Endothelin A-receptors and the coronary circulation

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ABSTRACT

We review the role of endothelin (ET) A-receptors (R) on the coronary circulation. ET-1 maintains the normal coronary artery tone. ET-1 plasma levels are increased during and after coronary angioplasty and this increase is related to myocardial ischaemia rather than to mechanical artery injury. ET_AR antagonists inhibit coronary artery vasoconstriction induced by ET release after coronary angioplasty in humans. ET promotes neointimal formation and ET_AR antagonism has been shown to inhibit restenosis after angioplasty in the animal model but not in humans. ET_AR blockade increases coronary blood flow, dilates distal coronary arterial segments and decreases coronary vascular resistance. Coronary collaterals are less sensitive than other coronary vessels to ET-1. ET_AR blockade decreases collateral blood flow and, consequently, perfusion of the ischemic myocardium.

Keywords: Endothelin; Coronary Circulation

1. INTRODUCTION

Diseases of the cardiovascular system account for the majority of morbidity and mortality in Western countries. Most forms of cardiovascular disease are associated with impaired vascular function in the cerebral, coronary, renal or peripheral circulation. Enhanced intermittent and/ or persistent vasoconstriction is one of the most important features of several forms of cardiovascular disease.

An important local vascular regulator is the 21-amino acid peptide endothelin (ET) with potent and characteristically sustained vasoconstrictor and vasopressor actions [1]. In the blood vessel wall, only endothelial cells produce the peptide and exclusively ET-1, except in disease states such as atherosclerosis, where smooth muscle cells may also contribute. Most of the ET-1 produced in the endothelium interacts with vascular smooth muscles, while only about one-third circulates and can be measured by radioimmunoassay techniques [2].

With intraluminal administration of ET-1, a transient vasodilation due to activation of nitric oxide and prostacyclin is observed followed by profound and sustained vasoconstriction which is mediated by ET_AR receptor activation and at least in certain blood vessels also by ET_BR receptors [3,4]. With higher concentrations of ET-1, only vasoconstriction is observed, although even then inhibition of a production of endothelium derived relaxing factors enhances the response to the peptide [5].

Brunner [6] compared coronary and interstitial ET-1 levels in perfused rat hearts under several experimental conditions. Basal ET-1 releasing into effluent was higher than in transudate, but basal ET-1 concentration was four-fold higher in transudate than in effluent. Following the removal of the endothelial cells, ET-1 release in the artery lumen decreased dramatically and was completely abolished in interstitial transudate, indicating that the peptide originated from the vascular endothelium [6]. When the coronary flow was reduced to an ischemic level, ET-1 secretion rates into effluent decreased by 60%, but increased 3- to 4-fold after reperfusion at normal flow. These data do not support a vasoconstrictor action of ET-1 in rats following ischemia/reperfusion, but rather point to a possible vasodilator role of the peptide under these conditions.

Thrombin and ischemia increase ET-1 production and up-regulate its receptors. In patients with unstable angina, increased staining for ET-1 can be demonstrated in coronary artery lesions removed by atherectomy [7]. ET-1 levels were measured in blood samples, obtained from the femoral vein of patients with stable angina, undergoing coronary rotational atherectomy. Patients undergoing plain balloon angioplasty were used as controls. Plasma levels of ET-1 were higher in patients undergoing balloon angioplasty, whereas in patients undergoing

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atherectomy, these were only mildly elevated [8] (**Figure 1**). The peripheral release of ET-1 during angioplasty is related to myocardial ischemia, rather than to endothelial injury [9] (**Figure 2**). Possible explanations for the smaller ET-1 secretion during atherectomy compared with balloon angioplasty are: 1) more calcified arteries may secrete less ET-1 during ischemia; 2) more diffusely diseased arteries may produce less ET-1 during ischemia, and 3) the destruction of the endothelium during rotational atherectomy is so extensive that it renders itself unable to produce and excrete ET-1 into the plasma.

Tahara, *et al.* [10] reported that ET-1 is increased in the coronary sinus after coronary angioplasty. ET-1 plasma levels have been shown to increase more in normotensive than in hypertensive patients after coronary angioplasty [11]. Thus, ET-l has a weaker vasomotor effect on the coronary vasculature in hypertensive patients than in normotensives [12], due to reduced responsiveness to ET-l by the small resistance arteries in the former. In patients undergoing angioplasty, ET-1 is increased more in patients with partially occluded coronary arteries than in patients with totally occluded vessels. Thus, the increase in ET-1 is another confirmation that ET-1 levels are related to myocardial ischaemia rather than to mechanical artery injury [9].

Biopsies from internal mammary arteries in patients undergoing coronary artery by-pass grafting showed that systemic hypertension is associated with increased ET-1 and ET_AR receptor mRNA expression, whereas insulin-dependent diabetes down-regulates ET_AR receptor mRNA expression [13]. This could help explain the differential response of hypertensive and diabetic animals and humans to external and internal stimulation and blockade of ET-1 and its receptors.
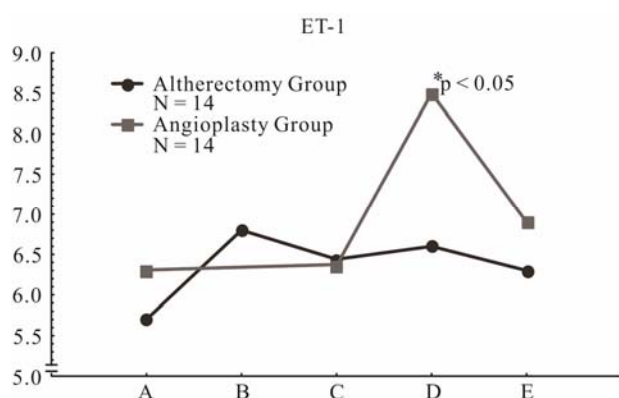

Figure 1. Plasma levels of Endotelin-1 were higher in patients undergoing balloon angioplasty, whereas in patients undergoing atherectomy, these were insignificantly raised. Letters A to E denote the phases during which blood samples were drawn. A is after the coronary artery engagement with the guiding catheter (baseline), B is after the end of the rotational atherectomy, C is after the first balloon inflation, D is immediately after the end of the procedure, and E is 4 hours later [8].
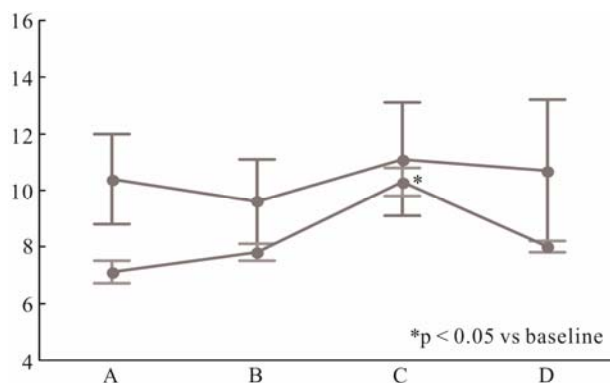

Figure 2. Endothelin-1 during coronary angioplasty in a group of patients with total (filled circles) and another with partial (open circles) artery occlusion *<0.05 vs baseline. Letters A to D denote the phases during which blood samples were drawn. A is after the coronary artery engagement with the guiding catheter (baseline), B is after the first balloon inflation, C is immediately after the end of the procedure, and D is 4 hours later [9].

2. ET-1 DURING ANGIOPLASTY

In a study utilizing the selective ET_AR antagonist BQ-123 in patients undergoing angioplasty [14], acute ET_AR receptor antagonism prevented the normal reduction of myocardial ischemia on repeated balloon inflations. This phenomenon may be explained by a "steal" effect through coronary collaterals; local ET_AR receptor antagonism with BQ-123 causes coronary vasodilatation (mainly at the distal coronary arterial segments), an increase in coronary blood flow, and a decrease in the coronary artery resistance [14] (**Figure 3**). ET_AR receptor antagonism may increase coronary blood flow and decrease coronary artery resistance and distal coronary pressure by dilating the distal arterial segments and the resistance arteries in the non-ischemic region and increasing coronary blood flow [15] (**Figure 4**).

Coronary vasoconstriction after coronary angioplasty has been attributed to a variety of mechanisms and it can be prevented by ET_A receptor blockade. Quantitative analysis of coronary angiography of the diameter of the distal segment of coronary arteries 25 minutes after coronary angioplasty, showed that intracoronary administration of BQ-123 hindered vasoconstriction of the distal segment [16] (**Figure 5**).

3. ET ANTAGONISTS IN CORONARY BLOOD FLOW

ET-1 and big ET-1 administration in rat hearts reduces coronary blood flow. However, BQ-123, an ET_AR receptor antagonist abolishes the cardiac effect of ET-1 [17]. Cannan, *et al.* [18] showed that low concentrations of exogenous ET-1 in dogs, which may mimic pathophysiological concentrations, result in coronary vasoconstriction mediated predominantly via the ET_AR, since such
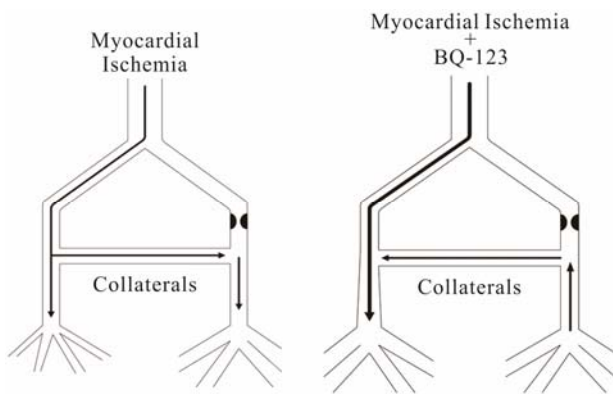
Figure 3. Schematic representation of coronary arterial bed, effects of myocardial ischemia, and possible effects of ET_AR antagonism (BQ-123). Coronary arteries can be divided into 2 functional components: large epicardial conductance arteries and smaller resistance arterioles. After significant narrowing of coronary artery, ischemic stimulus results in autoregulation of small resistance vessels and consequently maximal vasodilation in ischemic region. ET_AR antagonism, in nonischemic region, dilates distal arterial segments and resistance vessels, causing decrease in coronary artery resistance, increase in blood flow, and fall in distal coronary pressure. Fall in pressure at source of collaterals may diminish collateral flow and perfusion of ischemic myocardium. This deleterious effect is termed "coronary steal" [14].
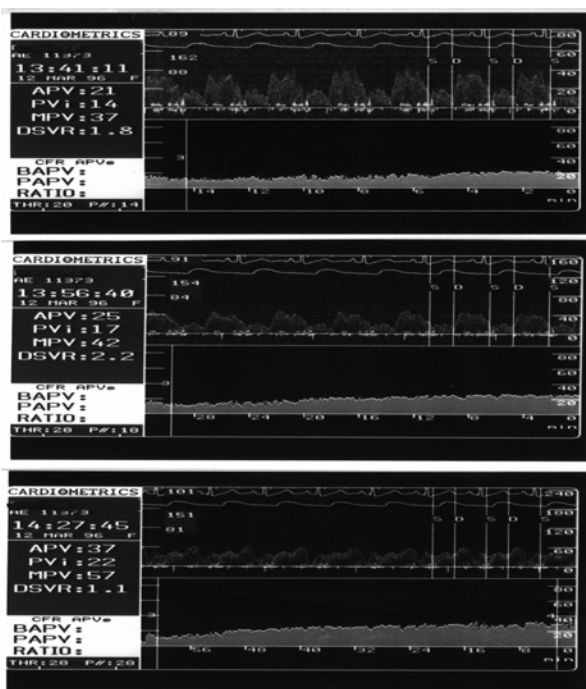

Figure 4. Coronary blood flow velocity in a patient with coronary artery disease 15 minutes (top) and 30 minutes (middle) after the initiation of BQ-123, an ET_AR blocker, infusion and after the end of the infusion (bottom). It can be seen that peak velocity integral (PVI) increases from 14 to 17 and 22 cm, respectively, while systolic blood pressure decreases from 162 to 154 and 151 mm Hg. Note that the blood flow velocity scale is different in the three recordings [15].
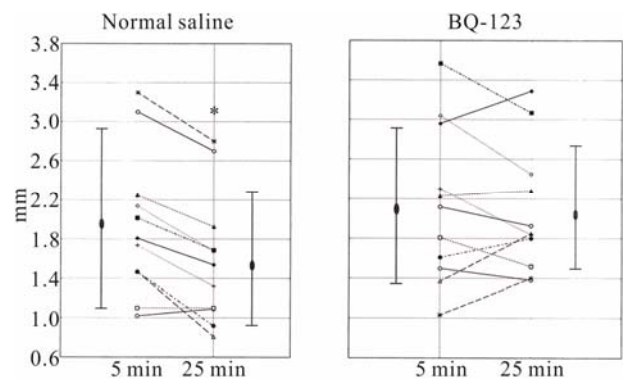

Figure 5. Line plots of the diameter of the distal arterial segments at 5 and 25 minutes after completion of angioplasty with BQ-123 (an ET_AR antagonist) (right) or saline control administration (left). *: $p < 0.05$ versus 5-minute postangioplasty [16].

vasoconstriction is significantly attenuated by ET_AR blockade. Pernow, *et al.* [19] showed that intravenous ET-1 administration decreases coronary sinus blood flow and increases coronary vascular resistance in humans.

Endogenous ET-1 maintains the normal coronary artery tone and thus regulates coronary blood flow. In patients undergoing coronary arteriography, administration of intracoronary BQ-123 led to an increase in blood flow in the left anterior descending coronary artery, an increase in the diameter of the distal segment of the coronary artery and a decrease in coronary vascular resistance (**Figure 4**) [15]. Moreover, changes in blood flow were similar in subjects with and without coronary artery disease [15]. In coronary artery disease patients, coronary artery compliance increased after intracoronary BQ-123 [20]. ET_AR dependent activity is impaired in diabetic patients; coronary artery diameter in diabetic patients increased far less in comparison to healthy subjects after administration of intracoronary BQ-123 [21]. In a similar manner, physiologic response to ET_AR blockade was also attenuated in hypertensive patients [22].

4. ET-1 ON THE CORONARY COLLATERAL CIRCULATION

Collateral vessels demonstrate heightened sensitivity to certain vasoconstrictors such as vasopressin, which can decrease blood flow to the dependent myocardium at doses that do not affect blood flow to normal myocardium. Rapps, *et al.* [23] found that collateral vessel rings constricted smaller-than-normal coronary arterial vessels to ET-1. An impaired collateral vasoconstrictor response might be expected to protect collateral blood flow when ET-1 levels are increased. In the work of Traverse, *et al.* [24], collateral blood flow did not significantly change although coronary sinus ET-1 concentrations exceeded 70 pg/ml. Only at the highest infusion rate, when the coronary blood concentration was 175 pg/ml, did colla-

teral blood flow decrease significantly. It was demonstrated that in the intact animal collateral vessels constrict similarly to normal vessels in response to ET-1.

Coronary collateral vessels can synthesise prostacyclin. Furthermore, in dogs with long-term coronary occlusion, prostacyclin appears to cause tonic collateral vessel dilatation [25] because cyclooxygenase blockade with indomethacin significantly decreased retrograde blood flow from the cannulated collateral dependent artery. Traverse, *et al.* [24] showed that prostacyclin production is important in blunting the vasoconstrictor effects of ET-1 in the collateral circulation. In contrast, the response of collateral vascular resistance to ET-1 in the normal zone was much less affected by inhibition of prostacyclin production. This is in agreement with previous findings that vasodilator prostaglandins are of greater importance in collateral than in normal coronary vessels.

Well-developed collateral vessels exhibit nitric oxide-mediated, endothelium-dependent vasodilation in response to agonists such as acetylcholine or bradykinin [26-28]. However, there are indications that vasodilatation of collateral vessels resulting from ET-1-stimulated production of nitric oxide could also improve perfusion of the collateral-dependent region. ET-1 could alter blood flow to the collateral-dependent myocardium by influencing vasomotion of the resistance vessels in the collateral zone. As we know, receptor-mediated, endothelium-dependent dilation has been shown to be impaired in microvessels chronically perfused by collateral vessels [28].

Donckier, *et al.* [29] studied 30 conscious chronically instrumented dogs before, during and after a 10-min coronary artery occlusion performed either during ET-1 or during saline infusion. Left anterior descending artery blood flow decreased equally during occlusion with either ET-1 or saline. Both endocardial and epicardial blood flow in ischemic regions also decreased during artery occlusion but were threefold greater with ET-1 than with placebo. These results showed that ET-1 increases collateral blood flow in the ischemic myocardium in dogs.

By combining coronary wedge pressure, obtained by means of a wave wire, with simultaneously recorded aortic pressure, obtained by means of the guiding catheter, and central venous pressure at maximum arterial vasodilation, a quantitative index of collateral flow can be calculated. This index, called fractional collateral blood flow, expresses actual collateral flow as a ratio to normal maximum myocardial perfusion. A lower ratio indicates a higher impairment in the collateral perfusion of the ischemic myocardium. After repeated balloon inflations, the coronary wedge pressure, in a group of patients administered BQ-123, decreased, whereas in the control group it increased. These results indicate that acute ET_AR antagonism decreases coronary collateral circulation in patients with coronary artery disease during angioplasty. Therefore, ET_AR antagonism may increase coronary blood flow and decrease coronary artery resistance and distal coronary pressure by dilating the distal arterial segments and the resistance arteries in the nonischemic region [14].

5. ETA ANTAGONISTS AND INHIBITION OF RESTENOSIS

In addition to its actions on vascular smooth muscle cells, ET-1 is also a potent mitogen in several cultured cell lines of both cardiovascular and noncardiovascular origin [30]. ET-1 also induces the expression and release of several proto-ongogenes and growth factors, the latter of which may be synergistic [31-34].

Douglas, *et al.* [35] studied the role of endogenous ET-1 in neointimal formation after rat carotid artery balloon angioplasty. They showed that ET-1 promotes neointimal formation in vivo and that it is involved in the pathogenesis of angioplasty-induced lesion formation in the rat. They showed also the protective effect of the nonpeptide ETR antagonist SB 209670 (ET_AR and ET_BR antagonist) in neointimal formation, indicating that this substance can serve as a useful adjunct to coronary angioplasty, attenuating the degree of vascular restenosis observed after vascular wall injury. The same investigators showed that neither chronic nor acute ET_AR blockade after giving BQ-123, an ET_AR blockade, is sufficient to inhibit angioplasty-induced neointima formation in the rat. They implicated a significant role for the ET_BR subtype, either exclusively or in concert with ET_AR activation, in the pathogenesis of neointima formation in the rat. The administration of BQ-123 in patients with stable angina undergoing angioplasty, failed to show any difference in restenosis after 6 months, as analyzed by quantitative coronary arteriography and intravascular ultrasound [36].

6. CONCLUSION

ET-1 maintains normal coronary artery tone. ET_AR assume a cornerstone role on the regulation of coronary circulation. There is an upregulation of ET_AR in hypertension and a downregulation in diabetes. ET is a potent promoter of neointimal formation, and ET_AR blockade inhibits restenosis after angioplasty in animal model. The secretion of ET during myocardial ischemia and reperfusion is related to ischemia, rather than to endothelial injury. ET_AR antagonism increases coronary blood flow in healthy coronary arteries, but may reduce coronary blood flow in diseased segments, via a coronary steal phenomenon. Moreover, ET_AR blockade increases the diameter of distal coronary arterial segments and decreases coronary vascular resistance. Coronary collaterals have decreased sensitivity to ET-1, and ET_AR antagonism de-

creases collateral blood flow and perfusion of the ische-mic myocardium.

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