Rapid Communication

Serum levels of vascular endothelial growth factor in patients with acute myocardial infarction undergoing reperfusion therapy

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INTRODUCTION

Vascular endothelial growth factor (VEGF), also termed vascular permeability factor, is known to be a potent endothelial-cell-specific angiogenic mitogen secreted from tumour cells and cells exposed to hypoxia. Therefore, VEGF has been proposed as the most likely candidate in tumour neovascularization as well as in ischaemia-induced collateral vessel formation, particularly in conditions such as acute myocardial infarction. Evidence has accumulated that myocardial ischaemia strongly induces the expression of VEGF mRNA in the heart, and administration of VEGF in vivo has been shown to enhance the collateral blood flow to ischaemic myocardium [1, 2]. However, little is known about the release of VEGF in acute myocardial infarction and the effects of coronary reperfusion on the circulating levels of VEGF. Here we report the circulating levels of VEGF in patients with acute myocardial infarction undergoing early coronary reperfusion therapy.

METHODS

Nineteen patients with acute myocardial infarction were studied. All of these patients underwent successful reperfusion therapy in an early phase (11 had percutaneous transluminal coronary angioplasty, and eight had percutaneous transluminal coronary recanalization). Serum VEGF concentration was measured by a quantitative sandwich enzyme immunoassay (R & D Systems, Inc., Minneapolis, MN, U.S.A.) with a monoclonal antibody specific for VEGF coated on to the microtitre plate and an enzyme-linked polyclonal antibody specific for VEGF. The sensitivity of the assay was 9.0 pg/ml (according to the manufacturer). The mean (±SD) serum VEGF concentration in 19 healthy control subjects was 5.6(±9.0) pg/ml.

Key words: hypoxia, myocardial infarction, reperfusion therapy, vascular endothelial growth factor.
Abbreviations: bFGF, basic fibroblast growth factor; VEGF, vascular endothelial growth factor.
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RESULTS AND DISCUSSION

Figure 1 shows the serum concentration of VEGF in patients with acute myocardial infarction before and 20–30 min after reperfusion therapy. In all patients, serum VEGF levels before reperfusion (252.4 ± 158.1 pg/ml, mean ± SD) were markedly increased as compared with those in healthy control subjects. In these patients, the serum VEGF levels returned almost completely to the normal control range within 20–30 min after reperfusion (6.34 ± 19.1 pg/ml mean ± SD). In two patients, the serum VEGF levels were still moderately elevated after reperfusion, and in one of these, new occlusion of the distal branch occurred during the reperfusion therapy. The serum level of VEGF in one patient with acute myocardial infarction after unsuccessful reperfusion therapy was still markedly increased (data not shown). There was a statistically significant difference (P = 0.0001) between the concentrations before and after reperfusion therapy.

This study clearly showed that serum levels of VEGF in patients with acute myocardial infarction after unsuccessful reperfusion therapy was still markedly increased (data not shown). There was a statistically significant difference (P = 0.0001) between the concentrations before and after reperfusion therapy.

This study clearly showed that serum levels of VEGF in patients with acute myocardial infarction were markedly increased and that these rapidly returned to normal levels by early reperfusion, indicating that circulating levels of VEGF acutely reflect the myocardial ischaemia.

We also measured the circulating levels of basic fibroblast growth factor (bFGF), another potent angiogenic mitogen, in these patients. However, there was no significant correlation between the levels of bFGF and the state of myocardial ischaemia (data not shown). This may partly be explained by the fact that bFGF lacks a hydrophobic signal sequence for secretion and hypoxia does not upregulate bFGF expression [3]. Endothelin, a potent vasoconstrictor peptide, is known to be upregulated by hypoxia [4]. It was reported that circulating levels of endothelin were significantly increased in patients with acute myocardial infarction and that the levels were decreased by early reperfusion [5, 6]. However, the extent of changes in endothelin concentration was modest (at most 3-fold) and the decrease in endothelin concentration after reperfusion was very slow [5, 6].

Recently, we have found that cardiac myocytes contain an abundance of VEGF in their cytoplasm, rapidly secrete VEGF in response to hypoxia, and that hypoxia-induced signal transduction in cardiac myocytes is mediated by autocrine release of VEGF (Y. Seko, N. Takahashi, Y. Nanya, K. Tobe, T. Kadowaki and Y. Yazaki, unpublished work). This strongly suggests that VEGF released from the ischaemic myocardium may play a pivotal role in cardiac adaptation to ischaemic stresses as well as being one of the most sensitive indicators of myocardial ischaemia. We are currently investigating whether VEGF can be an indicator not only of stable and unstable angina but also of subclinical myocardial ischaemia, such as silent myocardial ischaemia.

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