numerous workers have documented that angiotensin-converting enzyme (ACE) inhibitors have antihypertensive and antihypertrophic effects, which in most cases are attributed to decreased angiotensin II (Ang II). However, reports ascribing some of the cardiovascular effects of ACE inhibitors to kinin potentiation have been published for a number of years. In an article in the present issue of Hypertension, Gohlke et al \(^1\) used an experimental model of genetic hypertension, the stroke-prone spontaneously hypertensive rat (SHRSP), to study whether long-term treatment with low, non-antihypertensive doses of an ACE inhibitor (ramipril) might have an effect on cardiac function that is dependent on kinins. They tested left ventricular (LV) function using an isolated perfused heart preparation. Hearts from untreated SHRSP had indications of ischemia, as judged by low coronary flow as well as abnormalities of cardiac metabolism when compared with hearts from normotensive Wistar-Kyoto (WKY) rats. They reported that low doses of the ACE inhibitor resulted in increased LV contractility and coronary flow and improvements in metabolic indicators of ischemia. Neither blood pressure nor cardiac hypertrophy was altered; thus, the changes were independent of lowering of afterload or attenuation of cardiac hypertrophy. The antihypertensive dose of the ACE inhibitor resulted in decreased ventricular hypertrophy and normalization of the heart. Chronic treatment with a \(\beta_2\) kinin receptor antagonist abolished the effects of both ACE inhibitor doses on cardiac function, but the antihypertensive and antihypertrophic effects of the high ACE inhibitor dose were not affected. Thus, endogenous kinins at least partially mediate the chronic effects of ACE inhibitors on cardiac function and metabolism but play no role in their antihypertensive and antihypertrophic effects.

This latter finding contrasts with a previous report by Linz and Schölkens \(^2\) in which it was shown that the same kinin antagonist prevented the antihypertensive and antihypertrophic effects of ramipril as well as the antihypertrophic effect of low but not antihypertensive doses of the ACE inhibitor in hypertensive rats with aortic coarctation. In an attempt to explain this discrepancy, Gohlke et al \(^1\) suggested that kinins are primarily involved in mediating the antihypertrophic effects of ACE inhibitors when angiotensin is high. Evidence to support this contention is not available, nor is it apparent how high angiotensin levels could influence the role of kinins. However, using the same aortic coarctation model, we \(^3\) were unable to reproduce the findings of Linz and Schölkens, a result in accord with that of Gohlke et al.

Hoe 140 has no cardiovascular effects when given to untreated rats; thus, kinins may normally be present in subthreshold concentrations. By inhibiting kinin metabolism, treatment with ACE inhibitors appears to increase the concentration of kinins to levels that are now sufficient to affect some cellular functions, such as metabolism, but not others, such as blood pressure or cardiac adaptive responses to increased afterload. Therefore, cardiac ACE should be an important regulator of intracardiac kinin levels. It is not obvious whether all parameters in the venous effluent of the hearts treated with ramipril alone were different from those treated with the kinin antagonist as well; because of the intrinsic variability of the isolated perfused heart model, it would have been reassuring to include a ramipril-treated group when the effects of Hoe 140 were being tested. Without such direct comparison, there may be reservations about the strength of the conclusions regarding endogenous kinins.

Where could the kinins come from? There is evidence that a tissue kallikrein-kinin system exists in the rat heart, and that it contains and releases a kininogenase indistinguishable from glandular kallikrein and also contains the mRNA coding for this enzyme. Vascular tissue also contains and releases kallikrein.\(^4,5\) Cardiac kinin levels are reportedly much higher than blood levels.\(^7\) Thus, cardiac kinins may be generated continuously by a local kallikrein-kinin system.

There is another possible pathway by which kinins may be generated within the heart. Kinins may be present because the plasma kallikrein/high molecular weight kininogen system is activated, which occurs when the contact phase of coagulation (the Hageman-dependent pathway) is triggered.\(^8\) Vascular damage and exposure to nonendothelial surfaces can activate this pathway. Because endothelial cells contain high molecular weight kininogen, the endothelium may be a source of kinins.\(^9,12\) Thus, variations in activation of the contact phase of coagulation may be reflected in variable contribution of kinins to the effects of ACE inhibitors. However, there is no definitive evidence that the contact phase of activation is chronically activated in any model of hypertension.

The data of Gohlke et al \(^1\) suggest that isolated hearts of vehicle-treated SHRSP are both hypertrophic and ischemic. Cardiac hypertrophy may be associated with a

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reduction in both capillary density and coronary flow reserve. It appears that hearts of SHRSP are characterized by coronary vasoconstriction, because coronary flow is lower in vehicle-treated SHRSP than in WKY rats. It may be argued that 20-week-old SHRSP require much higher perfusion pressures than normotensive rats to maintain a normal coronary supply-demand balance, because their mean blood pressure so much higher. Because all hearts were perfused at the same pressure (65 mm Hg), the differences could merely be due to the use of a suboptimal perfusion pressure in the in vitro studies. Perhaps the hearts of SHRSP may be ischemic only at the perfusion pressure used, which for SHRSP may be suboptimal. However, in the study of Gohlke et al the pattern of biochemical changes seen in hearts from SHRSP made normotensive by treatment with ramipril was the same as in those with a non-antihypertensive dose of the ACE inhibitor. Thus, the improvements in cardiac function and metabolic steady state are a consequence of ACE inhibitor treatment independent of changes in afterload. However, this is based on blood pressure measurements by tail plethysmography in anesthetized rats, and 24-hour determinations of blood pressure are needed to confirm that blood pressure did not change with low ACE inhibitor doses.

The effects of low or high doses of the ACE inhibitor on LV function and metabolism were indistinguishable. This implies that maximal changes were already achieved with the non-antihypertensive dose. How could non-antihypertensive doses of ACE inhibitors induce steady-state metabolic improvement and increase coronary blood flow? Low doses of ACE inhibitors may not be able to decrease plasma levels of Ang II. It seems reasonable to postulate a different mechanism. Hearts treated with ACE inhibitors may have a higher kinin output than controls, leading to increased coronary flow. Alternatively, the changes are durable and reflect improved tissue perfusion and metabolic steady state, which are indirectly dependent on cardiac kinins. Gohlke et al suggest that cardiac kinins may not have increased to levels high enough to result in coronary vasodilation. Values for blood or heart kinins are much lower than that. There is little information as to what the response to chronic increases in kinins would be; nevertheless, the improved functional metabolic steady state of the SHRSP hearts may not be due to vasodilation alone. In their recent work on SHR, the same group reported that early-onset treatment with the same non-antihypertensive or antihypertensive doses of ramipril led to a similar increase in capillary length density. Therefore, it is possible that the observed improvement in LV function, coronary flow, and cardiac metabolism may have resulted from increased capillary density through augmented angiogenesis. Because these results are quite relevant to an understanding of the mechanisms of action of ACE inhibitors, they need to be confirmed. Because Ang II is known to be angiogenic, it could not be predicted that ACE inhibitors would result not in less but in enhanced angiogenesis. It remains to be shown that the improved LV function and metabolic steady state of SHRSP hearts induced by ACE inhibitors are linked to increased angiogenesis and that such vascular effects depend on kinins acting through the B2 receptor. The findings of Gohlke et al suggest this should be considered.

Treatment with a non-antihypertensive dose of ramipril returned the performance of the isolated SHRSP hearts to near normal even though hypertrophy secondary to the high load was not affected. The implications of these findings are interesting: changes in cardiac metabolism and function can be dissociated from the events leading to hypertrophy. ACE inhibitors do not need to decrease blood pressure or cardiac hypertrophy to induce a noticeable improvement in cardiac performance. Impaired perfusion of the myocardium during hypertrophy may be more important than hypertrophy per se as a cause of LV dysfunction. The work of Gohlke et al suggests that cardiac kinins increased by local inhibition of ACE heighten coronary flow and are at least partly responsible for altering the metabolic and functional status of the hypertrophic left ventricle. It needs to be determined whether or not kinins mediate part of the effect of ACE inhibitors on cardiac function in models other than SHRSP.

The notion that ACE inhibitors can have beneficial effects independent of changes in afterload (and blockade of Ang II formation) is provocative. Interesting observations in animals are frequently used to imply clinical advantages. Although it is premature to suggest that these studies have clinical relevance, they are potentially significant and need to be reproduced. Once confirmed, these studies may at least lead to a new level of understanding as to how ACE inhibitors protect the myocardium.

References

**KEY WORDS** • angiotensin-converting enzyme inhibitors • heart • kallikrein • kinins • hypertrophy • ventricular function, left • rats, inbred SHR
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