Refractory heart failure — drugs and devices

See page 2275, doi:10.1053/euhj.2001.2693 for the article to which this Editorial refers

Refractory heart failure is difficult to define. In clinical practice, the syndrome is recognized when patients continue to be symptomatic or develop recurrence of heart failure despite optimal contemporary pharmaco-therapy proven to be of benefit in clinical trials. What is the initial optimal therapy for systolic left ventricular failure today?

During the last three decades, there have been considerable advances in the understanding of the pathophysiological mechanisms of systolic left ventricular failure and its rational management. The pivotal role of ventricular remodelling characterized by increasing end-systolic and end-diastolic volumes and decreasing ejection fraction in the pathogenesis of progressive heart failure has been established. Myocardial architectural changes resulting from concurrent myocyte hypertrophy, myocyte loss, fibroblast growths and collagenosis are integral to the histopathological processes of ventricular remodelling. A shift in the pattern of protein synthesis, similar to that of the fetal state, has been thought to be the mechanism of myocyte hypertrophy and is mediated by activation of myocyte membrane receptors, regulated by a number of growth factors. Various neurohormones, including angiotensin II, aldosterone, catecholamines, endothelins and cytokines are well-recognized myocardial growth factors. Activation of angiotensin II, aldosterone, endothelins and transforming growth factor also stimulate fibrosis.

Apoptosis has been thought to be the principal mechanism of myocyte loss. However, ischaemic myocardial necrosis is also a potential mechanism of myocyte loss. Myocardial ischaemia is known to occur in patients with heart failure resulting from either ischaemic or non-ischaemic dilated cardiomyopathy[1]. Although not all the potential mechanisms for the initiation and perpetuation of ventricular remodelling are known, the contributions of certain neurohormones appear to be established. The renin–angiotensin system is activated early in patients with left ventricular systolic dysfunction even before overt heart failure develops. Both circulating and tissue angiotensins promote ventricular and vascular remodelling, and contribute to myocardial ischaemia and haemodynamic abnormalities. Angiotensin II also impairs endothelial function and promotes atherosclerosis and thrombosis. The rationale for angiotensin II inhibition therapy is apparent. Indeed, angiotensin II inhibition is associated with an improvement in right and left ventricular function, in symptoms and functional class and in survival of patients with mild, moderate or even severe congestive heart failure, resulting from left ventricular systolic dysfunction. In a pooled analysis of 32 randomized trials of angiotensin converting enzyme inhibitors vs placebo in symptomatic patients with congestive heart failure (n=7105) the relative risk of total mortality decreased by 23% and that of death or hospitalization for treatment of congestive heart failure by 35%[2]. It is of interest that ACE inhibitor therapy was also associated with decreased risk of fatal myocardial infarction (20%).

The decreased risk of myocardial infarction with ACE inhibitors may not be related to their anti-remodelling effect, but maybe due to improved endothelial function, and reduction of prothrombotic and proinflammatory effects of angiotensin II. Angiotensin II subtype 1 blocking agents (AT1 blockers) have not been shown to be better than ACE inhibitors but can be used if ACE inhibitors are not tolerated. Like the renin–angiotensin system, the sympathetic nervous system is activated early in patients with left ventricular systolic dysfunction, even before the development of clinical heart failure. Increased systemic and cardiac adrenergic activity contributes to ventricular and vascular remodelling and haemodynamic abnormalities of heart failure. Enhanced cardiac adrenergic activity may impair myocardial perfusion and also increase myocardial oxygen demand. Thus potential exists for ischaemic myocyte necrosis. Direct cytotoxic effects of catecholamines also promote apoptosis and myocyte loss. The rationale for beta-blocker therapy in the management of chronic systolic left ventricular failure is apparent.

Recent randomized clinical trials have documented that chronic adrenergic inhibition therapy along with chronic angiotensin II-inhibition therapy is associated with increased left ventricular ejection fraction, improvement in symptoms and functional class and decreased risks of mortality in patients with mild, moderate and even severe heart failure due to left ventricular systolic dysfunction. In the U.S. carvedilol heart failure study, the relative risks of total mortality decreased by 65% with carvedilol, a non-selective beta-blocker with alpha-receptor blocking and antioxidant properties[3]. In the CIBIS-II trial, the use of

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Veterans Administration Heart Failure Trial II,
heart failure recon
recent meta-analysis of beta-blockers in congestive
properties also decreased the relative risk of total
mortality by 34% and of sudden death by 41%. A
recent meta-analysis of beta-blockers in congestive
heart failure reconfirmed the survival benefit of the
addition of beta-blockers to angiotensin converting
enzyme inhibitors. It was estimated that there were
3-8 lives saved and four fewer hospitalizations per 100
patients treated in the first year after therapy. In the
COPERNICUS trial, in which patients with severe
left ventricular systolic dysfunction (ejection fraction
<25%) and symptomatic at rest or with minimal
activity were enrolled, there was a 35% reduction in
the relative risk of total mortality. Thus, optimal
contemporary pharmacotherapy for symptomatic
chronic systolic heart failure should include
concurrent angiotensin II and adrenergic inhibitors.
Diuretics are required to relieve congestive symptoms
and digitalis is used at least in selected patients
for symptomatic improvement, although survival
benefits of diuretics alone or in combination with
digitalis has not been demonstrated.

In the Veterans Administration Heart Failure Trial-I, the addition of hydralazine and isosorbide
dinitrate to digitalis and diuretics resulted in a
decrease in the relative risk of mortality of patients
with mild to moderately severe heart failure (the
2 year mortality rate decreased by 34%) in the Veterans Administration Heart Failure Trial II, hydralazine-isosorbide dinitrate combinations and the ACE inhibitor enalapril were compared and enalapril was found to decrease the relative risk of mortality by a greater magnitude than that with hydralazine-nitrate. Thus ACE inhibitors are prefer-
erable to hydralazine-nitrate combinations for initial
therapy for symptomatic systolic left ventricular
failure. Recently, it was reported that the addition of the aldosterone-antagonist spironolactone to ACE
inhibitors, digitalis and diuretics was associated with
a reduction in the relative risk of cardiovascular
mortality by 31%, and that due to congestive heart
failure progression by 36% and sudden death 29%. Thus, spironolactone should also be used when indi-
cated in symptomatic patients already treated with
ACE inhibitors.

In patients with ischaemic cardiomyopathy, HMG-Co-enzyme reductase inhibitors (statins) and antiplatelet agents (aspirin) should be included in the pharmacotherapy of heart failure (Table 1), as these agents can decrease the risk of adverse cardiac events and even development of heart failure.

However, despite these well-documented beneficial
modern pharmacotherapies, physicians encounter
patients who continue to be symptomatic or have
recurrent exacerbations of heart failure. How often
does the syndrome of refractory heart failure occur?
To the best of my knowledge, an accurate estimate is
not available and difficult to determine. Nevertheless,
an analysis of recent ‘beta-blocker’ trials may provide
some information regarding the risks of worsening
and progression of heart failure despite angiotensin II
and adrenergic inhibition therapy. In the U.S.
Carvedilol Trial, the frequency of death or hospital-
ization for cardiovascular reasons was 15.8% in mildly
symptomatic patients, clinical progression of heart failure occurred in 11% of patients during
12 months of follow-up. In the CIBIS-II trial, the
hospital admission rate for worsening heart failure was 12% in a recent meta-analysis of beta-
blockers in congestive heart failure, the annual mor-
tality rate was between 10%–12%, despite beta-blocker
therapy. In the COPERNICUS trial, the annual
mortality rate was approximately 20% despite beta-
blockers and angiotensin converting enzyme inhibitor
therapy in patients requiring one or more hospital-
izations for treatment of heart failure in the
RALES Study, although the beneficial effect of
spironolactone was documented, the mortality at 12
months in the treatment group was approximately
20%. Thus, despite remarkable advances in our
understanding of the pathophysiology and manage-
ment of heart failure, the syndrome of ‘refractory
heart failure’ will continue to be encountered in
clinical practice although it is likely to be delayed
with the contemporary therapy.

Table 1 Contemprary optimal initial pharmacotherapy

| Adequate doses of angiotensin converting enzyme inhibitors (angiotensin receptor blocking agents in selected patients when angiotensin converting enzyme inhibitors are not tolerated) |
| Adequate doses of beta-blockers |
| Adequate doses of hydralazine-nitrates when angiotensin converting enzyme inhibitors or angiotensin receptor blocking agents are not tolerated |
| Spironolactone in selected patients |
| Diuretics and digitals for relief of symptoms |
| Antiplatelet agents and statins in ischaemic dilated cardiomyopathy |

Table 1 Modern pharmacotherapy for symptomatic systolic left ventricular failure

Adequate doses of beta-blockers
Adequate doses of hydralazine-nitrate combinations and Veterans Administration Heart Failure Trial II, heart failure reconfirmed the survival benefit of the addition of beta-blockers to angiotensin converting enzyme inhibitors. It was estimated that there were 3-8 lives saved and four fewer hospitalizations per 100 patients treated in the first year after therapy. In the COPERNICUS trial, in which patients with severe left ventricular systolic dysfunction (ejection fraction <25%) and symptomatic at rest or with minimal activity were enrolled, there was a 35% reduction in the relative risk of total mortality. Thus, optimal contemporary pharmacotherapy for symptomatic chronic systolic heart failure should include concurrent angiotensin II and adrenergic inhibitors. Diuretics are required to relieve congestive symptoms and digitalis is used at least in selected patients for symptomatic improvement, although survival benefits of diuretics alone or in combination with digitalis has not been demonstrated. In the Veterans Administration Heart Failure Trial-I, the addition of hydralazine and isosorbide dinitrate to digitalis and diuretics resulted in a decrease in the relative risk of mortality of patients with mild to moderately severe heart failure (the 2 year mortality rate decreased by 34%). In the Veterans Administration Heart Failure Trial II, hydralazine-isosorbide dinitrate combinations and the ACE inhibitor enalapril were compared and enalapril was found to decrease the relative risk of mortality by a greater magnitude than that with hydralazine-nitrate. Thus ACE inhibitors are preferable to hydralazine-nitrate combinations for initial therapy for symptomatic systolic left ventricular failure. Recently, it was reported that the addition of the aldosterone-antagonist spironolactone to ACE inhibitors, digitalis and diuretics was associated with a reduction in the relative risk of cardiovascular mortality by 31%, and that due to congestive heart failure progression by 36% and sudden death 29%. Thus, spironolactone should also be used when indicated in symptomatic patients already treated with ACE inhibitors. In patients with ischaemic cardiomyopathy, HMG-Co-enzyme reductase inhibitors (statins) and antiplatelet agents (aspirin) should be included in the pharmacotherapy of heart failure (Table 1), as these agents can decrease the risk of adverse cardiac events and even development of heart failure. However, despite these well-documented beneficial modern pharmacotherapies, physicians encounter patients who continue to be symptomatic or have recurrent exacerbations of heart failure. How often does the syndrome of refractory heart failure occur? To the best of my knowledge, an accurate estimate is not available and difficult to determine. Nevertheless, an analysis of recent ‘beta-blocker’ trials may provide some information regarding the risks of worsening and progression of heart failure despite angiotensin II and adrenergic inhibition therapy. In the U.S. Carvedilol Trial, the frequency of death or hospitalization for cardiovascular reasons was 15.8% in mildly symptomatic patients, clinical progression of heart failure occurred in 11% of patients during 12 months of follow-up. In the CIBIS-II trial, the hospital admission rate for worsening heart failure was 12% in the recent meta-analysis of beta-blockers in congestive heart failure, the annual mortality rate was between 10%–12%, despite beta-blocker therapy. In the COPERNICUS trial, the annual mortality rate was approximately 20% despite beta-blockers and angiotensin converting enzyme inhibitor therapy in patients requiring one or more hospitalizations for treatment of heart failure in the RALES Study, although the beneficial effect of spironolactone was documented, the mortality at 12 months in the treatment group was approximately 20%. Thus, despite remarkable advances in our understanding of the pathophysiology and management of heart failure, the syndrome of ‘refractory heart failure’ will continue to be encountered in clinical practice although it is likely to be delayed with the contemporary therapy.
Table 2  Refractory heart failure

<table>
<thead>
<tr>
<th>Pharmacotherapy</th>
<th>presently available</th>
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<tbody>
<tr>
<td>Aldosterone antagonists</td>
<td>potential to improve symptoms and survival</td>
</tr>
<tr>
<td>Amiodarone</td>
<td>potential to improve survival and possibly symptoms</td>
</tr>
<tr>
<td>Calcium channel blockers</td>
<td>not proven to be of benefit to improve symptoms or survival</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Pharmacotherapy</th>
<th>not available or approved</th>
</tr>
</thead>
<tbody>
<tr>
<td>TNFα antagonants</td>
<td>may improve symptoms in selected patients. Not proven to improve survival</td>
</tr>
<tr>
<td>Endothelin antagonists</td>
<td>may improve symptoms not proven yet to improve survival</td>
</tr>
<tr>
<td>Angiotensin receptor blocking agents</td>
<td>may improve symptoms, survival benefit not proven</td>
</tr>
</tbody>
</table>

<table>
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<tr>
<th>Non-pharmacological interventions</th>
<th></th>
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<tbody>
<tr>
<td>Dual chamber pacing</td>
<td>may improve symptoms in selected patients, survival benefit not proven</td>
</tr>
<tr>
<td>Resynchronization therapy</td>
<td>improves symptoms and functional class, survival benefit not proven</td>
</tr>
<tr>
<td>Ultrafiltration</td>
<td>may improve symptoms, does not improve prognosis</td>
</tr>
<tr>
<td>CPAP therapy</td>
<td>improves ventricular function in selected patients, survival benefits not firmly established</td>
</tr>
<tr>
<td>Assist-devices</td>
<td>effective as bridge to cardiac transplants, long-term survival benefit not established</td>
</tr>
</tbody>
</table>

It has been estimated that in the United States of America each year 40 000 or more patients progress to end-stage heart failure\(^{[11]}\). What therapies can be offered to such patients? If the patients are not desperately ill with cardiogenic shock or a persistently low output state, pharmacological manoeuvres with diuretics, non-glycosidic inotropic agents and combinations of ACE inhibitor, AT\(_1\) blockers and vasodilators are frequently employed in patients waiting for cardiac transplantation, or in patients with end-stage heart failure but who are not candidates for cardiac transplantation. Newer inotropic agents are also being investigated as a ‘pharmacological bridge’ to cardiac transplant or to beta-blocker therapy\(^{[12]}\). In selected unstable patients not considered to be good candidates for immediate beta-blocker therapy or in patients with atrial fibrillation or non-sustained ventricular tachycardia, amiodarone might be of benefit.

Long-acting, relatively vasoselective dihydro-pyridines, such as calcium channel blocking agents do not influence survival, often do not improve clinical status and have a very limited role in the management of refractory heart failure. The new neurohormonal modulators, such as endothelin antagonists, atrial and brain natriuretic peptides, and vasopeptidase inhibitors are under clinical investigation. Similarly, the potential benefits of anticytokines and immunomodulators in the management of refractory heart failure need to be established. Although some non-pharmacological interventions, such as dual chamber pacing, biventricular pacing, ultrafiltration and CPAP therapy may improve the clinical status of selected patients, the long-term prognosis with such therapies remains unchanged.

The long-term symptomatic improvement or survival benefit of non-transplant surgical approaches, such as left ventricular volume reduction, reconstruction procedures, and mitral valve repair have not been firmly established. Thus, cardiac transplantation remains the most effective treatment to improve the prognosis of patients with truly refractory heart failure. In patients with rapidly deteriorating clinical and functional status, use of ventricular assist devices also remains a most effective treatment as a ‘bridge to transplantation’\(^{[13]}\).

In this issue, Clark and colleagues report their experiences with the use of ventricular assist devices as a bridge to ‘transplantation’ in patients with end-stage heart failure\(^{[14]}\). The study focused on assessing the effects of the devices on cytokines, complement and body weight. Circulatory support with devices caused only a transient reduction in tumour necrosis factor a and interleukin 6, which suggested that improved haemodynamics do not prevent elaboration of cytokines which are known to produce adverse effects on myocardial function and architecture.

It is of interest that, in the five long-term surviving patients without transplantation supported by assist-devices, there was no change in the levels of cytokines. It is not known, however, whether there was attenuation of renin-angiotensin-aldosterone and adrenergic activity. Although the incidence of adequate and persistent myocardial functional recovery with assist-devices is very low, as has been observed in this study and in previous studies, it is an important observation, as the understanding of the potential mechanisms of this phenomenon may provide newer therapies for refractory heart failure\(^{[14,15]}\). Further researches will also be required in the design and function of the circulatory assist devices, as the mortality of patients supported by the presently available devices remain very high,
approximately 50%, as reported by Clark et al. in this issue\textsuperscript{[14]}.

Further research will also be required to discover alternative therapies for cardiac transplantation as the number of donors will always be much lower than the potential recipients. Research into cellular, molecular and genetic biology and technology to promote angiogenesis and myocytogenesis, to attenuate undesirable myocyte apoptosis and necrosis and to preserve myocardial functional and structural integrity should be encouraged if a substantial improvement in the prognosis of patients with refractory and end-state heart failure is desired\textsuperscript{[16]}. Meanwhile, we the practising physicians, should continue to provide best, contemporary supportive therapies for clinically refractory heart failure (Table 2).

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References


