

What has been and can be achieved by pharmacological manipulation of neuroendocrine responses?

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Research into therapeutic strategies to manipulate the neuroendocrine responses activated in heart failure has been intense. Alongside classic drugs with proven efficacy such as β -adrenergic blockers and angiotensin-converting enzyme inhibitors, alternative strategies are being developed to block the sympathetic nervous system, the renin-angiotensin system, endothelin, as well as numerous cytokines and enzyme systems known to play a major role in the pathogenesis of heart failure. These include angiotensin II-receptor blockers (whose role is still controversial), monoclonal antibodies to block tumor necrosis factor- α , endothelin-receptor blockers, matrix metalloproteinase blockers, neutral endopeptidase blockers, and aldosterone blockers. Most of these agents are currently undergoing clinical trials, the results of which are eagerly awaited.

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Although it has been known since the time of Starling that there is an exuberant neuroendocrine response to the failing circulation, recognition of the importance of this problem has only come about in the past 15 to 20 years. It now seems clear that there are a host of neurohormones and cytokines that are important in the pathogenesis of heart failure.¹ Given the somewhat spectacular success of the angiotensin-converting enzyme (ACE) inhibitors for the treatment of heart failure, intense interest has developed regarding alternative strategies to block excessive neuroendocrine and cytokine responses (*Table I*). Most of the successes to date have been related to inhibition of the adrenergic nervous system through β -blockers and attenuation of the renin-angiotensin system with the use of ACE inhibitors. However, new strategies are now developing that are designed to block endothelin, a vasoconstrictor-mitogenic neurohormone known to be increased in patients with heart failure. Specific antibodies have been developed against tumor necrosis factor- α (TNF- α). Matrix metalloproteinase (MMP) inhibitors are also being studied in an attempt to abrogate excessive slippage between myocardial fibers,

a mechanism presumed to be operative during left ventricular remodeling. This overview is designed to briefly discuss some of these strategies and suggest new potential therapies for modulating neurohormone, cytokine, and enzyme activity in heart failure.

ADRENERGIC NERVOUS SYSTEM INHIBITORS

There is a considerable amount of data to indicate that increase in circulating plasma norepinephrine levels is a potent and reliable indicator of a poor prognosis in patients with congestive heart failure.² More than a simple marker of severe heart failure, plasma norepinephrine has consistently been demonstrated to correlate with the severity of the disease and provide independent prognostic information. The precise mechanism whereby plasma norepinephrine is increased in patients with heart failure remains to be determined. The most recent data would suggest that excessive spillover or release of norepinephrine is the dominant mechanism,^{3,4} but the genesis of this perturbation is unclear.

The β -adrenergic blockers have emerged as the most promising form of new therapy for the treatment of congestive heart failure.



NEUROHORMONE / ENZYME/CYTOKINE	ANTAGONIST	CLINICAL OUTCOME
Norepinephrine	β -Blockers	Reverse remodeling
	Tyrosine hydroxylase inhibitors	?
	Moxonidine	?
Angiotensin II (Ang II)	Angiotensin-converting enzyme inhibitors	↗ bradykinin, ↗ nitric oxide Prevents remodeling Improves survival
	Ang II blockers	?
Tumor necrosis factor- α (TNF- α)	Monoclonal antibodies	?
	Amiodarone	
	Digoxin	?
Endothelin (ET)	Bosentan	Prevents remodeling in animals
	ET _A blockers	
Matrix metalloproteinases (MMPs)	MMP inhibitors	Antislippage?
Atrial natriuretic factor (ANF)	Neutral endopeptidase inhibitors	Natriuresis
Aldosterone	Spironolactone	Improves survival

Table I. Neurohormone/cytokine/enzyme manipulation in heart failure.

Although their use in heart failure dates back to experience with these drugs in Scandinavia during the 1970s,⁵ there has always been a serious concern that adding negative inotropic agents to the failing circulation may exacerbate the clinical syndrome. New data with the nonselective β -adrenergic blocker carvedilol indicate that the need for hospitalization and mortality is reduced with the cautious introduction and careful titration of this drug in patients with New York Heart Association class II and III heart failure.⁶ Carvedilol is somewhat unique in that it has little selectivity, is a potent antioxidant, and has peripheral vasodilating properties modulated through α -adrenergic blocking activity. Unlike metoprolol, there is no increase in membrane-bound β -adrenergic receptor density following the use of carvedilol.⁷ Although the precise mechanism of action of carvedilol is undoubtedly complex, its long-term use is

associated with a reduction in the progression of heart failure.

Additional strategies designed to block the sympathetic nervous system are now emerging. Drugs that inhibit tyrosine hydroxylase, an enzyme step in the synthesis of norepinephrine, are currently under study. To date, it is unclear whether this strategy will have any noticeable advantage over that of conventional β -receptor blockers. There is additional interest in the use of centrally acting antiadrenergic agents such as moxonidine and clonidine. Clonidine acts on α_2 -adrenergic receptors to inhibit the flow of sympathetic traffic from the brain to the periphery. Moxonidine acts on a specific imidazoline-1 receptor in the brain and potently inhibits central nervous system sympathetic drive to the periphery. The renin-angiotensin system is also partially blocked by moxonidine. Although these drugs are currently

marketed for the treatment of hypertension, they may have potentially beneficial effects in the treatment of heart failure. More clinical studies will be necessary to better position these therapies.

ACE INHIBITORS

The ACE inhibitors have emerged as the treatment of choice for patients with congestive heart failure. They are now undoubtedly as beneficial therapy in patients with functional class I to IV heart failure. Virtually all patients with left ventricular dysfunction and heart failure should be treated with an ACE inhibitor unless there is an obvious contraindication such as shock, hyperkalemia, or a rapidly rising serum creatinine. There is seemingly a trend for patients to be underdosed with ACE inhibitors, and most experts now recommend that these agents be titrated to the doses used in the large clinical trials. For example, enalapril should be

titrated to 10 mg twice a day, captopril to 75 mg three times a day, and lisinopril should be used in doses of 20 mg per day. Obviously, not all patients will tolerate maximal doses, and individual patients will still require an adjustment of dosage.

Despite extensive investigation over the past two decades, the precise mechanism whereby ACE inhibitors benefit patients with heart failure is incompletely understood.

Data are emerging to suggest that prolonged inhibition of the renin-angiotensin system does not occur with these agents, and there is likely an "escape" phenomenon despite persistent therapeutic efficacy. There has long been a belief that ACE-inhibitor-associated incremental changes in bradykinin at the tissue level may have important pharmacologic activity, but this has never been proven conclusively to be an operative long-term mechanism. Clearly, their benefit is not simply a matter of afterload reduction, since there are numerous agents that reduce peripheral vascular resistance, but fail to demonstrate the obvious benefits of ACE inhibitors. It may be that their antiadrenergic properties, although relatively modest, are an important adjunctive mechanism.

ANGIOTENSIN II-RECEPTOR BLOCKERS

Angiotensin II-(Ang II) receptor blocking drugs are now being widely used to treat hypertension. Their role in the management of patients with heart failure has been less well defined. These interesting agents are not a simple substitute for ACE inhibitors, but their usage continues to grow both for the treatment of hypertension and heart failure. Because there are no definitive long-term survival data in patients with heart failure treated

with Ang II blockers, and because there are many uncertainties regarding their potential antiremodeling properties, the Ang II blockers should be reserved for the treatment of hypertension until more data become available. Nonetheless, there remains widespread interest in their use, and they may well emerge as an important treatment for patients with heart failure, either added to or in lieu of ACE inhibitors.

REDUCTION OF TNF- α

There is a growing awareness that TNF- α is important in the pathogenesis of left ventricular remodeling. Circulating levels are increased in patients with heart failure,⁸ and this cytokine is well known to stimulate myocardial growth and hypertrophy. It is possible that much of the excessive TNF- α is produced locally by the cardiac myocyte. In addition to promoting myocyte hypertrophy, an essential component of left ventricular remodeling, TNF- α may also modulate programmed cell death or apoptosis. There is much interest in developing tissue-specific therapies to reduce TNF- α . Both amiodarone and digoxin are associated with reductions in circulating levels of TNF- α , but whether this mechanism is important in the management of patients with heart failure remains to be conclusively demonstrated. It is likely that tissue-specific monoclonal antibodies will be developed that effectively block excessive TNF- α , and clinicians must eagerly await the results of these intended studies.

ENDOTHELIN-RECEPTOR BLOCKERS

Endothelin (ET) is a potent vasoconstrictor substance that is endogenously released in patients with

heart failure. In addition to promoting peripheral vasoconstriction and adding to the afterload stress of heart failure, endothelin has important mitogenic effects including both myocyte hypertrophy and enhancement of the interstitial cardiac matrix. It seems quite likely that endothelin is important in the progressive left ventricular remodeling that characterizes heart failure. Animal studies have suggested that the introduction of endothelin-receptor blockers following experimental acute myocardial infarction is associated with a lessening of left ventricular remodeling and an improvement in survival.⁹ Whether or not specific endothelin_A- or endothelin_B-receptor blockade is more important than nonspecific blockade of both receptors has yet to be carefully worked out. Bosentan, a nonspecific ET_A and ET_B blocker, is associated with acute hemodynamic improvement. Undoubtedly, more specific ET-receptor blockers, including ET converting-enzyme inhibitors, will emerge in the near future.

MATRIX METALLOPROTEINASE BLOCKERS

The complex problem of left ventricular remodeling has been the subject of numerous experimental and human investigations. There is now a growing awareness that the cardiac myocytes are held together by a precise network of interstitial collagen struts, which are important in the overall mechanical function of the left ventricle in vivo. Heart failure, particularly as a result of myocardial infarction, is associated with dissolution of these interstitial collagen struts. This enzymatic step is largely mediated by a series of matrix metalloproteinases (MMPs). The net result is that the individual cardiac



myocytes may slip apart, a process known as "myocardial slippage."

It is believed by some that myocardial slippage is responsible in part for the cavity dilation that occurs during progressive left ventricular remodeling. Agents that specifically block the activity of these MMPs have been developed and are currently being studied in patients with cancer in order to prevent metastasis. It is likely that they will be investigated in experimental heart failure as antislippage agents.

NEUTRAL ENDOPEPTIDASE INHIBITORS

Although atrial natriuretic peptide (ANP) has not emerged as an important treatment for patients with heart failure, drugs designed to block the degradation of ANP are currently under both experimental and clinical investigation. The neutral endopeptidase (NEP) inhibitors have been associated with increased plasma levels of atrial natriuretic factor (ANF), and in principle should improve renal blood flow and natriuresis. NEP inhibitors are currently undergoing clinical trials and may eventually have a role as therapeutic agents for the treatment of heart failure.

ALDOSTERONE BLOCKERS

Lastly, the strategy of blocking aldosterone may be an important adjunctive treatment for patients with heart failure. Aldosterone is known to be associated with deposition of both the replacement and interstitial fibrosis that occurs during progressive left ventricular remodeling. A large, randomized controlled clinical trial has recently been completed and indicates that spironolactone improves survival in patients with advanced heart failure.

CONCLUSION

In summary, there is no question that excessive neuroendocrine and cytokine activity is very important in the pathogenesis of the heart failure syndrome and may be the driving force behind progressive left ventricular remodeling. Armed with this information, the pharmaceutical industry has begun to develop numerous therapeutic agents designed to manipulate these neuroendocrine cytokine and enzyme responses. It is clear that ACE inhibitors and β -adrenergic blockers stand out as classic examples of how neuroendocrine modulators may emerge as important therapy. In the near future we will likely see more data regarding the potential use of other neuroendocrine and enzyme modulators, including new strategies designed to block the sympathetic nervous system, the renin-angiotensin system, endothelin, as well as numerous cytokines and enzyme systems known to be important in the genesis of heart failure.

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