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MINIREVIEW

Heart Failure and Angiotensin Converting Enzyme Inhibition: Problems and Perspectives

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Summary

Heart failure has become the most widely studied syndrome in cardiology over the recent years. Despite the encouraging achievements by angiotensin converting enzyme (ACE) inhibitors, the mortality of patients with chronic heart failure remains high. There are several factors which can potentially be responsible for the fact that about 80% of patients with a failing heart defy protection by ACE inhibitors: different activation of tissue and systemic renin-angiotensin system (RAS) in a particular heart disease and the distinct ability of various ACE inhibitors to block cardiac ACE, alternative pathways for angiotensin II formation (chymase), genetic polymorphism of the RAS system and the complexity of neuroendocrine activation. Moreover, chronic heart failure can provoke disturbances in the reactivity of peripheral vessels and metabolism of striated muscles. These factors may then potentiate the vicious circle of heart failure. New therapeutic approaches, which could further reduce the mortality in patients with heart failure involve angiotensin II type 1 receptor antagonists, beta-blockers, aldosterone antagonists and blockers of the endothelin receptor. A number of questions associated with functions of the RAS still remain open and their solution could be of substantial benefit for patients with a failing heart.

Key words

Heart failure • ACE inhibitors • Angiotensin II receptor antagonists • Beta-blockers • Local angiotensin II • Chymase • Neurohumoral activation

Despite remarkable achievements in the management of heart failure in recent years, the number of patients suffering from heart failure is increasing. The reduction of mortality in patients with heart failure, aging of the population and advanced diagnostic approaches are the potential reasons. As Beamish (1994) stated, "the golden age of cardiology is giving way to the decade of heart failure". ACE inhibitors, whose effectiveness and tolerance exceeded expectations, have become the most promising drugs in cardiology. The fact that despite successful interventions the mortality of heart failure remains high encourages investigators to search for new pathophysiological insights and new therapeutic strategies. Two issues are discussed in the present paper: a) factors, which may potentially influence the effectiveness of ACE inhibition in chronic

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heart failure, and b) perspectives of the therapeutic approach.

Twenty percent mortality reduction - much or little?

Three classical trials of treatment with ACE inhibitors in chronic heart failure after severe myocardial infarction – AIRE (The AIRE Study Investigators 1993), SAVE (Pfeffer *et al.* 1992) and TRACE (The TRACE Study Group 1994) – reported a mortality reduction of about 20 %. This is certainly an encouraging result. On the other hand, we have to address the question why the rest of the population with a failing heart escapes the protection provided by ACE-inhibition. The answer is complex and may involve several issues potentially influencing the effectiveness of ACE inhibition.

1. Different activation of tissue and systemic RAS

Patients with the highest neuroendocrine activation appear to receive the greatest benefit from treatment with ACE inhibitors (Swedberg *et al.* 1990). Although it is now possible to assess the activity of systemic RAS, there is almost no possibility of investigating tissue RAS. This system might potentially be as important as the systemic one (Dzau and Hirsch 1990, Šimko and Šimko 1997). It has been suggested that while the circulatory neuroendocrine system is activated in the stress of acute heart failure, the tissue RAS becomes dominant in a stabilized hemodynamic situation (Dzau and Hirsch 1990, Dzau 1992). It has also been shown that tissue ACE expression is increased in atherosclerotic plaques of the coronary vasculature in humans (Diet *et al.* 1996). Moreover, local RAS seems to play an important role in the development and maintenance of hypertrophy of the left ventricle (Šimko 1994, 1996, Šimko *et al.* 1997, Pecháňová *et al.* 1997), right ventricle (Pelouch *et al.* 1997) and aorta (Šimko *et al.* 1998).

Different ACE inhibitors have distinct abilities to block the cardiac RAS, but this property of each individual inhibitor need not be consistent with its effect on systemic RAS. In doses equipotent for plasmatic ACE inhibition, enalapril administration to animals showed only a minimal (20 % decrease in ACE activity) and short-lasting (for 1 hour) inhibition of cardiac ACE, compared with the modest inhibition of cardiac ACE (40 to 60 %) after lisinopril and fosinopril lasting for approximately 8 hours and with nearly complete blockade of cardiac activity persisting for 24 to 48 hours after captopril or zofenopril (Cushman *et al.* 1989). If this applies to humans, then patients with activated cardiac or vascular RAS may benefit more by receiving an ACE inhibitor with a prolonged and potent tissue RAS inhibitory effect.

2. Alternative pathways of angiotensin II formation

Converting enzyme is not the only enzyme responsible for the conversion of Ang I to Ang II. Chymase, cathepsin G, tonin and other proteases have also been suggested to come into play (Weber *et al.* 1995). Urata and Ganten (1994) showed in biopsies from the human myocardium that chymase was the clue enzyme converting around 85% of Ang I to Ang II. Consequently, ACE inhibitors could potentially inhibit the formation of only about 15% of cardiac angiotensin II. This surprising finding is in contradiction with the assumption that elimination of cardiac ACE accounts for a substantial part of the protective effect of ACE inhibitors (Dzau 1988). Angiotensin II type 1 receptor antagonists are supposed to block the cardiac angiotensin II effect more efficiently than ACE inhibitors (Pitt *et al.* 1997). Moreover, confirmation of the above mentioned results might potentially induce a search for a chymase inhibitor.

3. *Genetic background of the RAS*

One of the most discussed issues of the RAS is the problem of its genetic variability. The genetic background involves genes for renin, angiotensinogen, ACE and angiotensin II type 1 receptor (AT_1) (Harrap 1996). D/I polymorphism proved to exist for ACE appears to be of the greatest clinical importance. It is represented by the presence-insertion (I) or absence-deletion (D) of a small stretch in the chain of DNA. Although D/I polymorphism does not appear itself to be responsible for the potential genetic programming of the RAS, it is presumably a marker of mutation at some other site in the ACE gene (Harrap 1996). People with the D/D genotype (carrying two copies of the D allele) have plasma ACE concentrations substantially higher (by about 60 %) than individuals with the I/I genotype (O'Dell *et al.* 1995). The D/D genotype was found to be more frequent in subjects with myocardial infarction (Cambien *et al.* 1992), ischemic or idiopathic dilated cardiomyopathy (Raynolds *et al.* 1993), electro-cardiographic evidence of left ventricular hypertrophy (Schunkert *et al.* 1994) and sudden death in hypertrophic cardiomyopathy (Marian *et al.* 1993). However, several studies have not confirmed the relation of D/I polymorphism with myocardial infarction (Bohn *et al.*

1993) or dilated cardiomyopathy (Montgomery *et al.* 1995). Presumably, a particular genotype for other parts of the RAS cascade should also be present together with the D/D genotype for the genetic dependence of a certain cardiovascular disease on the RAS to become manifest. When the D/D genotype was associated with a genetic subtype encoding the highly active variant of the AT_1 receptor, the potential for myocardial infarction was higher than in either variant alone (Tiret *et al.* 1994). Despite the many aspects, which are not clear in this area, D/I polymorphism seems to be an independent risk factor in some cardiovascular disorders, especially ischemic heart disease. It does not seem unreasonable to speculate that in those patients with a failing heart, who have the D/D genotype, the RAS may be more involved and they could thus potentially more benefit from the inhibition of this system.

4. Interaction of ACE inhibitors with the failing periphery

It has gradually become clear that the traditional concept of heart failure with decreased cardiac output due to cardiac disorders and consequent hypoperfusion of peripheral organs (Šimko 1997) does not involve all the relevant factors. Recent data suggest that exercise tolerance and tissue perfusion are much more impaired in some patients than the function of the chronically failing heart. Dysfunction of the endothelium is supposed to participate in these changes (Drexler 1995). Three of the vasoactive substances produced by the endothelium – NO, endothelin and cyclooxygenase-dependent endothelium-derived contracting factor – may play a role in congestive heart failure (Vanhoutte 1996), while depressed vasodilative NO production and excessive endothelin-1 release are presumably decisive. These changes in endothelial function can lead to deterioration of the endothelium-dependent dilation of resistance vessels and flow-dependent dilation of large conduit vessels (Drexler 1995). As the chronic administration of ACE inhibitors improves the impaired vasodilative ability of coronary arteries in patients with coronary artery disease (Mancini *et al.* 1997) or of resistance vessels in patients with chronic heart failure (Drexler *et al.* 1995), the RAS seems to participate in endothelial dysfunction. Moreover, the dysfunction of skeletal and respiratory striated muscles (Coats 1996), based presumably on both hypoperfusion and deterioration of oxidative metabolism (Bernocchi *et al.* 1996), should also be considered. On the other hand, regular physical exercise (Coats 1996) and ACE inhibition (Aubier 1996) seem to be effective in preventing or reversing skeletal muscle wasting. These changes in the endothelium and striated muscles might contribute to the transition from compensated to decompensated failure of the heart (Šimko and Šimko 1996). The question arises: What is the cause-effect interplay between failure of the heart and of the periphery (Šimko and Šimko 1996)? Definitely, once the periphery is impaired, it can contribute to the maintenance and progression of the vicious circle in chronic heart failure.

5. Complexity of neuroendocrine activation

Blocking of the RAS may just be one component in the mosaic of desirable interventions in patients with an activated neurohumoral system. As was suggested (Dzau 1992), two cohorts of hormones seem to be fighting in the organism with chronic heart failure: the sympathetic system, Ang II, aldosterone, endothelin and arginine-vasopressin are on the one side of the barricade, having positive inotropic, vasoconstrictive and proliferative effects. Nitric oxide, atrial natriuretic factor and prostacyclin are on the opposite side exerting negative inotropic, vasodilative and antigrowth activities. Whether the dominance of either of these two systems is desirable or deleterious for the body depends presumably on the period when a particular system is activated. The dominance of the first group of hormones can be useful in acute hemodynamic stress by supporting the cardiac output with predominant perfusion of the vital organs. In the long run, however, it may prove deleterious, while the relative dominance of the second hormonal system might improve prognosis. Antagonists of angiotensin II receptors type AT_1, beta-blockers, and potentially endothelin antagonists and aldosterone antagonists are the prospective candidates for the treatment of chronic heart failure.

The pathophysiological background of the protection by angiotensin II type 1 receptor antagonists, beta-blockers, and potential protection by aldosterone antagonists and inhibitors of endothelin receptors

1. Angiotensin II type 1 receptor antagonism

It is known that the harmful effect of the RAS can also be blocked at levels different from that of ACE. The most promising seem to be substances blocking angiotensin II type 1 receptors such as losartan, valsartan, candesartan, etc. They exhibit some potential advantages in comparison to ACE inhibitors. As was mentioned above, angiotensin II may be produced by alternative pathways (e.g. chymase), so that ACE inhibition may only partially prevent the production of

angiotensin II. This problem can be avoided by blocking angiotensin II receptors. Furthermore, ACE inhibition decreases bradykinin degradation thus supporting nitric oxide and prostacyclin production, supposed to participate in cardiovascular protection (Juggi *et al.* 1993). On the other hand, increased bradykinin levels can be responsible for some of the side effects of ACE inhibitors (Israili and Hall 1992), which may account for the ACE inhibitor non-compliance of some heart failure patients.

There is encouraging clinical evidence on the beneficial effect of the angiotensin II type 1 antagonist losartan. The ELITE trial lasting for 48 weeks compared the effect of ACE inhibitors captopril and losartan in patients over 65 with heart failure due to systolic left ventricular dysfunction. Losartan was found to be superior to captopril with respect to its better tolerance and a more pronounced mortality reduction. The apparent advantage of losartan in decreasing the mortality rate is primarily due to a reduced incidence of sudden cardiac death (Pitt *et al.* 1997). The better protection provided by losartan compared to captopril seems to be associated with the incomplete cardiac angiotensin II inhibition by captopril and the consequent enhancement of local cardiac norepinephrine release (Rump *et al.* 1998). However, the reduction in mortality with losartan compared to captopril was not the primary endpoint of the ELITE study. The results of this study are therefore being confirmed on a larger scale randomized trial in which total mortality is the primary aim (ELITE II) (Pitt 1997).

Although these results cannot be extrapolated to younger heart failure patients, they appear to be very promising. The good tolerance and efficacy along with the potential electrical benefit of angiotensin II receptor 1 antagonists may represent a new era in decreasing the harmful effects of activated RAS in patients with heart failure.

2. Beta blockade

Angiotensin II supports the action of the sympathetic system by facilitating the release of norepinephrine from sympathetic nerve endings (Xiang *et al.* 1985). ACE inhibitors might act in part as indirect β-adrenergic blockers limiting the cardiotoxic and vasoconstrictive effects of excessive sympathetic nervous system activation in chronic heart failure (Lorell 1994). This potential beta-lytic effect of ACE inhibitors is obviously not sufficient, as some beta-blockers have been shown to be effective in additional symptomatic improvement in chronic heart failure patients treated by ACE inhibitors while survival was improved especially by carvedilol (Packer *et al.* 1996). This non-selective beta-blocker with α_1-lytic and antioxidant properties reduced the mortality of patients with moderate, mild or even severe heart failure (with ejection fraction less than 35 %) treated by ACE inhibitors, diuretics and digoxin by 65 % in a six-month study (Packer *et al.* 1996). The underlying mechanism is not clear and may involve decreased oxygen demands by reducing cardiac contractility and the heart rate, alpha-lytic systemic vasodilatation with a reduction of the afterload, antioxidant and scavenging effects limiting the toxic effect of norepinephrine and prevention of deleterious myocardial growth (Bristow 1993, Staněk 1997). Many questions concerning the protection by beta-blockade are as yet to be solved. Nevertheless, on the basis of the present data carvedilol can be expected to be included into the regular arsenal of drugs for heart failure treatment in the near future (Kvasnička 1997, Staněk 1997). It has been recommended, however, that beta-blockade by carvedilol should be considered for preventing of progressive clinical heart failure rather than for treating refractory failure of the heart (Chatterjee 1996).

3. Aldosterone antagonism

It was thought for a long time that ACE inhibitors also affect the production of aldosterone by preventing Ang II formation. The decreased production of aldosterone leads to spare potassium; hence, potassium sparing diuretics have not been recommended or have even been directly forbidden to be given together with ACE inhibitors to prevent hyperkalemia (Pitt 1995). However, it has been gradually revealed that aldosterone escapes from ACE inhibitory control in a number of patients suffering of chronic heart failure (Struthers 1995). This may be accounted for by the fact that Ang II is not the only one but just one of the major aldosterone regulators. The level of the adenocorticotrophic hormone and the potassium concentration can also strongly influence aldosterone production (Zannad 1995).

Excessive aldosterone concentrations can be harmful in several respects (Zannad 1995). Aldosterone increases water and Na^+ retention and maintains the circulating volume, and thus a high cardiac preload, increases potassium and magnesium losses, lowers high density cholesterol levels and deteriorates the function of vascular endothelium. Moreover, aldosterone stimulates hypertrophic growth and fibrosis underlying progressive

adverse myocardial remodeling. A depression of baroreflex sensitivity and the potential vascular effects of aldosterone contributing to general vasoconstriction should also be taken into account (Zannad 1995). Thus, the aldosterone antagonist spironolactone may become an additional drug in heart failure treatment, especially in patients with a tendency to hypokalemia. The results of the RALES study should shed more light on this problem (Pitt 1995).

4. Endothelin receptor blockade

The peptide endothelin-1 is the most potent vasoconstrictor, able to augment the vasoconstrictor effect of Ang II, of the sympathetic nervous system and of arginine vasopressin. It has a particularly pronounced vasoconstrictor effect on the renal vasculature decreasing renal plasma flow and the glomerular filtration rate. Moreover, endothelin-1 is a potent proliferative factor participating in hypertrophic growth and rebuilding of the myocardium. It also provokes coronary vasoconstriction, contributing potentially to the development of myocardial ischemia (Haynes and Webb 1993). Endothelins are considered to be potentially involved in the pathophysiology of human essential hypertension (Schiffrin 1995).

Plasma concentrations of endothelin-1 are increased two- to threefold in patients with heart failure and correlate well with the severity of heart failure (Cody *et al.* 1992). Correlation between plasma Ang II and endothelin-1 concentrations in patients with heart failure (Good *et al.* 1994) and the suppression of plasma endothelin-1 concentrations in patients with heart failure by high doses of lisinopril (Davidson *et al.* 1996) suggest an interdependence of the RAS and the endothelin-1 system. It has been suggested that inhibition of endothelin-1 might contribute to the beneficial action of already established drugs used in heart failure treatment (Love and McMurray 1997). This idea does not seem unrealistic as the selective antagonist of type A endothelin receptors (ATE) BQ-123 improved the survival of rats with myocardial infarction-induced heart failure (Sakai *et al.* 1996). Furthermore, the ATE receptor blocker bosentan improved the hemodynamics in patients with a failing heart (Kiowski *et al.* 1996). A potentially new approach to the management of heart failure based on endothelin receptor blockade seems to be emerging.

Conclusions

The leading position of ACE inhibitors in the management of patients with a failing heart appears to be justified (Opie 1995, Pfeffer 1995). ACE inhibitors are effective in manifested heart failure and in patients with a reduced ejection fraction without clinical manifestations. They are protective in both systolic and diastolic dysfunction (Johnstone *et al.* 1994, Šimko and Riečansky 1996). Moreover, ACE inhibition might prevent the progression of atherosclerosis and reduce the incidence of atherosclerotic complications in high risk patients without heart dysfunction (Lonn *et al.* 1994, The HOPE Study Investigators 1996). Other drugs, which inhibit excessive neurohormonal activation, may exert an additional effect in reducing morbidity and mortality. The angiotensin II type 1 receptor antagonist losartan and the beta-blocker carvedilol have proved their clinical importance in improving survival and will probably become part of the standard treatment in heart failure. The success of ACE inhibition, angiotensin II receptor antagonism and beta-blockade encourages the assumption that attenuation of the action of other stress hormones (aldosterone, endothelin) might further promote the effect of the established therapy. Only a more complex understanding of the pathogenesis of heart failure can help to extend the therapeutic arsenal in treating the syndrome of chronic heart failure.

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