Review Article

# Significance of Endothelin-1 in Myocardial Infarction

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It is well known that neurohormonal changes play an important role in the evolution of an acute myocardial infarction (AMI).[1,2] They are mainly generated in response to myocardial damage in order to maintain the patient's haemodynamic stability. Endothelin-1 (ET-1) is one of the major endogenous substances involved in the pathogenesis and evolution of a myocardial infarction. There is also evidence suggesting that ET-1 is an important prognostic marker in patients with AMI.[1,2]

ET-1 is a 21-amino acid peptide and represents the major isoform of the endothelin peptide family,[1,2] which also includes ET-2, ET-3 and ET-4. The endothelin peptides are produced by endothelial and smooth muscle cells, neural, renal, pulmonary and inflammatory cells. ET-1 is the most potent vasoconstrictor known. The inactive precursor is converted into its active form by ET converting enzyme. ET-1 acts through two receptors, ET-A and ET-B. ET-A receptors lead to increased intracellular calcium concentrations and induce vasoconstriction and cell proliferation. ET-B receptors mediate the release of nitric oxide and prostacyclin and therefore cause vasodilatation. They are also involved in the clearance of ET-1 and inhibit the action of ET converting enzyme.[1-3]

ET-1 has also been found to play an important role in the pathogenesis of hypertension, congestive heart failure and regulation of renal function.[3] In the current review, we will focus on the role of ET-1 in the pathogenesis and evolution of AMI.

## The pathogenetic role of ET-1

The effects of ET-1 on the heart are multiple.[1,2,4] Normal ET-1 plasma levels produce a positive inotropic effect through an increase in intracellular calcium, whereas elevated plasma levels of ET-1 result in a decline in cardiac output. This is because ET-1 has a predominantly vasoconstrictive effect, at both peripheral and coronary level, thus resulting in increased afterload and reduced myocardial perfusion. ET antagonists have an adverse effect on myocardial contractility in healthy individuals with normal ET-1 plasma levels but improve contractility in patients with advanced ventricular dysfunction.[1,4]

The regulation of ET-1 synthesis is a complex process that occurs mainly at the mRNA level.[5] The factors that modulate its expression act by increasing or decreasing levels of ET-1 mRNA.[6] Expression of the ET-1 gene in endothelial cells is regulated by numerous factors, including but probably not limited to thrombin, transforming growth factor-β, shear stress, tumour necrosis factor-α, interleukin-1, insulin, angiotensin II, nitric oxide and hypoxia.[7]

There is evidence suggesting that ET-1 contributes to the process of atherosclerosis.[2] ET-1 levels are positively correlated with the extent of atherosclerosis. Other

studies have shown that in patients with coronary artery disease tissue ET-1 levels are related to the extent of angina.[2,3] ET-1 promotes direct vasoconstriction, induces smooth muscle cell proliferation, stimulates adhesion of neutrophils to the endothelium and platelet aggregation.[8,9] It also antagonises the action of nitric oxide. The latter is a vasodilator known to have antiproliferative and antithrombotic properties. Therefore, an imbalance between the two contributes to atherogenesis.[2,3] Various risk factors for atherosclerosis, such as diabetes mellitus, smoking and hypercholesterolaemia, enhance endothelial ET-1 secretion.[10,11] Oxidised low density lipoprotein cholesterol induces the production of ET-1 by human macrophages and enhances the release of ET-1 by endothelial cells.[12]

The findings of recent studies suggest that ET-1 plays an important role in causing myocardial infarction, post-infarct scar formation, left ventricular remodelling and the no-reflow phenomenon.[1-3] In patients with uncomplicated AMI, ET-1 plasma levels rise within hours, peak at 6 hours and return to normal within 24 hours. In patients with AMI complicated by pulmonary oedema or cardiogenic shock ET-1 levels remain elevated for a longer period.[13] The increased plasma ET-1 levels during an AMI are the result of both stimulated cardiac and extracardiac production of ET-1. In a recent study, Tsutamoto et al investigated whether ET-1 is extracted through the heart or produced by it in the acute phase of an anterior myocardial infarction.[14] They found that ET-1 levels were higher in the aortic root than in the coronary sinus. This suggests that ET-1 is predominantly extracted across the heart. It is well known that ET-1 has very potent vasoconstrictor properties. It causes stenosis of atherosclerotic coronary arteries, thus contributing to the pathophysiology of acute myocardial infarction.[1] It has been shown that the intracoronary delivery of ET-A receptor antagonists induces marked dilatation (21%) of atherosclerotic, stenotic coronary vessels compared to a less significant dilatation (7%) of smooth coronary vessels.[15] These findings are supported by the results of another study, in which Zeiher et al investigated whether the presence of ET-1 in active coronary atherosclerotic plaques contributes to the increased vasoreactivity of the active lesions in unstable angina.[16] It was found that the active coronary atherosclerotic plaques contain significant amounts of ET-1, suggesting that ET-1 plays an important role in the segmental coronary hyperreactivity observed in unstable angina. It is very likely that ET-1 not only enhances vascular tone itself, but also amplifies the contractions induced by other vasoconstrictors, leading to arterial spasm.

In the post-myocardial infarction period, ET-1 contributes to the healing of the infarction. This is likely due to its inflammatory, proliferative and fibrotic properties. It promotes cardiac fibroblast proliferation, adhesion molecule expression and extracellular matrix deposition. ET-1 levels are much higher in the infarcted area than in healthy myocardium, suggesting that ET-1 contributes to the stabilisation of scarring.[1] A significant correlation has been demonstrated between transcardiac extraction of ET-1 in the acute phase of myocardial infarction and left ventricular ejection fraction and left ventricular end-diastolic volume index after one month.[14] This indicates that ET-1 contributes to the evolution of myocardial infarction and the post-infarction ventricular remodelling.

### Prognostic significance of ET-1

Many factors have been found to be important prognostic markers in patients with AMI. Yip et al evaluated the predictive value of circulating ET-1 with respect to the 30-day outcome in ST-segment elevation acute myocardial infarction (STEMI) treated with primary percutaneous intervention.[17] It was shown that the 30-day composite major adverse clinical outcomes (advanced Killip score $\geq 3$, severe congestive heart failure) and 30-day mortality were strongly associated with a high ET-1 level, unsuccessful reperfusion, low left ventricular ejection fraction ($<50\%$), multi-vessel disease and female sex. The high ET-1 level and unsuccessful reperfusion were the only independent predictors of 30-day major adverse clinical outcome and mortality. Another important finding of this study was that patients with multi-vessel disease had substantially higher ET-1 levels than those with single vessel disease. Advanced Killip score was also an independent predictor of elevated circulating levels of ET-1. An explanation for this finding could be that advanced Killip score is associated with slow coronary blood flow, which results in global ischaemia. This in turn induces increased ET-1 secretion in order to maintain the haemodynamic status. However, the ET-1-induced coronary and peripheral vasoconstriction increases myocardial oxygen demand by increasing afterload and further reduces coronary blood flow and oxygen supply. Therefore, ET-1 induced vasoconstriction could extend the ischaemic zone and lead to infarct expansion. In another study, ET-1 post-infarction plasma levels were found to be a strong predictor

of 1-year survival, independent of other factors known to be associated with poor prognosis.[18]

### ET-1 and reperfusion therapy

It is well known that coronary reperfusion therapy has improved the prognosis of patients with STEMI. However, the restoration of epicardial blood flow by thrombolysis or primary angioplasty does not always imply reperfusion, even if the stenosis is successfully eliminated.[19] It has been observed that in almost 40% of patients undergoing primary percutaneous intervention, myocardial perfusion in infarct-related artery territory remains inadequate despite restoration of coronary artery patency. This is the result of structural damage to the microvasculature, sufficient to prevent restoration of normal blood flow to the myocardial cells, and is known as the no-reflow phenomenon.[19] A study was carried out to investigate the clinical factors related to the development of no-reflow phenomenon in patients who underwent successful coronary reperfusion with primary coronary angioplasty within 24 hours after the onset of an anterior wall STEMI.[20] It was demonstrated that the absence of preconditioning angina, the extent of myocardial damage (number of Q waves), the size of the risk area (wall motion score) and TIMI flow grade 0 on initial coronary angiography were the factors related to the no-reflow phenomenon. The number of Q-waves was the strongest predictive factor.

In an experimental study, Galiuto et al examined whether ET-A antagonist administration at the time of coronary reperfusion preserves post-ischaemic microvascular flow.[21] Twenty dogs were subjected to 90 minutes of left anterior descending artery occlusion followed by 180 minutes of reperfusion. They were randomised into two groups: 10 controls and 10 treated with LU 135252 (ET-A antagonist). The drug was administered 5 minutes before reperfusion. The results showed that in the animals treated with an ET-A antagonist, microvascular flow was mostly preserved. The use of the drug was associated with a threefold reduction in the extent of no-reflow and a twofold reduction in infarct size.

A recent study by Nicoli et al investigated the relationship between ET-1 plasma levels and no-reflow in a group of patients treated with primary percutaneous intervention for STEMI.[22] Seventy patients with a first AMI were included in the study. The no-reflow phenomenon was observed in 61% of the patients. ET-1 plasma levels were found to predict angiographic no-reflow after successful primary percutaneous intervention. The different mechanisms through which ET-1 could mediate no-flow are the following: ET-1 causes microvascular vasoconstriction, stimulates adhesion of neutrophils to the endothelium and therefore favours intravascular plugging and increases microvascular permeability, causing oedema which leads to compression of the microvasculature.[8,22-24] Therefore, ET-1 antagonists might have a role to play in the management of no-reflow. It was also observed that an anterior location of a myocardial infarction was another independent predictor of no-reflow, while CK-MB levels tended to be higher in patients with no-reflow.

A very recent study by Adlbrecht et al examined whether the constituents of thrombi in STEMI patients contribute to microcirculatory dysfunction.[25] The investigators analysed fresh coronary thrombi from 35 STEMI patients treated with percutaneous coronary intervention. ET levels were significantly higher within the thrombi than in the peripheral plasma. It was also observed that the amount of ET and white blood cells aspirated from target vessels was correlated with the magnitude of ST-segment resolution. The latter was attributed to regional improvement of microcirculatory function.

There is also evidence to suggest that ET-1 plays an important role in the pathophysiology of reperfusion injury.[26] This refers to the deleterious effects of reperfusion leading to further progression of already existing ischaemic damage.[27] Acute myocardial infarction followed by reperfusion results in accelerated necrosis of irreversibly injured myocytes, as well as induction of lethal injury to reversibly injured cells. Polymorphonuclear leukocytes are major participants in the reperfusion-initiated inflammation.[28] ET-1 is not only a potent vasoconstrictor but also a stimulator of polymorphonuclear leukocyte aggregation and adhesion. ET-1 contributes to myocardial ischaemia and reperfusion injury by activation of the ET-A receptor. Selective blockade of the ET-A receptor may protect the heart from reperfusion injury. The cardioprotective effect seems to be related to inhibition of polymorphonuclear leukocyte-induced myocardial injury and preserved production of nitric oxide. In another study by Bohm et al, it was found that the dual ET(A)/ET(B) receptor antagonist bosentan attenuates ischaemia/reperfusion-induced endothelial dysfunction in humans *in vivo*.[29]

### Conclusion

ET-1, which is known to have very potent vasoconstrictive properties, plays an important role in the patho-

genesis and evolution of AMI.[1-3] It is also involved in post-infarction ventricular remodelling and is an independent prognostic marker in AMI patients.[14,17,18] It has been shown that ET-1 is a significant predictor of the no-reflow phenomenon and is also involved in the pathophysiology of reperfusion injury.[22,25,27-29] Therefore, the use of ET-1 antagonists may have a role to play in the management of no-reflow and reperfusion injury.

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