



# ACE inhibition in ischemic heart disease: what is the relevance of the control of the neuroendocrine response?

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*Neuroendocrine systems are central to key heart disease processes such as cardiovascular remodeling, fibrosis, apoptosis, paradoxical coronary constriction, and salt-and-water retention. The neuroendocrine response to severe ischemia leads to increased arterial pressure and afterload, and compounds myocardial oxygen debt. Acute ACE inhibition in pacing-induced ischemia modulates vasoconstrictor hormone secretion, while chronic ACE inhibition appears to improve myocardial ischemia via long-term neurohormone-mediated structural effects. Thus, inhibition of angiotensin II formation itself inhibits the sympathetic system, and possibly also aldosterone and endothelin secretion. Crucially, it also reduces the breakdown of bradykinin. Long-term improvement in coronary structure and endothelial function during chronic ACE inhibition normalizes the paradoxical vascular response to neuroendocrine stimuli.*

**Keywords:** angiotensin-converting enzyme; neuroendocrine response

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Neurohormonal activation is pivotal to the development of heart failure and its progression to end-stage cardiac disease. Although many different mechanisms underlie the development of the disease, circulating or local tissue neurohormonal systems are central to the more important processes, including cardiovascular remodeling, fibrosis, apoptosis, inappropriate vasoconstriction, and salt-and-water retention. In advanced stages, the picture of neurohormonal and peptide activation includes the sympathetic system, the renin-angiotensin system, aldosterone, vasopressin, endothelin, the natriuretic peptides, and cytokines. In the early stages of failure and in the preceding phase of asymptomatic ventricular dysfunction, an increase in circulating catecholamines, aldosterone, and natriuretic peptides is observed. Of these, the natriuretic peptides are the first to increase and, besides their hemodynamic effects, may serve to temporarily inhibit the activation of vasoconstriction and growth-promoting neurohormones, such as norepinephrine and angiotensin II.

It is as yet unclear whether this picture differs between ischemic and nonischemic cardiomyopathy, either in the symptomatic or asymptomatic phase of heart failure.

As there is now accumulating evidence that myocardial ischemia per se stimulates certain neurohormones, one might hypothesize that heart failure due to ischemic cardiomyopathy is accompanied by more intense neurohormonal activation.

## WHAT IS THE EVIDENCE THAT MYOCARDIAL ISCHEMIA LEADS TO NEUROHORMONAL STIMULATION?

### The sympathetic system

Global ischemia in a rodent Langendorff model results in progressive cardiac norepinephrine release, which starts approximately 10 minutes after the onset of ischemia.<sup>1</sup> This time interval corresponds with a reversal of the uptake-1 mechanism in nerve endings, from uptake

### SELECTED ABBREVIATIONS AND ACRONYMS

<b>CATS</b>	Captopril And Thrombolysis Study
<b>ANP</b>	atrial natriuretic peptide
<b>SAVE</b>	Survival And Ventricular Enlargement Trial
<b>SOLVD</b>	Studies Of Left Ventricular Dysfunction



to release, under the influence of increased  $\text{Na}^+/\text{H}^+$  exchange and sodium uptake in the nerve ending. Of interest, in the acute phase of ischemia, there is net uptake of norepinephrine by the heart due to prejunctional inhibition of norepinephrine release, most likely the result of increasing levels of adenosine. In humans, pacing-induced myocardial ischemia also leads to a reversal of cardiac norepinephrine release to net uptake during and immediately after the ischemic episode, at a time that hypoxanthine, a breakdown product of adenosine, is significantly increased in the venous effluent of the ischemic area.<sup>2,3</sup>

With continued severe ischemia resulting in myocardial infarction, norepinephrine release from the infarcted area continues with, ultimately, a complete loss of cardiac norepinephrine levels during the first days of coronary occlusion.

In patients with an acute infarct, plasma and urinary catecholamine levels rise within 1 hour of the onset of symptoms, depending on the magnitude and severity of the insult. This observation appears to be relatively consistent and has been observed in several studies conducted from the sixties to the eighties.<sup>4-6</sup>

In contrast, whether circulating catecholamine levels, which reflect the activity of the sympathetic system, rise during exercise- or stress-induced ischemia, has been less clear for many years. Early studies did not find significantly elevated levels over and above those induced by exercise per se, possibly due to the low sensitivity of early analytic techniques.

However, more recently, marked increases in circulating norepinephrine levels have been observed, correlat-

ed with the severity of ischemia, and significantly higher than circulating catecholamine levels in patients with coronary artery disease who, despite similar exercise levels, did not become ischemic.

Similar observations have been made in patients who developed myocardial ischemia during incremental atrial pacing (*Figure 1, see next page*). Whereas this form of testing does not affect circulating catecholamines in the absence of ischemia, patients who developed severe ischemia significantly increased arterial and coronary venous norepinephrine and epinephrine levels, by 70% and 40%, respectively, whereas patients with less ischemia also activated their sympathetic system, but to a lesser extent and for a shorter period.<sup>7</sup> Importantly, changes were not due to the stress of anginal pain, as similar levels of ischemia resulted in equal increases in norepinephrine in both symptomatic and asymptomatic patients.<sup>8</sup>

### The renin-angiotensin system

In the same studies, more severe ischemia also activated the renin-angiotensin system. In patients with severe ischemia, arterial angiotensin II levels rose by 50% (*Figure 1*).<sup>7</sup> No changes were observed in the coronary venous effluent. Neither was angiotensin II affected in milder forms of ischemia. Activation of the renin-angiotensin system has been reported minutes after coronary occlusion, with progressive increases in both renin and angiotensin II.<sup>9,10</sup> Nephrectomy prevented this neurohormonal activation. Whether a reduction in cardiac output and renal perfusion in severe ischemia or the concomitant sympathetic stimulation causes this activation of the renin-angiotensin system is unknown. The direct effect

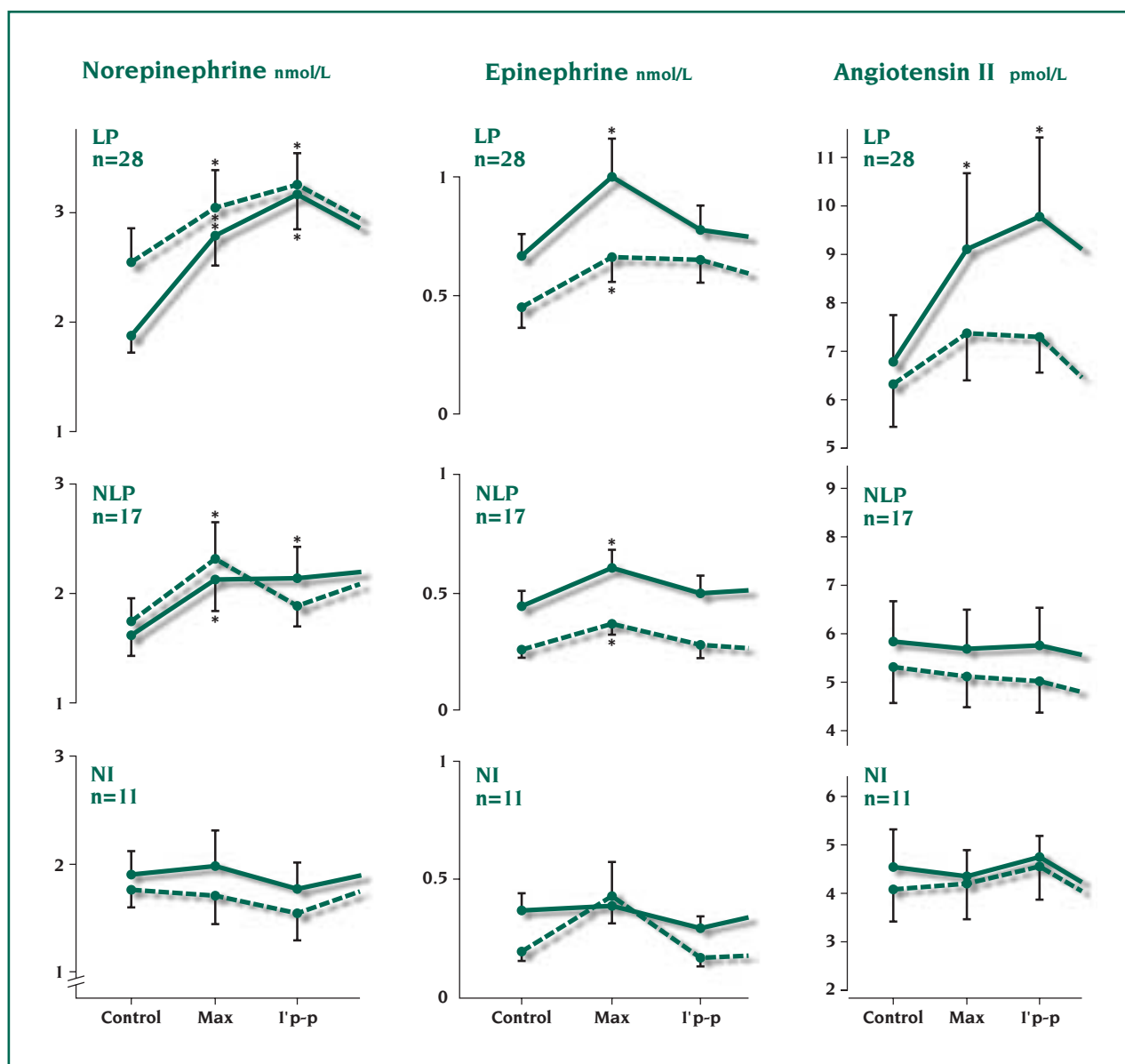
is a significant increase in the strong vasoconstrictor neurohormone angiotensin II. As the sympathetic system is activated simultaneously, arterial vasoconstriction is likely to occur.

### Natriuretic peptides

In the model of pacing-induced ischemia, both arterial and coronary venous atrial natriuretic peptide (ANP) levels increase markedly, and cardiac ANP release is augmented.<sup>11</sup> Cardiac ANP release is most pronounced 1 minute after pacing, when the effect of fast atrial contractions can be discarded, suggesting a direct effect of ischemia and ischemia-induced left ventricular (LV) filling pressures. Increased ANP levels also accompany exercise-induced stress in patients with ischemic LV dysfunction and significantly correlate with ischemia-induced changes in ejection fraction.<sup>12</sup> As such, ANP could be a marker of ischemic cardiac dysfunction. Whether it has additional effects, counteracting the vasoconstricting effects of norepinephrine or angiotensin II, is unclear.

### ISCHEMIA-INDUCED NEUROHORMONAL ACTIVATION AND VASOCONSTRICTION

In humans, neurohormonal stimulation such as that occurring during short periods of stress- or exercise-induced ischemia definitely results in systemic vasoconstriction, leading to increased arterial pressures and afterload. As such, it is likely to increase myocardial oxygen demand, further augmenting the ischemic episode that initiated the neurohormonal response. Importantly, simultaneous, extensively enhanced cardiac ANP release and subsequent increased arterial ANP do not counteract this vasoconstrictive effect.



**Figure 1.** Effect of incremental atrial pacing on arterial (solid line) and coronary venous (broken line) norepinephrine, epinephrine, and angiotensin II in patients who develop severe ischemia (LP), mild ischemia (NLP), and patients who, despite similar pacing levels, do not become ischemic (NI). In the latter group, pacing does not affect neurohormones. In contrast, in both mild and severe ischemia, norepinephrine and epinephrine levels are significantly increased and, in severe ischemia, arterial angiotensin II levels are also increased. \* $P < 0.05$  vs control; Max, maximal pacing heart rates; 1'p-p, 1 minute post pacing.

Modified from ref 7: Remme WJ, Kruissen HACM, Look MP, Bootsma M, De Leeuw PW. Systemic and cardiac neuroendocrine activation and severity of myocardial ischemia in humans. *J Am Coll Cardiol.* 1994;23:82-91. Copyright © 1994, The American College of Cardiology.

Indirect evidence also suggests that coronary vasoconstriction ensues following myocardial ischemia. During exercise and angina, the lesion area of stenotic coronary arteries constricts, whereas normal coronary segments dilate. The presence of abnormal endothelial function, as

demonstrated by vasoconstriction after intracoronary acetylcholine, appears to be a prerequisite. Although in these studies neurohormonal activation was not measured, the observation that other stimuli that activate the sympathetic system—such as the cold pressor

test—also result in vasoconstriction in coronary segments with abnormal endothelial function, whereas normal coronary segments dilate, strongly suggests the involvement of neurohormonal, ie, sympathetic, activation.<sup>13</sup> That sympathetic activation indeed underlies coronary



vasoconstriction during ischemia is suggested by an enhanced coronary vasoconstricting response to acute  $\beta$ -blockade in these circumstances, most likely the result of sympathetic activation of unopposed  $\alpha$ -adrenergic receptors.<sup>14</sup>

### **PREVALENCE OF ISCHEMIA-INDUCED NEUROHORMONAL ACTIVATION**

As neurohormonal activation and its sequelae depend on the severity of ischemia, this becomes more of an issue in clinical conditions in which severe ischemia predominates. Thus, severe ischemia during stress or exercise leads to greater activation and more pronounced systemic vasoconstriction.

Cardiac sympathetic nervous activity is increased in patients with unstable angina compared with those with stable angina.<sup>15</sup> One might speculate that this increase leads to enhanced sympathetically induced coronary vasoconstriction and contributes to progressive myocardial ischemia in these patients.

Neurohormonal activation is also more pronounced in patients with LV dysfunction compared with patients with normal function, despite a similar degree of myocardial ischemia,<sup>16</sup> as measured by myocardial lactate production and ischemic electrocardiographic changes. During pacing-induced ischemia, the increase in arterial and coronary venous norepinephrine and epinephrine levels is approximately two times greater in LV dysfunction, and so is the effect on systemic vascular tone. Moreover, in LV dysfunction, arterial angiotensin II levels increase, even in moderate ischemia, but not in patients with normal function. Is this observation clinically relevant?

### **ACE INHIBITION AND MYOCARDIAL ISCHEMIA—EFFECTIVE IN PATIENTS WITH HEART FAILURE AND/OR ASYMPTOMATIC LV DYSFUNCTION**

Several large, controlled studies, such as the Survival And Ventricular Enlargement trial (SAVE) and Studies Of Left Ventricular Dysfunction (SOLVD), designed to evaluate the long-term effect of angiotensin-converting enzyme (ACE) inhibition on mortality and morbidity in patients with heart failure or asymptomatic LV dysfunction, observed a significant, unexpected effect on myocardial ischemia in terms of reduction in the frequency of myocardial infarction and unstable angina.<sup>17,18</sup> It is tempting to consider at least a partial anti-ischemic effect of the ACE inhibitors through modulation of neurohormonal activation and prevention of secondary systemic and coronary vasoconstriction during ischemia, as the latter is pronounced in this patient group, at least during stress-induced myocardial ischemia. Unfortunately, in SAVE and SOLVD, the anti-ischemic effect occurred relatively late after the institution of therapy, on average after 6 to 12 months. This suggests different mechanisms are involved through which ACE inhibitors reduce ischemia. Rather than acute, hemodynamically linked properties, long-term structural effects seem more likely. That this may indeed be the case is suggested by a large array of animal and human studies, indicating that ACE inhibitors: (i) have antiproliferative and antiatherogenic effects on the vascular wall; (ii) improve abnormal endothelial function; (iii) restore abnormal fibrinolytic balance in coronary artery disease; and (iv) prevent cardiac remodeling and dilatation following an insult or pressure overload, thereby restoring

myocardial wall stress and reducing oxygen demand. Alone or in concert, these properties may eventually lead to a structural, anti-ischemic effect and potentially to secondary prevention of coronary artery disease. Where do neurohormones fit in?

### **ACE INHIBITORS REDUCE MYOCARDIAL ISCHEMIA THROUGH NEUROHORMONAL MODULATION**

ACE inhibition affects different neurohormonal systems. First, the conversion of angiotensin I to angiotensin II is inhibited. The resultant reduction in angiotensin II has a marked inhibitory effect on the sympathetic system at different levels. Potentially, the reduction in angiotensin II should further reduce aldosterone and endothelin secretion. However, the relevance of these neurohormones in acute ischemia is not well known.

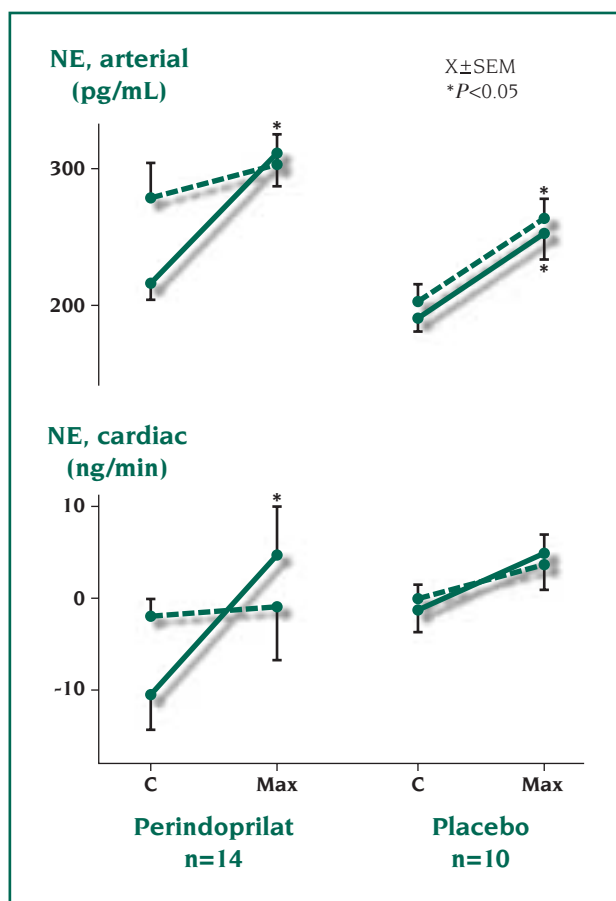
In addition to the effect on angiotensin II, ACE inhibition also reduces the breakdown of bradykinin, which in broad terms may be viewed as the counterpart of angiotensin II, having antigrowth effects, improving endothelial dysfunction, and inducing marked vasodilation. Bradykinin appears pivotal to the improvement of abnormal endothelial function by ACE inhibitors, as these effects are prevented by concomitant administration of a bradykinin B<sub>2</sub> receptor antagonist.<sup>19</sup> Similarly, the antiremodeling effect of ACE inhibition in cardiac models of hypertrophy is counteracted by bradykinin receptor antagonists.<sup>20</sup> Whether bradykinin interferes with ACE inhibitor modulation of ischemia-induced neurohormonal activation is less clear. Immediately following full ACE inhibition (eg, by 90% to 95%), sympathetic activation initially increases, as measured by

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circulating norepinephrine levels. This effect does not seem temporarily related to ACE inhibitor-induced vasodilation, which suggests a bradykinin-related effect. Effects are small and of short duration, however, with a peak effect after 5 to 10 minutes, tapering off thereafter. To test the acute effect of ACE inhibition on ischemia-induced neurohormonal activation, a model of incremental atrial pacing was used, with two identical tests, the first in the untreated condition and the

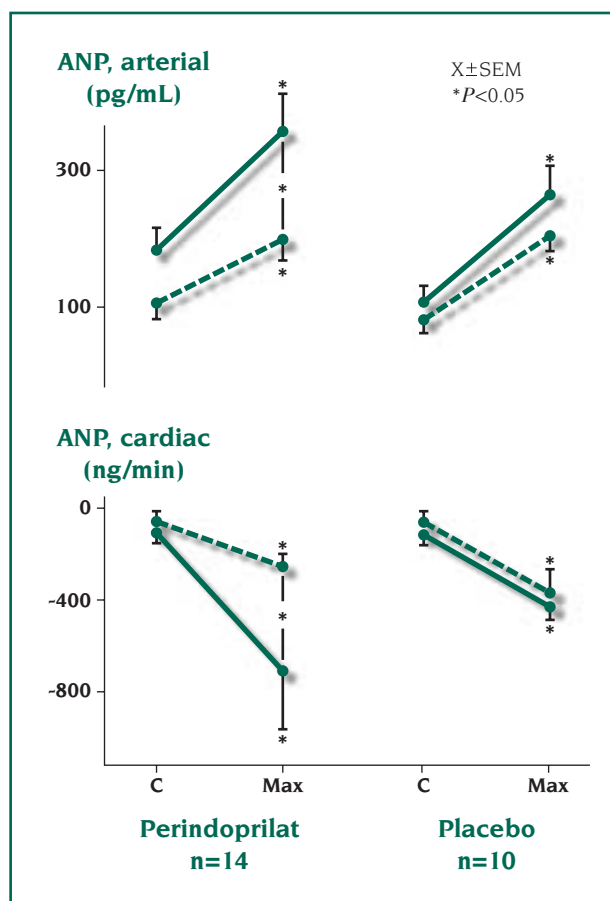
second, approximately 1 hour later, 15 minutes after intravenous administration of the ACE inhibitor under study or placebo. This allows the effects to be studied under stable, resting, and supine conditions, and reproducible hemodynamic, metabolic, and neurohormonal effects to be obtained.<sup>21</sup> With sufficient ACE inhibition achieved (approximately 90% and an approximate 50% reduction in circulating angiotensin II levels), several ACE inhibitors, eg, perindo-

prilat and enalaprilat, significantly modulated the increase in arterial norepinephrine and epinephrine levels and resulted in a change from cardiac norepinephrine uptake to the normal net release pattern (Figure 2).<sup>11,16,22</sup> In addition, in those studies in which an increase in arterial angiotensin II was found during the untreated pacing test, this was similarly prevented following ACE inhibition. Moreover, ACE inhibition reduced ANP release during ischemia (Figure 3).<sup>11</sup> In contrast,



**Figure 2.** Effect of ACE inhibition with perindoprilat on arterial norepinephrine (NE) levels and cardiac NE balance during two sequential incremental atrial pacing stress tests, the first before intervention (solid line), the second after intervention (broken line). Ischemia-induced neurohormonal activation, ie, increase in arterial norepinephrine, is identical during pacing before and after placebo. In contrast, perindoprilat significantly reduces the increase in arterial norepinephrine levels. C, control; Max, maximal pacing. Values are  $x \pm SEM$ ; \* $P < 0.05$ .

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**Figure 3.** Effect of ACE inhibition with perindoprilat on arterial atrial natriuretic peptide (ANP) levels and cardiac ANP balance during two sequential incremental atrial pacing stress tests, the first before intervention (solid line), the second after intervention (broken line). Ischemia-induced neurohormonal activation, ie, increases in arterial ANP, is identical during pacing before and after placebo. In contrast, perindoprilat significantly reduces the increase in arterial ANP levels. C, control; Max, maximal pacing. Values are  $x \pm SEM$ ; \* $P < 0.05$ .

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activation of these neurohormones and peptides was reproducible in placebo-treated patients. Consequently, this modulation of vasoconstricting neurohormones prevented the systemic vasoconstriction observed during the control test. In a similar type of study, ACE inhibition has also been shown to reduce ischemia-induced coronary vasoconstriction.<sup>23</sup>

As, therefore, myocardial oxygen demand is less, and supply is improved, ACE inhibition should result in less ischemia. This is indeed what has been observed in those studies in which ACE inhibition was sufficient, ie, approximately 90%, but not observed or observed to a lesser extent when the acute inhibition of ACE was smaller.

Of note, the anti-ischemic effect of ACE inhibition under these conditions is more pronounced in patients with LV dysfunction than in those with normal function, and follows a more pronounced reduction in circulating neurohormones and subsequent greater reduction in systemic vasoconstriction and myocardial oxygen demand, despite a similar degree of ischemia under baseline stress conditions.<sup>24</sup>

### THE ANTI-ISCHEMIC EFFECTS OF ACE INHIBITION— IS THE CONTROL OF NEUROENDOCRINE RESPONSE RELEVANT?

Ischemia reduction through modulation of neurohormonal activation very likely contributes to the overall anti-ischemic profile of ACE inhibitors. When and to what extent is difficult to assess, as neurohormonal measurements during ACE-inhibitor intervention are required, but are unlikely to be carried out under normal clinical conditions.

Clinical studies in which neurohormones were determined during ischemia and ACE-inhibitor therapy other than with the agents mentioned above are not available. Hence, we can only speculate. As there appears to be no short-term benefit from orally administered ACE inhibitors in patients with stable angina, it is unlikely that significant neurohormonal modulation during ischemia and subsequent prevention of systemic and coronary vasoconstriction play an important role under these conditions.

be related to a reduction in ventricular volumes. However, in that study, anti-ischemic effects were already apparent after 3 months at a time when changes in volumes were moderate, which suggests that mechanisms other than an effect on wall stress are involved. Modulation of ischemia-induced neuroendocrine activation may play a role in patients with persistent ischemia after myocardial infarction, particularly as ventricular dysfunction is present. It is tempting to speculate that over time this modulation

Placebo-controlled study	ACE inhibitor	Objective criteria	Angina
Daly et al, 1985 <sup>25</sup>	captopril	+	+
Strozzi et al, 1987 <sup>26</sup>	captopril	+	+
Jackson et al, 1987 <sup>27</sup>	cilazapril	-	-
Rietbrock et al, 1988 <sup>28</sup>	enalapril	+	?
Vogt et al, 1988 <sup>29</sup>	enalapril	-	-
Gibbs et al, 1989 <sup>30</sup>	enalapril	-	-
Odenthal et al, 1991 <sup>31</sup>	benazepril	-	-
Van den Heuvel et al, 1995 <sup>32</sup>	enalapril	-	-

**Table I.** Variable anti-ischemic efficacy of short-term ACE inhibition in stable angina.

Several studies have been performed comparing an ACE inhibitor versus placebo for only a few weeks (2-6 weeks), and using exercise tests or 24-hour Holter recordings to test the anti-ischemic properties of the ACE inhibitor under study. Nearly all were negative in the sense that there were neither ischemic electrocardiographic changes nor were anginal symptoms reduced (*Table I*).<sup>25-32</sup> In contrast, Sogaard et al demonstrated that long-term treatment with ACE inhibition in patients with persistent ischemia after myocardial infarction significantly reduced the frequency of ischemic events and improved exercise tolerance.<sup>33</sup> These authors suggested that the reduction in ischemic events could

might lead to progressively less vasoconstriction, as, concomitantly, endothelial function improves. Of interest, in the long-term follow-up of the Captopril And Thrombolysis Study (CATS),<sup>34</sup> in which late anti-ischemic effects were reported, when the double-blind medication was stopped after 1 year, more ischemic events were reported in patients who were previously on captopril compared with placebo-treated patients. Again, this could be due to an abnormality in cardiovascular structure and function, eg, a repeated disturbance of endothelial function or a rebound phenomenon resulting from interrupted modulation of neurohormonal activation during ischemia.

However, since neurohormones were not measured in these studies, the latter can only be assumed. Nevertheless, the possibility remains that modulation of neurohormonal activation and subsequent improvement in coronary and systemic vasomotor tone during ischemia may be one of the mechanisms through which chronic ACE inhibition improves myocardial ischemia. It is postulated that this effect gains in importance over time following a long-term improvement in coronary structure and endothelial function during chronic ACE inhibition, which then leads to normalization of the abnormal vascular response to neurohormonal stimuli.

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