Plasma Endothelin Determination as a Prognostic Indicator of 1-Year Mortality After Acute Myocardial Infarction

Torbjørn Omland, MD; Rolv Terje Lie, PhD; Asbjørn Aakvaag, MD, PhD; Torbjørn Aarsland, RN; Kenneth Dickstein, MD, PhD

Background Plasma endothelin concentrations are increased in the acute phase of myocardial infarction and in chronic heart failure. Since endothelin may contribute to hemodynamic deterioration by potent vasoconstrictory and cardiotoxic actions, increased plasma levels may be associated with an unfavorable prognosis after myocardial infarction.

Methods and Results We tested the hypothesis that plasma endothelin determination in the subacute phase of myocardial infarction is related to subsequent survival and assessed whether plasma endothelin measurements provide additional prognostic information to that obtained from clinical and biochemical variables previously known to be associated with high mortality. Plasma endothelin determination was obtained from 142 patients (average age ±SD, 67.8±10.1 years) on day 3 after documented myocardial infarction and was related to 1-year mortality. Sixteen patients died during the follow-up period. In a univariate Cox proportional-hazards model, day 3 plasma endothelin concentrations were significantly related to mortality (P<.0001). Patient age, previous treatment for systemic hypertension, presence of clinical heart failure, and plasma atrial natriuretic factor levels were all related to mortality in univariate analysis but provided no additional prognostic information to that obtained from endothelin determination in a multivariate model.

Conclusions Plasma endothelin concentrations are strongly related to outcome after myocardial infarction and provide prognostic information independent of clinical and biochemical variables previously associated with a poor prognosis. (Circulation. 1994;89:1573-1579.)

Key Words • endothelin • prognosis • myocardial infarction • heart failure

Raised circulating concentrations of the endothelium-derived 21-amino-acid vasoconstrictor peptide endothelin have recently been reported during the early hours after acute myocardial infarction. Although a sustained elevation of circulating endothelin is observed in patients with complicated myocardial infarction, plasma levels decline rapidly in uncomplicated cases. Furthermore, in chronic heart failure and in myocardial infarction with heart failure, plasma endothelin concentrations and pulmonary capillary wedge pressure correlate closely. Since endothelin possesses potentially harmful pathophysiological properties and in addition may function as a marker of the degree of left ventricular dysfunction and subsequent elevation of filling pressure, persistent high plasma levels might be associated with a poor prognosis after myocardial infarction.

To test this hypothesis, blood samples for endothelin determination were obtained from 142 patients in the subacute phase of myocardial infarction and were related to 1-year mortality. Second, the predictive power of endothelin was compared with other established risk factors of mortality after myocardial infarction in a multivariate Cox proportional-hazards regression model.

Methods

Study Design and Patient Population

Venous blood for determination of endothelin and atrial natriuretic factor was prospectively obtained on day 3 after onset of symptoms from 142 patients with documented myocardial infarction (average age ±SD, 67.8±10.1 years) admitted to a single coronary care unit during a 6-month recruitment period. Patient characteristics are summarized in Table 1. All patients participated in the randomized, placebo-controlled, double-blind Cooperative New Scandinavian Enalapril Survival Study (CONSENSUS II), which addressed the effect on mortality of enalapril treatment initiated early after symptom debut in patients with acute myocardial infarction. The study was approved by the Regional Ethics Committee, and informed consent was obtained from all patients participating.

The diagnosis of myocardial infarction was based on the combination of chest pain of more than 20 minutes’ duration and standard ECG criteria compatible with acute myocardial infarction or enzymatic evidence of myocardial necrosis. Exclusion criteria included supine blood pressure <100/60 mm Hg, cardiogenic shock, need for pressor support, hemodynamically significant valvular stenosis, and severe congestive heart failure (New York Heart Association class IV). Clinical examinations were performed regularly during the hospitalization phase and at 1, 3, and 6 months. Clinical heart failure was defined as pulmonary congestion warranting treatment with diuretics.

Venous plasma samples were also obtained on day 3 after symptom debut from 14 control patients (age, 59.3±14.2 years) admitted to the coronary care unit with acute chest pain but without evidence of myocardial necrosis. Patients with a
history of a previous myocardial infarction or chronic cardiac or renal failure were not included in the control group.

**Blood Sampling Procedures and Hormonal Assays**

Blood samples were drawn by direct venipuncture after at least 30 minutes of supine rest. For plasma endothelin analysis, samples were collected into chilled tubes containing EDTA. For atrial natriuretic factor analysis, samples were collected into chilled tubes containing EDTA and aprotinin (500 kalikrein inactivator units/mL blood). Test tubes were immediately placed on ice and centrifuged within 30 minutes. Plasma samples were stored at −70°C until analyzed.

Endothelin in plasma was measured with a reagent kit from Nichols Institute Diagnostics BV, Wichen, the Netherlands, according to the procedure recommended by the manufacturer. Briefly, the method included acidification of 2 mL of plasma with 3.0 mL of 4% acetic acid and subsequent application onto a Sep-Pac C18 column (Millipore). After the column was washed twice with 3 mL of water and once with 3 mL of 25% ethanol in water, the sample was eluted by application of 1 mL of 4% acetic acid in 86% ethanol in water. After evaporation under nitrogen, the residue was reconstituted with assay buffer. The results presented have not been corrected for losses encountered during the extraction procedure.

In a control sample with a concentration of 9.2 pg/mL, we obtained a within-assay precision of 11.8% (n=10) and a between-assay precision of 10.1% (n=10). The sensitivity of the assay, expressed as precision of zero calibrator (mean±2 SD) was calculated to be 1.4 pg/mL.

The assay was calibrated with endothelin-1. According to the manufacturer, the cross-reactivities to endothelin-2 and endothelin-3 are 52% and 96%, respectively, and the cross-reactivity to big endothelin-1 is 7%. No significant cross-reactivity to other substances has been reported.

Plasma atrial natriuretic factor concentrations were measured by radioimmunoassay after extraction on a C18 octadecyl silica microcolumn using a kit from Amersham International, England, as described previously.14

**Statistics**

Because the hormone plasma levels were not normally distributed, logarithmic transformation of these values was performed to meet the criteria for the statistical analyses used. However, to permit direct comparison with results from other studies, data are presented as nontransformed means±SEM.
The prognostic value of our variables was tested in a Cox proportional-hazards regression analysis with the program 2L in BMDP. Estimates of risk ratios for each of the selected variables were computed from the Cox proportional-hazards model. Kaplan-Meier estimates of the survival functions were plotted for high and low plasma endothelin levels with the 75th percentile as a cut-off point. Linear regression analysis was used to assess the relation between continuous variables. Unpaired t tests were used to contrast mean values between groups. \( \chi^2 \) tests with Yates' correction were used to contrast proportions between groups. When expected frequencies were <5, Fisher's exact test was used.

**Results**

**Plasma Endothelin During Acute Myocardial Infarction**

Plasma endothelin concentrations averaged 5.6±0.3 pg/mL in 142 patients with myocardial infarction. In comparison, plasma endothelin levels in the 14 control patients admitted to hospital with acute chest pain without evidence of myocardial necrosis averaged 3.7±0.3 pg/mL \( (P = .005) \). Patients with clinical heart failure during the hospitalization phase \( (n=40) \) had significantly higher plasma endothelin levels than the non-heart failure group \( (n=102) \) \( (7.2±0.8 \text{ versus } 4.9±0.2 \text{ pg/mL}; P<.001) \). Plasma concentrations of atrial natriuretic factor were also increased in the heart failure group compared with the non-heart failure group \( (170.3±16.6 \text{ versus } 89.3±4.9 \text{ pg/mL}; P<.001) \).

Day 3 plasma endothelin and atrial natriuretic factor concentrations correlated significantly \( (n=142; r=.41; P<.001) \). A weak but statistically significant correlation between plasma endothelin levels and peak creatine kinase MB fraction concentrations \( (r=.20; P=.019) \) and between plasma endothelin levels and age \( (r=.29; P<.001) \) was evident.

There was no statistically significant difference in plasma endothelin levels between groups when patients were subdivided according to in-hospital treatment with thrombolytic therapy, angiotensin-converting enzyme inhibitors (enalapril), or \( \beta \)-adrenergic receptor blockers.

**Plasma Endothelin and 1-Year Mortality**

Sixteen patients died of cardiac causes during the 1-year follow-up period (11%). In addition, 1 patient died of a noncardiac cause on day 94 and was subsequently censored from the analysis. Comparison between deceased patients and survivors revealed significantly elevated day 3 plasma endothelin levels in the former group \( (9.2±1.5 \text{ versus } 5.1±0.2 \text{ pg/mL}, P<.001) \) as well as elevated plasma atrial natriuretic factor levels \( (171.2±22.8 \text{ versus } 105.0±6.5 \text{ pg/mL}, P=.002) \). The Figure depicts Kaplan-Meier survival functions with patients subdivided according to the 75th percentile day 3 plasma concentration of endothelin.

In a univariate Cox proportional-hazards model, plasma endothelin concentrations were strongly related to survival \( (P<.0001) \). Table 2 summarizes the univariate relation between variables previously known to be associated with a poor prognosis after myocardial infarction and mortality. With the exception of female sex, none of these variables provided additional prognostic information after introduction of plasma endothelin in a multivariate model (Table 3). Based on the Cox proportional-hazards regression model, risk ratio estimates were calculated for the various risk factors. The risk ratio estimates based on the univariate Cox models are presented in Table 4A, whereas adjusted risk ratio estimates based on the multivariate model are presented in Table 4B.

Since the patients in this study were recruited from a randomized trial investigating the effect on mortality of the early administration of the converting enzyme inhibitor enalapril after myocardial infarction, we also wanted to assess the possibility of an interaction between enalapril therapy and subacute plasma endothelin levels. When patients were stratified according to treatment with enalapril versus placebo, the predictive value of log-endothelin levels was significantly greater in the placebo group than in the enalapril group \( (P=.041) \), suggesting interaction between angiotensin-converting enzyme inhibition and endothelin production. To illustrate this phenomenon, an interaction term was included in the analysis.
Table 3. Multivariate Relation Between Various Demographic, Clinical, and Biochemical Variables and 1-Year Mortality After Myocardial Infarction According to a Cox Proportional-Hazards Model (Final Model)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Coefficient</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>In Endothelin</td>
<td>3.1608</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>In Atrial natriuretic factor</td>
<td>.2808*</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>.8271*</td>
<td></td>
</tr>
<tr>
<td>Male sex</td>
<td>−1.4625</td>
<td>.0066</td>
</tr>
<tr>
<td>Systemic hypertension</td>
<td>.1483*</td>
<td></td>
</tr>
<tr>
<td>In-hospital heart failure</td>
<td>.4945*</td>
<td></td>
</tr>
</tbody>
</table>

*Factors not included in the model.

included in the Cox proportional-hazards model, as shown in Table 5.

Discussion

Since the discovery of endothelin by Yanagisawa and coworkers in 1988,9 extensive research has been performed to clarify its role in cardiovascular pathophysiology.10 However, clinical studies in myocardial infarction are few and comprise relatively small numbers of patients.1-5,8 Although previous investigations have demonstrated elevated plasma endothelin levels in patients with cardiogenic shock and pulmonary edema,8,17 the present investigation is the first to describe a relation between endothelin determination obtained in the subacute phase of myocardial infarction and 1-year mortality. Furthermore, the relatively large sample size permitted evaluation of the prognostic value of endothelin not only in univariate but also in multivariate analysis, revealing the novel observation that plasma endothelin is a powerful prognostic aid providing information independent of various clinical and biochemical variables. In fact, clinical evaluation of heart failure and atrial natriuretic factor level determination, both known to be strong predictors of mortality after myocardial infarction,18-21 provided no additional prognostic information after introduction of endothelin into the model.

In patients with chronic heart failure, plasma levels of atrial natriuretic factor and norepinephrine are related to mortality.22,23 However, as we reported previously, in patients with myocardial infarction, plasma norepinephrine determination failed to provide additional prognostic information to that obtained from clinical classification of heart failure, even though plasma norepinephrine values were significantly related to mortality in univariate analysis.21 Together, these results suggest that the subacute plasma endothelin values may provide prognostic information superior to that obtained from plasma norepinephrine determination.

Rationale for Subacute Endothelin Determination

The plasma profile of endothelin in the acute phase of myocardial infarction has previously been investigated in several small-scale studies1-4 that demonstrate a rapid increase in plasma endothelin levels after admission, with a peak occurring approximately 6 hours after onset of symptoms, followed by a gradual decline toward normal values in uncomplicated myocardial infarction. In contrast, in patients with either persistent hypotension, pulmonary edema, postinfarction ischemia, or early reinfarction, sustained elevation of plasma endothelin concentrations was observed 72 hours after symptom debut.1 Consequently, to evaluate the possible relation between plasma endothelin levels and prognosis, it appeared reasonable to select the subacute phase as the time point for blood sampling, since it would detect patients with persistent versus patients with transient elevation of plasma endothelin concentrations. An additional argument favoring blood sampling in the subacute rather than the acute phase was the assumption that both plasma endothelin production and degradation are in a relatively steady state in the subacute phase, whereas the concentrations measured acutely might change dramatically within hours.1

Endothelin Production After Myocardial Infarction: Potential Sites and Stimuli

The main stimulus for and site of endothelin production during and after acute myocardial infarction remain to be established. During experimental myocardial ischemia in dogs, endothelin levels increase in parallel in the coronary sinus and the aorta, followed by an increase in net myocardial endothelin production in the early reperfusion period.24 However, a high myocardial content of endothelin has been observed as long as 48 hours after reperfusion.25 Interestingly, simultaneous sampling of blood from different vascular beds in patients with chronic heart failure reveals no significant differences in plasma endothelin levels, compatible with a generalized systemic activation of endothelin production in chronic heart failure.26 It is therefore possible that acute ischemia may function as a trigger for cardiac endothelin production in the early phase of myocardial infarction, whereas peripheral hypoperfusion secondary to reduced cardiac output may represent a stimulus for subsequent persistent systemic endothelin production.

Interaction with other neurohumoral systems may also play a role in the augmented endothelin production following myocardial infarction. Experimental work indicates that catecholamines, angiotensin II, and arginine vasopressin may stimulate endothelin production.9,27,28 In this context, it is noteworthy that enalapril appeared to influence the relation between plasma endothelin levels and mortality. A possible explanation is that converting enzyme inhibition and reduced angiotensin II formation might result in decreased endothelin production. However, this effect may be recognizable only in patients with pronounced neurohumoral activation, explaining why no significant difference in plasma endothelin concentrations was demonstrable between the enalapril and the placebo groups regarded as a whole. However, because of the extensive concomitant medical treatment the patients received, caution is warranted in interpreting these results.

A decreased clearance rate may also contribute to sustained elevation of plasma endothelin levels. Recent reports suggest involvement of both the kidney29 and the lung30,31 in the clearance of endothelin. Pulmonary congestion and renal artery vasconstriction with secondary hypoperfusion are both common complications to myocardial infarction that may affect the ability of the kidney and the lung to clear endothelin from the circulation.
TABLE 4. Risk Ratio Estimates

<table>
<thead>
<tr>
<th>Variable</th>
<th>Risk Ratio Estimate</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. Based on univariate Cox proportional-hazards models</td>
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<tr>
<td>Endothelin &lt;4.9 pg/mL</td>
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<td>0.5-16.8</td>
<td>.0002</td>
</tr>
<tr>
<td>Endothelin 4.9-6.5 pg/mL</td>
<td>2.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Endothelin &gt;6.5 pg/mL</td>
<td>12.6</td>
<td>2.8-56.7</td>
<td></td>
</tr>
<tr>
<td>Atrial natriuretic factor &lt;93.6 pg/mL</td>
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<td></td>
<td>.0032</td>
</tr>
<tr>
<td>Atrial natriuretic factor 93.6-128.1 pg/mL</td>
<td>6.2</td>
<td>1.3-30.9</td>
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</tr>
<tr>
<td>Atrial natriuretic factor &gt;128.1 pg/mL</td>
<td>8.9</td>
<td>1.9-42.1</td>
<td></td>
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<tr>
<td>No heart failure</td>
<td>1.0</td>
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<tr>
<td>Heart failure</td>
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<td>1.9-13.9</td>
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<tr>
<td>Hypertension</td>
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<td>1.0-6.7</td>
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</tr>
<tr>
<td>Female sex</td>
<td>2.6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age &lt;70.0 y</td>
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<td></td>
<td>.0708</td>
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<tr>
<td>Age 70.0-75.3 y</td>
<td>3.4</td>
<td>1.0-11.7</td>
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<tr>
<td>Age &gt;75.3 y</td>
<td>3.3</td>
<td>0.9-11.6</td>
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</tr>
<tr>
<td>B. Based on the multivariate Cox proportional-hazards model</td>
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<td></td>
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<td>Endothelin &lt;4.9 pg/mL</td>
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<td>.0116</td>
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<tr>
<td>Endothelin 4.9-6.5 pg/mL</td>
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<td>0.3-13.4</td>
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<tr>
<td>Endothelin &gt;6.5 pg/mL</td>
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<td>1.5-40.7</td>
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<td>Atrial natriuretic factor &lt;93.6 pg/mL</td>
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<td>Atrial natriuretic factor 93.6-128.1 pg/mL</td>
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<tr>
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<td>Heart failure</td>
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<td>Hypertension</td>
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<td>Male sex</td>
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<td>Female sex</td>
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<tr>
<td>Age 70.0-75.3 y</td>
<td>2.7</td>
<td>0.6-11.4</td>
<td></td>
</tr>
<tr>
<td>Age &gt;75.3 y</td>
<td>1.1</td>
<td>0.3-4.9</td>
<td></td>
</tr>
</tbody>
</table>

Cl indicates confidence interval.
*Cutoff points represent median and 75th percentile values.

Endothelin and Mortality: Potential Mechanisms

Several factors may contribute to the relation between high plasma endothelin concentrations and mortality. In chronic heart failure, elevated plasma endothelin levels have been linked to the degree of pulmonary hypertension, reflected in close correlations with pulmonary capillary wedge pressure and pulmonary resistance.6 Recently, fair correlations between plasma endothelin levels and pulmonary capillary wedge pressure, pulmonary artery mean pressure, pulmonary vascular resistance, and cardiac index have been observed in patients 24 hours after acute myocardial infarction.7 These findings suggest that endothelin plays a role in the pathophysiology of heart failure and may be a marker of disease severity and outcome.

TABLE 5. Interaction Between Enalapril and Log-Transformed Plasma Endothelin Levels on Survival Based on a Cox Proportional-Hazards Model

<table>
<thead>
<tr>
<th></th>
<th>Total Model</th>
<th>Reduced Model</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Coefficient</td>
<td>SE</td>
</tr>
<tr>
<td>Enalapril</td>
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<td>2.80</td>
</tr>
<tr>
<td>Endothelin</td>
<td>1.67</td>
<td>0.90</td>
</tr>
<tr>
<td>Interaction term</td>
<td>2.60</td>
<td>1.34</td>
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dial infarction. The connection between plasma endothelin and prognosis suggests that endothelin reflects elevation in left atrial pressure secondary to left ventricular dysfunction. However, the correlation between plasma levels of endothelin and atrial natriuretic factor (the latter known to be closely related to cardiac filling pressures), although significant, is poor according to the present data set, suggesting that additional actions of endothelin may be of greater importance.

Endothelin is believed to exert its effects predominantly as an autocrine and/or paracrine substance, and the physiological relevance of circulating endothelin remains to be established. However, infusion studies in dogs and in humans suggest that circulating endothelin in picomolar concentrations may exert physiological actions. Furthermore, administration of a monoclonal antibody against endothelin during experimental myocardial infarction reduces infarct size substantially in a rat model. Thus, circulating endothelin, via its potent vasoconstrictory actions, may contribute to infarct extension at pathophysiological concentrations. Animal experiments also suggest that endothelin may have direct cardiotoxic effects as well as arrhythmogenic effects. The relation between sustained augmented endothelin production after myocardial infarction and subsequent mortality might therefore be based on these harmful effects of circulating endothelin.

Limitations

The patient exclusion criteria suggest a selection bias, and a major concern is whether this bias may have influenced the relation between plasma endothelin and survival. However, we believe that exclusion of the patients with the most severe hemodynamic compromise results in underestimation rather than overestimation of the predictive value of endothelin since (1) these patients are known to have a poor prognosis and (2) plasma endothelin levels have been reported to increase in proportion to the severity of heart failure in acute myocardial infarction. Furthermore, in the evaluation of novel tools for risk stratification, emphasis should be placed on the prognostic information gained in addition to standard clinical evaluation. In this respect, the exclusion of patients in cardiogenic shock and with severe congestive heart failure on admission should not compromise the interpretation of the present results.

The proportion of patients with non-Q-wave infarctions is somewhat higher than in unselected materials, compatible with a certain selection bias in the present investigation. We believe that the entry criteria of the CONSENSUS II trial were the main cause of this bias. Accordingly, a similar proportion of non-Q-wave infarctions (41%) was observed in the main study. Furthermore, the mortality rate in this substudy appears to be comparable to that reported in recent investigations, suggesting that the present sample is not markedly different from unselected patients with myocardial infarction surviving 72 hours.

The cross-reactivity between different endothelin isoforms represents a potential limitation. Although endothelin-1, endothelin-3, and the preform big endothelin-1 are all found circulating in blood, endothelin-1 is probably of greater pathophysiological importance because of its greater contractile potency. Furthermore, plasma concentrations of endothelin-2 and endothelin-3 are not modified by coronary occlusion or reperfusion in experimental models. The plasma profiles of endothelin-1 and big endothelin-1 appear to be similar after myocardial infarction, indicating simultaneous release of the two from damaged endothelial cells and/or ischemic myocardium. The cross-reactivity between big endothelin-1 and endothelin-1 is therefore probably of minor importance in the interpretation of the present data.

The reported normal range of plasma endothelin concentrations varies considerably among laboratories. A potential explanation for this variation may be the differing specificities of the radioimmunoassays used. Consequently, before implementation of plasma endothelin determination as a prognostic tool, all laboratories should define their own normal range of values, valid only for the specific analytic procedure used. Accordingly, the cutoff level selected in this text pertains only to the present patient sample and analytic method and is not generally valid.

Conclusions

Circulating concentrations of the endothelium-derived vasoconstrictor peptide endothelin in the subacute phase after myocardial infarction appear to be strongly related to 1-year mortality rates after myocardial infarction. Whether the association is based on the function of endothelin as a marker of poor ventricular function or reflects direct pathophysiological actions or a combination of both remains to be established. Elucidating this issue and determining the site and stimulus for endothelin production after myocardial infarction should be major goals for future investigations.

Acknowledgments

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