction (AMI). Values are medians with interquartile ranges in brackets. * $p = 0.0002$ and $p < 0.0001$ v AMI and CSA, respectively.

(12.3 cells/ μ l) than in patients with CSA (5.2 cells/ μ l, $p = 0.0002$) and in healthy controls (1.2 cells/ μ l, $p < 0.0001$). Furthermore, the absolute number of CD34+ cells was significantly higher in patients with CSA than in healthy controls ($p < 0.0001$) (fig 1). The peak percentage of circulating CD34+ cells was similar in patients with AMI at each sampling time, in patients with ST elevation AMI and with non-ST elevation AMI, and in patients with anterior or non-anterior myocardial infarction. Major variability in the peak concentration of CD34+ cells was noted among patients with AMI ranging from 0.04–1%. At logistic regression analysis diabetes mellitus ($p = 0.0013$), family history ($p = 0.034$), hypertension ($p = 0.037$), and plasma concentrations of C reactive protein ($p = 0.0069$) were independent predictors of a higher number of circulating CD34+ cells. Notably, no correlation was found between peak concentration of circulating CD34+ cells and markers of myonecrosis.

DISCUSSION

Our findings indicate, firstly, that patients with acute and chronic ischaemic heart disease have a higher absolute number of circulating CD34+ cells than do healthy subjects. Secondly, among patients with ischaemic heart disease, those with acute coronary syndromes have a higher absolute number of circulating progenitor cells than do those with CSA; however, the higher number of circulating progenitor cells observed in patients with acute coronary syndromes appears to be due to an increase in total white blood cell count and not to a relative increase in the percentage of CD34+ cells. Lastly, a higher number of circulating CD34+ cells is predicted by some established risk factors for atherosclerosis (hypertension, diabetes mellitus, family history) and inflammation (plasma concentrations of C reactive protein) but not by the severity of the acute myocardial damage; indeed, markers of myonecrosis failed to predict CD34+ cell mobilisation.

The results of this study suggest that, among patients with ischaemic heart disease, spontaneous progenitor cell mobilisation is related to various mechanisms. On one hand, the higher concentration of progenitor cells in patients with chronic coronary artery disease than in controls (tonic mobilisation) indicates that coronary atherosclerosis alone is a sufficient trigger for haematopoietic progenitor cell mobilisation even in the absence of acute ischaemic stimuli. Indeed, compensatory progenitor cell mobilisation, phenotypically expressed by the percentage of circulating progenitor cells, appears to depend on a tonic process related to long lasting chronically active stimuli such as cardiovascular risk factors (hypertension, diabetes mellitus, family history) or chronic inflammation (C reactive protein). Tonic mobilisation of progenitor cells may be extremely helpful for the long term turnover and replenishment of a limited number of damaged vascular cells due to the atherosclerotic insult. Interestingly, major variability in the peak percentage of CD34+ cells was noted among patients with coronary artery disease, ranging from 0.04–1%, suggesting that the interplay between individual factors and environmental triggers has a major role in determining the magnitude of CD34+ tonic mobilisation. On the other hand, in the setting of acute myocardial ischaemia, when a variety of potentially haematopoietic progenitor cell mobilising factors are produced and released because of ischaemic damage, the higher number of circulating progenitor cells (phasic mobilisation) is achieved mainly by a non-specific increase in white blood cell production rather than by a specific increase in progenitor cell percentage. Notably, in the setting of acute myocardial ischaemia no correlation was found between peak concentration of circulating CD34+ cells and markers of myonecrosis suggesting that progenitor cell mobilisation is not correlated

with specific ischaemia related triggers; rather, it depends on the non-specific mobilisation of leucocytes.

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Computed tomographic pulmonary angiography and prognostic significance in patients with acute pulmonary embolism

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Background: Patients with acute pulmonary embolism (APE) present with a broad spectrum of prognoses. Computed tomographic pulmonary angiography (CTPA) has progressively been established as a first line test in the APE diagnostic algorithm, but estimation of short term prognosis by this method remains to be explored.

Methods: Eighty two patients admitted with APE were divided into three groups according to their clinical presentation: pulmonary infarction (n = 21), prominent dyspnoea (n = 29), and circulatory failure (n = 32). CTPA studies included assessment of both pulmonary obstruction index and right heart overload. Haemodynamic evaluation was based on systolic aortic blood pressure, heart rate, and systolic pulmonary arterial pressure obtained non-invasively by echocardiography at the time of diagnosis of pulmonary embolism.

Results: The mortality rate was 0%, 13.8% and 25% in the three groups, respectively. Neither the pulmonary obstruction index nor the pulmonary artery pressure could predict patient outcome. In contrast, a significant correlation with mortality was found using the systolic blood pressure (p<0.001) and heart rate (p<0.05), as well as from imaging parameters including right to left ventricle minor axis ratio (p<0.005), proximal superior vena cava diameter (p<0.001), azygos vein diameter (p<0.001), and presence of contrast regurgitation into the inferior vena cava (p = 0.001). Analysis from logistic regression aimed at testing for mortality prediction revealed true reclassification of 89% using radiological variables.

Conclusion: These results suggest that CTPA quantification of right ventricular strain is an accurate predictor of in-hospital death related to pulmonary embolism.

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