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Increased Plasma Endothelin-1 in the Early Hours of Acute Myocardial Infarction

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Endothelin is a novel endothelium-derived vasoactive peptide with potent vasoconstrictor action in the coronary bed; however, its possible contribution to myocardial ischemia and infarction is not known. Plasma endothelin-1 concentration was measured with use of a radioimmunoassay in serial venous samples from 22 patients over a 72 h period after acute myocardial infarction (14 patients with uncomplicated infarction [group I] and 8 patients with hemodynamic or ischemic sequelae [group II]). Twenty-two normal subjects and seven patients with stable angina served as the control subjects.

Endothelin-1 levels in patients with stable coronary disease were not different from those of normal subjects (0.62 ± 0.56 and 0.76 ± 0.38 pg/ml, respectively). In group I, plasma levels of endothelin-1 rose sharply after myocardial infarction, reaching a peak of 4.95 ± 0.78 pg/ml at 6 h after the onset of chest pain ($p < 0.05$ compared with values in control subjects) and returning rapidly toward the normal range by 24 h. Patients with complicated infarction (group II) demonstrated a similar rapid increase in plasma endothelin-1 to a peak value of 8.29 ± 1.95 pg/ml; however, plasma endothelin-1 remained elevated in these patients, becoming significantly different from values in group I at 48 and 72 h.

There was no correlation between peak increases in creatine kinase and peak endothelin-1 in either group, suggesting that the stimulus for elevation of endothelin-1 was not myocardial necrosis itself. Furthermore, left ventricular ejection fraction did not correlate with the increase in endothelin-1 in group I patients, whereas there was a significant inverse relation between ventricular function and plasma endothelin-1 in group II.

Therefore, the rapid increase in plasma endothelin-1 associated with the onset of infarction suggests that this peptide may provide a marker of endothelial perturbation in the early phase of coronary ischemia or even contribute to alterations in myocardial perfusion. The sustained increase in plasma endothelin-1 in patients demonstrating complications of myocardial infarction might reflect continuing ischemia or marked depression in ventricular function in these patients.

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Endothelin, a vasoactive peptide recently isolated from the supernatant of endothelial cells in culture (1), is a potent constrictor of isolated coronary arteries from animals (1,2) and humans (3–5). Endothelin produces marked increases in coronary vascular resistance in the isolated perfused heart (6–8) or when infused in vivo (9–11) and can lead to ischemia and death (11). Therefore, it has been suggested (11) that endogenous production of endothelin might contribute to myocardial ischemia and infarction in humans.

However, little is known about the local production and release of endothelin in animals and humans. Stimuli that damage endothelium have been reported (12–14) to greatly increase endothelin levels. Recently, we (15) developed a sensitive and specific assay for measuring endothelin in plasma and reported that circulating levels were markedly elevated in patients with cardiogenic shock. Because cardiogenic shock is a complex pathophysiologic state characterized by systemic hypoperfusion and multiorgan dysfunction, it is difficult to attribute the observed increases in circulating endothelin to an abnormality of any one vascular bed.

The aim of the present investigation was to determine whether myocardial infarction itself would result in elevated plasma endothelin levels. Therefore, circulating endothelin concentrations were measured in patients with acute myocardial infarction of varying severity, both with and without hemodynamic compromise or other complications. Frequent plasma samples were obtained as soon as possible from the onset of infarction to define the time course of release during myocardial infarction and the potential contribution of endothelin to the early phase of cardiac ischemia and injury.

Methods

Study patients. Twenty-two patients presenting with prolonged chest pain were diagnosed as having acute myocardial infarction by evolving electrocardiographic (ECG) ab-

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normalities, an increase in serum creatine kinase (CK) greater than twice the upper limit of normal and a significant increase in the CK MB isoenzyme level. When possible, venous blood samples for endothelin measurement were obtained as early as 2 h after the onset of chest pain and again at 4, 6, 8, 12, 24, 48 and 72 h. Samples were also drawn for CK at 4, 8, 12, 24, 48 and 72 h. Patients were admitted to the coronary care unit at the Royal Victoria Hospital and monitored closely for complications of myocardial infarction.

Patients were classified into two groups: group I showed no evidence of hemodynamic or ischemic complications, whereas group II had evidence of hemodynamic compromise defined as hypotension (blood pressure <90 mm Hg systolic unresponsive to infusion of saline solution), heart failure (rales more than half way up the chest with radiographic evidence of pulmonary edema and, when this measurement was available, mean pulmonary artery wedge pressure >18 mm Hg) or recurrent myocardial ischemia (recurrence of chest pain with ECG evidence of new ischemia or a second CK increase, or both). Transient ventricular arrhythmias alone during the study period were not considered sufficient to classify patients into group II.

Plasma endothelin was measured in 22 normal subjects and 7 patients with stable coronary artery disease undergoing cardiac catheterization. This study was performed in accordance with the guidelines of the Food and Drug Administration and the Health Protection Branch and was approved by the Royal Victoria Hospital Institutional Review Board (Ethics Committee) on October 2, 1989.

Measurement of endothelin and cardiac enzymes. Venous blood was collected in ethylenediamine tetraacetic acid (EDTA)-containing tubes and centrifuged at 1,800 *g* for 20 min at 4°C. Plasma was stored at −80°C for ≤1 week. Under these conditions, no decrease in measured endothelin plasma concentration was observed. Plasma endothelin was measured with use of a modification of the previously described radioimmunoassay (15). In brief, samples were loaded onto SepPak C18 cartridges (Waters), activated with methanol, 8 *M* urea and water and eluted with methanol, yielding a recovery of 75 ± 3.3%. Samples and standards (endothelin-1, Peninsula Laboratories) were reconstituted in assay buffer and incubated for 24 h with rabbit anti-endothelin-1 serum (Peninsula Laboratories) at 4°C. The addition of approximately 4,000 cpm of iodine-125 endothelin-1 (Peninsula Laboratories) was followed by a second 24 h incubation, and bound and free radioligand were separated using the second antibody method. Bound radioactivity data were evaluated after logit/log transformation and the immunoreactive endothelin-1 data were presented after correction for recovery.

The antibody exhibited a cross-reactivity of 10% with human "big" endothelin-1 and 5% with endothelin-3, but no cross-reactivity with unrelated peptides (namely, atrial natriuretic factor 1-28, brain natriuretic peptide, vasopressin, angiotensin I and II). The standard curve, defined by the equation logit B/Bo = 1.74 − 2.02 log pg endothelin-1 (where B = bound radioactivity in the presence of standard or sample, and Bo = bound radioactivity at zero concentration of endothelin-1), was very stable, with a midpoint (IC_{50}) of 7.23 ± 0.58 pg/tube. The limit of detection, defined as the least amount of immunoreactive endothelin-1 distinguishable from zero at 95% confidence, was 0.12 pg/tube. The intra- and interassay coefficients of variation were 9% and 12%, respectively. Serial dilutions of the plasma extract inhibited binding of radioligand in parallel with the standard curve. High pressure liquid chromatography of plasma extract demonstrated a dominant peak of immunoreactive endothelin-1 coeluting with synthetic endothelin-1.

Creatine kinase was measured in venous serum with use of an automated enzyme analyzer (Technicon RA 1000) and determination of CK MB isoenzyme was performed using the Sigma kit (RA 1000). Left ventricular ejection fraction was determined in all patients by radionuclide gated angiography.

Statistical analysis. Values are presented as mean values ± SEM. Significance of differences was determined using Student's *t* test. A p value < 0.05 was considered significant.

Results

Patient characteristics (Tables 1 and 2). Of the 22 patients with acute myocardial infarction, 14 (11 men and 3 women) met the criteria for group I and 8 (5 men and 3 women) for group II (Table 2). Patients in group II were significantly older than those in group I (66 ± 3 and 55 ± 3 years, respectively, $p < 0.05$) and demonstrated a higher incidence of anterior myocardial infarction (75% vs. 57%). Left ventricular ejection fraction was lower in group II than in group I (33 ± 5% and 42 ± 3%, respectively), but this difference was not significant. Thrombolytic therapy was administered to eight patients (57%) in group I and three (37%) in group II.

Control endothelin-1 levels. Mean plasma endothelin-1 concentration in 22 normal volunteers (mean age 33 ± 5 years) was 0.76 ± 0.38 pg/ml, with an upper limit of normal defined as the mean + 2 SD of 1.52 pg/ml. Seven patients (mean age 55 ± 8 years) undergoing cardiac catheterization for stable coronary artery disease constituted a second control group. These patients with stable exertional angina had a mean plasma endothelin level of 0.62 ± 0.56 pg/ml (not different from normal).

Time course of endothelin-1 levels after uncomplicated myocardial infarction (Fig. 1). Plasma endothelin-1 levels increased sharply after myocardial infarction from a value not significantly different from normal in four patients at 2 h from the onset of chest pain to a peak value of 4.95 ± 0.78 pg/ml at 6 h ($p < 0.05$). Thereafter, plasma immunoreactive endothelin-1 decreased rapidly to 1.75 ± 0.38 pg/ml by 24 h, remaining slightly above the normal range until 72 h. In contrast to the increase in CK, the peak increase in immunoreactive endothelin-1 occurred substantially earlier (6 vs.

Table 1. Clinical Data in 14 Patients With Uncomplicated Myocardial Infarction (group I)

Pt. No.	Site of MI	Age (yr)/ Gender	Thrombolysis	Killip Class	LVEF (%)	Peak ET (pg/ml)	Peak CK (U/liter)
1	Inf	63/M	No	I	45	6.36	1,285
2	Inf	44/M	STR	I	40	4.8	4,990
3	Inf	48/M	STR	I	55	5.51	240
4	Ant	40/M	TPA	I	30	3.51	1,455
5	Ant	53/M	STR	I	40	3.89	2,004
6	Ant	47/M	No	I	30	2.24	1,680
7	Ant	61/M	No	II	45	8.91	5,355
8	Ant	77/F	No	II	35	4.6	2,559
9	Ant	56/M	STR	I	55	2.6	1,548
10	Ant	53/M	STR	I	21	3.28	2,382
11	Inf	68/F	No	I	53	7.13	1,269
12	Ant	60/F	No	II	38	1.89	1,034
13	Inf	48/M	STR	I	45	9.67	3,536
14	Inf	54/M	STR	I	50	7.92	3,048
Mean		55.14			41.57	5.17	2,313.21
± SEM		2.57			2.62	0.67	380.78

Ant = anterior; CK = creatine kinase; ET = endothelin-1; F = female; Inf = inferior; LVEF = left ventricular ejection fraction; M = male; MI = myocardial infarction; Pt. = patient; STR = streptokinase; TPA = tissue plasminogen activator.

12 to 24 h) and was more strongly associated with onset of infarction.

Endothelin-1 in complicated versus uncomplicated infarction (Fig. 2 to 4). Peak levels of immunoreactive endothelin-1 tended to be greater in group II patients with complicated myocardial infarction than in group I patients with uncomplicated myocardial infarction (Tables 1 and 2, Fig. 2). Moreover, plasma immunoreactive endothelin-1 remained elevated in patients exhibiting complications in contrast to the rapid return toward the normal range observed in group I patients, becoming significantly different at 48 and 72 h. However, in neither group of patients was there a correlation between peak CK and peak endothelin-1 level (Fig. 3). The best example of this dissociation was provided by the patient with the smallest increase in CK (Patient 3), who demonstrated an increase in plasma immunoreactive endothelin-1 almost identical to the mean level for group I. Subsequent angiography showed a severely stenotic proximal right coronary artery subtending a large distal bed and near normal left ventricular function with only mild inferior hypokinesia. Similarly, there was no correlation between peak endothelin-1 level and left ventricular ejection fraction in patients with uncomplicated infarction (Fig. 4A). However, patients with complicated infarction demonstrated a significant inverse relation, with the highest plasma endothelin-1 levels found in patients with the lowest ejection fraction (Fig. 4B).

Discussion

Plasma endothelin-1 in uncomplicated versus complicated myocardial infarction. The present study demonstrates that levels of immunoreactive endothelin-1 in the venous blood were markedly elevated after myocardial infarction, even in the absence of hemodynamic sequelae. In contrast to previous studies (16,17), in this study plasma samples were obtained within the early hours after the onset of chest pain, and therefore the timing of the peak increase in endothelin-1 after myocardial infarction could be defined. In patients with

Table 2. Clinical Data in Eight Patients With Complicated Myocardial Infarction (group II)

Pt. No.	Site of MI	Age (yr)/ Gender	Thrombolysis	Killip Class	LVEF (%)	Peak ET (pg/ml)	Peak CK (U/liter)	Complication
15	Ant	62/M	No	III	48	4.63	1,460	Pulmonary edema
16	Inf	65/M	STR	I	50	5.56	921	RV infarction
17	Ant	80/F	No	III	25	10.6	2,735	Pulmonary edema
18	Ant	75/M	No	III	25	4.49	408	Pulmonary edema
19	Inf	56/M	STR	I	45	6.31	855	Recurrent ischemia
20	Ant	68/F	No	IV	14	20.8	944	Cardiogenic shock
21	Ant	65/M	No	IV	20	9.05	353	Cardiogenic shock
22	Ant	55/F	STR	I	40	4.92	2,937	Recurrent ischemia
Mean		65.75			33.38	8.29	1,326.63	
± SEM		2.85			4.62	1.95	328.82	

RV = right ventricular; other abbreviations as in Table 1.

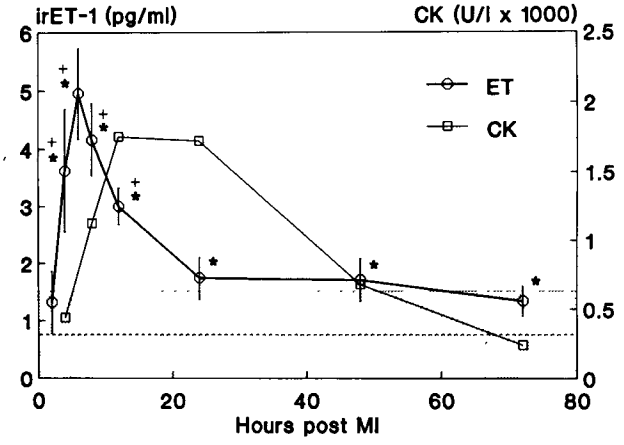


Figure 1. Time course of plasma immunoreactive endothelin-1 (irET-1) (**left ordinate, open circles**) and serum creatine kinase (CK) (**right ordinate, open squares**) for patients in group I. The time in hours after the onset of myocardial infarction (post MI) appears on the **abscissa**. The **dashed line** indicates the mean value of plasma immunoreactive endothelin-1 in normal subjects. The **shaded area** indicates normal range (mean ± 2 SD). * = $p < 0.05$ compared with values in normal subjects; + = $p < 0.05$ compared with the 2 h value.

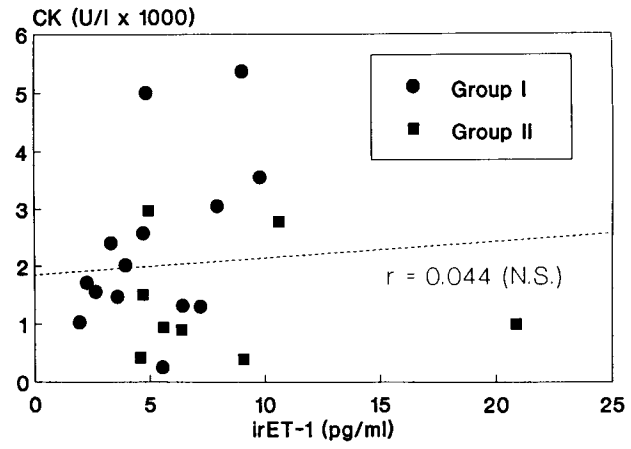
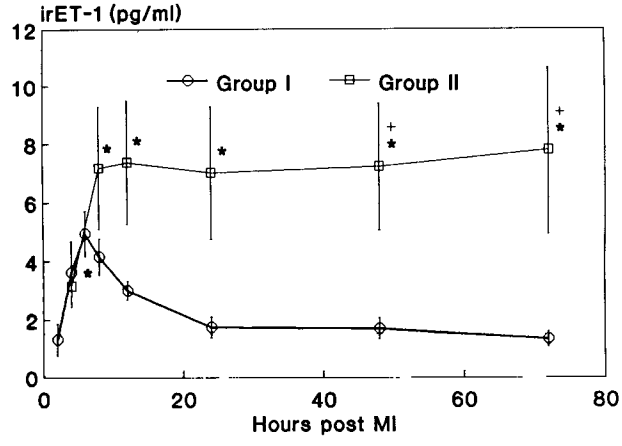


Figure 3. Peak elevation in creatine kinase (CK) (**ordinate**) is plotted against peak increase in immunoreactive endothelin-1 (irET-1) (**abscissa**) for patients with uncomplicated (group I) (**closed circles**) and complicated (group II) (**closed squares**) myocardial infarction.

uncomplicated infarction (group I), the increase in plasma endothelin-1 was strongly associated with the onset of the ischemic event (Fig. 1), reaching a maximum by 6 h compared with a maximal increase in CK occurring between 16 to 24 h and rapidly returning toward the normal range by 24 to 72 h. In contrast, in patients with complicated infarction (group II), endothelin-1 levels remained elevated, becoming significantly greater than in group I patients at 48 and 72 h.

Effect of endothelin-1 on coronary vasomotor tone. Whether these observed increases in plasma endothelin-1 could produce coronary vasoconstriction and further compromise coronary blood flow in patients after myocardial infarction is a crucial question. Even the highest plasma level measured (that is, 20 pg/ml [8 pmol/liter]) is probably below the threshold estimated to induce vasoconstriction in human arteries in vitro (3–5, 18,19). However, endothelin-1 concentrations of approximately 10 pmol/liter were found to produce a significant vasopressor response during infusion of the synthetic peptide in humans (20). In addition, the susceptibility of the coronary circulation to the vasoconstrictor action of endothelin may be greatly potentiated by damage to the coronary endothelium (7), particularly after an ischemic insult (21). Therefore, even relatively low circulating concentrations of endothelin may markedly alter coronary vasomotor tone in areas of ischemic damage associated with myocardial infarction.

Figure 2. Time course of plasma immunoreactive endothelin-1 (irET-1) (**ordinate**) in patients after uncomplicated (group I) and complicated (group II) myocardial infarction (MI). The time in hours after (post) the onset of myocardial infarction appears on the **abscissa**. The **shaded area** indicates the normal range. * = $p < 0.05$ compared with values in normal subjects; + = $p < 0.05$ compared with values in group I.



Stimuli that lead to release of endothelin from coronary vasculature. Endothelin-1 is a product of vascular endothelium (1) and likely achieves its highest concentration and greatest action at the local vascular site of its release (1,22). Thus, the concentration of endothelin within the coronary vasculature may be considerably higher than the levels measured in the circulating blood and well within the range of biologic action. The mechanism whereby the release of endothelin-1 is stimulated after myocardial infarction remains to be determined. In vitro studies (1,23–25) have shown that both hypoxia and thrombin can induce the release of endothelin from endothelial cells. Activation of the coagulation cascade at the site of a complex coronary stenosis with generation of thrombin is thought to initiate occlusive thrombosis (26). In addition, decreased delivery of oxygen leads to regional hypoxia and ischemia. Thus, these and other stimuli could induce the release of endothelin from the coronary vasculature after acute coronary occlusion. Indeed, myocardial infarction in animal models (27) has been shown to result in increased endothelin levels in the heart, possibly contributing to infarct extension, and ischemia/

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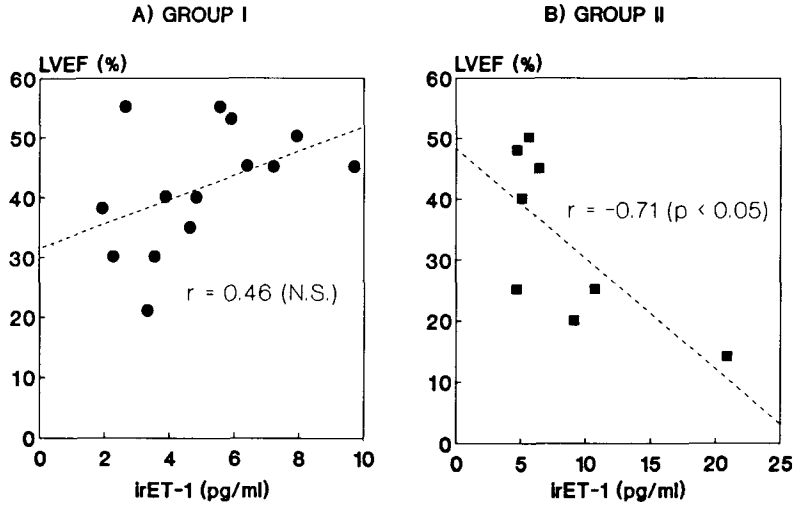

Figure 4. Left ventricular ejection fraction (LVEF) (**ordinate**) is plotted against immunoreactive endothelin-1 (irET-1) (**abscissa**) for patients with uncomplicated infarction (group I) (**panel A**) and patients with hemodynamic or ischemic complications (group II) (**panel B**).

reperfusion has been reported (28) to increase endothelin binding sites in cardiac membranes.

Correlation of endothelin-1 and CK levels. In the present study, there was no correlation between peak elevations in plasma CK and immunoreactive endothelin-1 after myocardial infarction, suggesting that increase in the latter may not be related to myocardial necrosis itself, but to other vascular events associated with infarction, such as the degree of coronary ischemia. Plasma endothelin may be a marker of endothelial cell perturbation (22) that precedes frank necrosis or occurs in areas adjacent to the zone of infarction. This is in agreement with observations in individual patients that substantial increases in circulating endothelin-1 were found even in association with only a small infarct as determined by cardiac enzyme and functional criteria (Table 1).

Mechanism of sustained increases in plasma endothelin-1. Patients with complicated myocardial infarction demonstrated a rapid increase in plasma immunoreactive endothelin-1 similar to that in the patients with uncomplicated infarction (Fig. 2). However, in contrast to the group with uncomplicated infarction, this increase was sustained over the study period rather than being transient. This might explain the more prolonged elevation in plasma endothelin described in earlier studies (16,17) that did not differentiate between these two groups. Sustained increases in endothelin might reflect continued ischemia due to incomplete infarction or infarct extension in some patients (Table 1). However, it is likely that the mechanism of elevated endothelin was multifactorial in patients demonstrating hemodynamic compromise and may have included systemic hypoperfusion and multiorgan ischemia (15), the effect of circulating catecholamines or pressor agents (for example, norepinephrine) (1) and decreased pulmonary (29–31) or renal (32) clearance as a result of lung congestion or decreased renal blood flow.

Correlation with left ventricular function. In group I patients, there was no correlation between left ventricular function and peak endothelin levels (Fig. 4A), a finding consistent with the concept that in the absence of hemodynamic complications, the extent of ischemia rather than the actual area of necrosis might be a crucial determinant of endothelin release. In contrast, after complicated infarction, the highest levels of endothelin-1 were observed in patients with the lowest ejection fraction (group II) (Fig. 4B). This again suggests that depressed myocardial performance contributed importantly to the more marked and sustained elevations in endothelin-1 observed in this group. Despite the development of hemodynamic complications in many of the group II patients, the peak CK increase tended to be lower than in group I patients (Tables 1 and 2). This apparent discrepancy between the size of infarction by enzyme criteria and its hemodynamic consequences can be explained if preexisting depression of left ventricular function made some patients unable to tolerate even small areas of further damage. In addition, a higher proportion of group I patients received thrombolytic therapy; thus in some patients an early "washout" on reperfusion might have raised the peak serum CK level in relation to infarct size.

Conclusions. Plasma endothelin levels increase significantly after uncomplicated acute myocardial infarction and might provide a marker of endothelial cell perturbation in the early phase of myocardial ischemia. Because endothelin levels in plasma are near maximal at a time when CK is barely elevated, this could assist in the diagnosis of important myocardial ischemia soon after its onset. In addition, plasma concentrations of endothelin might also reflect abnormalities of systemic perfusion in states of markedly depressed cardiac performance. The potential role of this potent vasoconstrictor peptide in the pathophysiology of myocardial infarction and its hemodynamic complications are areas of important future research.

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