Ischemic Cardiomyopathy and Treatment of Heart Failure by ACE Inhibitors and β-Receptor Blockers

Yongxin Lu, MD
Runlin Gao, MD

At the beginning of the millennium, the renowned cardiology professor Dr. Bristow stated: “The medical treatment of heart failure has undergone a remarkable transition in the past 10 years. The approach has changed from a short-term hemodynamic/pharmacological paradigm to a more long-term reparative strategy that aims to favorably alter the biological performance of the failing heart[1]”. The paradigm shift is based on our new understanding that chronic heart failure is caused primarily by a progressive process known as cardiac remodeling. Heart failure treatment should be aimed to alter the biological defects of the heart and reverse cardiac remodeling. When does cardiac remodeling begin? This process begins at *Stage A* in patients at high risk for heart failure, like those with atherosclerosis, hypertension, diabetes mellitus, etc. In addition to causing initial direct insult to the heart, these disorders are known to activate endogenous neurohormonal systems, cytokines and other factors, leading to further deterioration of the biological performance of the heart, and acceleration of the process of cardiac remodeling. Cardiac remodeling is a self-perpetuating process and may occur even in the absence of a new insult to the heart. Thus, chronic heart failure is a progressive disorder and its management should begin early before the onset of heart failure symptoms. Early therapeutic interventions introduced even before the appearance of left ventricular structural and functional changes have been shown to reduce cardiovascular morbidity and mortality in large clinical trials. The renin-angiotensin-aldosterone system (RAS) and the sympathetic nervous system are known to play an important role in cardiac remodeling. Administrations of angiotensin-converting-enzyme (ACE) inhibitors and ß-receptor blockers have been shown to reverse cardiac remodeling and reduce mortality in many large-scale, randomized, double-blinded clinical trials of chronic heart failure[2].

In China, chronic heart failure is prevalent, affecting 0.9% of the general adult population[3]. Thus, prevention and management of heart failure has become a major and growing public health issue in our country.

ACE Inhibitors in Heart Failure

ACE inhibitors have multiple beneficial actions in heart failure. They exert cardioprotective effects primarily by blocking the conversion of angiotensin I to angiotensin II and hydrolysis of kinins. Other actions include reduction of the sympathetic nervous system activity, inhibition of hydrolysis of angiotensin 1-7, and improvement of endothelial function. ACE inhibitors also have been shown to exert an antifibrotic effect via inhibition of the hydrolysis of N-acetyl-seryl-aspartyl-lysyl-proline (Ac-SDKP)[4]. In short, ACE inhibitors reverse cardiac remodeling. In addition, they exert beneficial effects in the treatment of atherosclerosis, hypertension, and diabetes mellitus; all of these are known risk factors for heart failure.

ACE inhibitors have been shown to prevent development of heart failure in subjects with a history of atherosclerotic vascular disease, diabetes mellitus, or hypertension plus one or more cardiovascular risk factors. This was demonstrated by HOPE and EUROPA trials. However, because the reduction of new onset heart failure by ACE inhibitors was not a primary or secondary endpoint in either study, and because this finding was not confirmed by the PEACE trial using a different ACE inhibitor, the level of recommendation for the use of ACE inhibitors for high risk *Stage A* patients was changed from Class I to Class IIa in the new 2005 ACC/AHA heart failure guidelines[2].

For patients with cardiac structural abnormalities or remodeling and reduced left ventricular ejection fraction (LVEF), ACE inhibitors should be used even if heart failure symptoms are absent. Long-term treatment with ACE inhibitors has been shown to delay the onset of heart failure symptoms and decrease the risk of death and hospitalization for heart failure in asymptomatic patients with left ventricular systolic dysfunction. In a 12-year follow-up study to the SOLVD-Prevention Trial, the authors report that treatment with enalapril for three to four years improved survival beyond the original trial period in asymptomatic patients with left ventricular systolic dysfunction[5].

For patients with a history of myocardial infarction, ACE inhibitors must be used regardless of LVEF and should be administrated orally within the first 24 hours of acute ST elevation myocardial infarction (STEMI), if hypotension is not present. On the other hand, in subjects with systolic blood pressure <100 mmHg, early administration of ACE inhibitors after acute myocardial infarction could be hazardous, as demonstrated with captopril within the first 36 hours of acute myocardial

infarction in the Chinese Cardiac Study 1 (CCS1)[6].

ACE inhibitors have been evaluated in more than 8300 heart failure patients in more than 39 placebo-controlled randomized clinical trials, including SOLVD, CONSENSUS and V-HeFT-II. ACE inhibitors have been used to reduce the risk of death and the combined risk of death or hospitalization in the patient population regardless of age, sex, use of ß-blockers or diuretics, degree of left ventricular systolic dysfunction, and etiology of heart failure. Present evidence supports the use of ACE inhibitors in the treatment of heart failure and the drug of choice for inhibition of RAS. ACE inhibitors should be prescribed for all patients with heart failure and reduced LVEF unless otherwise contraindicated[2.7.8].

Some patients with refractory end-stage heart failure, in whom hypotension and renal insufficiency are common, may not be able to tolerate even small doses of ACE inhibitors. If systolic blood pressure is <80 mmHg, ACE inhibitors should not be administered.

The use of ACE inhibitors in heart failure therapy is a class effect. Studies have not shown that tissue ACE inhibitors are superior to non-tissue ACE inhibitors. ACE inhibitor therapy should be initiated at low doses, with progressive increments until either a maximal target dose or an intermediate level of doses that have been chosen for background therapy is reached. It is not necessary to delay ß-blocker use until a target dose of ACEI is reached. In clinical studies of heart failure, the beneficial effect of ß-blockers on mortality was observed even in subjects receiving no ACE inhibitors. Many of the subjects included in the trials were not on the maximal doses of ACE inhibitors, suggesting that intermediate doses of ACE inhibitors are sufficient to produce a survival benefit. Also, in studies comparing high- and medium-doses of ACE inhibitors, reduction of mortality appeared to be similar between the two groups, although the incidence of hospitalization for heart failure was lower in the high-dose ACE inhibitor group.

In order to avoid first-dose hypotension, especially in the elderly, ACE inhibitors should be administered to heart failure patients at a decubitus position. The drugs of choice should be those with a long half-life and they should be started at a reduced dose. We compared the first-dose blood pressure response to 2 mg perindopril and 6.25 mg captopril in 167 heart failure patients. The incidence of first-dose hypotension was much smaller in patients receiving the long-acting ACE inhibitor perindopril (10.1%), compared to the short-acting captopril (20.5%, P<0.05). All

first-dose hypotensive responses were asymptomatic and were only discovered through ambulatory blood pressure monitoring[9].

A meta analysis has shown that the addition of aspirin does not attenuate the beneficial effects of ACE inhibitors in patients with heart failure[10]. However, in heart failure patients without coronary heart disease in whom aspirin is not clearly indicated, aspirin probably should not be administered. ACE inhibitors also should not be used together with nonsteroidal anti-inflammatory medications.

Van de Meel, et.al. showed that serum ACE activity was markedly reduced in the anemic patients with heart failure during ACE inhibitor therapy. There was a correlation between Ac-SDKP and proliferation of erythroid progenitor cells[11]. Thus, the possibility that ACE inhibitors cause mild anemia in heart failure patients exists, but this mild side effect is clearly offset by the striking effect of ACE inhibitors on the reduction of death in such patients.

ß-Blockers in Heart failure

ß-Blockers have been evaluated in more than 20,000 patients with heart failure and reduced LVEF in more than 20 placebo-controlled clinical trials. Among them, CIBIS-II and MERIT-HF trials were terminated prematurely because all-cause mortality was reduced significantly by the ß-blockers. In these two studies, bisoprolol and metoprolol-CR/XL therapy reduced total mortality (hazard ratio [HR] 0.66 in both trials) and the rate of hospitalization and sudden death (HR, 0.56 and 0.59, respectively). In patients with stable severe heart failure and LVEF<25% (COPERNICUS), carvedilol produced a 35% decrease in risk of death and a 24% decrease in the combined risk of death or hospitalization. Evidence is now present that these three ß-blockers are beneficial for all patients with stable heart failure, including women and the elderly, as well as patients with different etiologies (diabetes, ischemic, nonischemic) and severity of cardiomyopathy. All professional society practice guidelines, including the Chinese Cardiology Society Heart Failure guidelines, recommend that ß-blockers be used in patients with stable heart failure and reduced LVEF, patients with cardiac remodeling and left ventricular dysfunction, as well as patients with history of myocardial infarction. However, in clinical practice only 22-35% of patients with heart failure are prescribed ß-blockers. Why is the ß-receptor blocker therapy underutilized? First, it is possible that some physicians working in small rural clinics still think that heart failure is a hemodynamic disorder and continue to apply the “positive inotropic agents, diuretics, vasodilators” regimen in the management of heart failure. Second, ß-blockers have a negative inotropic effect

and may cause clinical deterioration of heart failure in susceptible subjects. Some general practitioners could be concerned about the potential side effects and may worry that they do not know enough to manage the clinical decompensation if it arises. Third, some physicians are concerned about other known side effects of ß-blockers and thus are hesitant to prescribe ß-blockers to certain groups of heart failure patients, such as the elderly, and people with diabetes mellitus and chronic obstructive pulmonary disease.

Many clinical trials have demonstrated that cAMP dependent positive inotropic agents increase the mortality in patients with chronic heart failure. The findings challenge the traditional “pump failure” theory and support cardiac remodeling as a primary pathophysiologic mechanism for chronic heart failure. In a sense, chronic heart failure is a state of neurohormonal imbalance. It is now well recognized that administration of neurohormonal antagonists decreases mortality in patients with heart failure.

ß-Blockers exert cardioprotective effects principally by inhibiting the adverse effects of the sympathetic nervous system stimulation. Long-term activation of the sympathetic nervous system has been shown to induce cardiac hypertrophy, increase ventricular volume, trigger cell death or apoptosis, increase heart rate, provoke cardiac arrhythmias, and cause endothelial dysfunction among other effects. These deleterious effects of sympathetic stimulation can be inhibited by ß-blockers. As stated previously, ß-blockers not only reduce the total mortality, but also the incidence of sudden death in patients with heart failure. ß-Blockers are the only class of anti-arrhythmic drugs that have been shown to prevent sudden death and decrease mortality in heart failure patients. The beneficial effects of ß-blockers may also arise from their inhibitory actions on atherosclerosis, hypertension, cardiac arrhythmia, myocardial ischemia and cardiac remodeling. These actions help prevent progression of heart failure and are useful in the treatment of cardiac structural and functional abnormalities.

To promote a wider use of ß-blockers in heart failure, we should convey to treating physicians and their patients with heart failure the following three points. First, it should be recognized that the goal of ß-blocker therapy is to prevent further progression of heart failure, with reduction of sudden death and all-cause mortality. Thus, even if a patient does not show subjective improvement, he should be continued on the long-term ß-blocker therapy as long as it is tolerated. Second, the biological effects of ß-blockers are time-dependent. ß-Blockers may cause acute depression of

cardiac function immediately after initiation of therapy, but over a long period of time, lead to improvement of cardiac function and reduction of the risk of worsening heart failure. Patients should not discontinue ß-blockers suddenly by themselves. Heart failure may worsen if the ß-blocker is stopped abruptly. If a patient needs to stop the ß-blocker therapy, it should be reduced gradually under physician supervision. Third, physicians should learn how to use ß-blockers correctly. ß-Blockers should be initiated at very low doses, followed by gradual increases at two to four week intervals, with a goal to achieve either a target dosage or a target heart rate (55-60 beats/min). In a MERIT-HF subgroup analysis, with a similar target heart rate (67 beats/min), patients in the lower-dose group had similar benefits as the high-dose group. Thus, the target heart rate is a useful marker for inhibition of the cardiac sympathetic activity. In addition, physicians should ask patients to weigh themselves daily. If significant weight gain occurs, the patient should be instructed to increase his doses of diuretics.

During ß-blocker therapy, if a patient develops fluid retention, his diuretics should be increased. On the other hand, if his clinical status deteriorates, the ß-blocker may be gradually reduced or stopped. Intravenous positive inotropic drugs may be considered; levosimendan is preferred, while ß-receptor agonists such as dobutamine should be avoided. Also, as soon as the patient's clinical condition is restabilized, he should be considered for resumption of the ß-blocker therapy.

ß-Blockers can be used safely and effectively in elderly patients with heart failure. In the SENIORS trial of heart failure patients aged 70 years and older, nebivolol decreased the combined endpoint of death and hospitalization[12]. In the BRING-UP 2 study, only 14% of heart failure patients with LVEF < 0.25 and aged > 70 years discontinued ß-receptor blockers because of adverse effects[13]. Carvedilol also has been shown to be well tolerated and effective in elderly patients with heart failure in the COLA II study[13].

In a meta-analysis of the CIBIS-II, MERIT-HF and COPERNICUS trials, diabetic patients have been shown to derive clinical benefit from ß-blocker therapy, with a 24% reduction of death[14]. Some physicians, however, are worried that the ß-blocker therapy would mask the state of hypoglycemia. It is advised that for patients with insulin-dependent diabetes, selective $ß_1$-blockers be employed. The non-selective ß-blockers may mask some alarming physical signs of hypoglycemia, like shakes and tachycardia, but other signs such as diffuse perspiration may still occur.

For some patients with chronic obstructive pulmonary disease and heart failure, the benefit of $ß_1$-blocker therapy far exceeds the risk. Selective $ß_1$-blockers are not contraindicated, but should be used with caution. On the other hand, asthma is a contraindication for the ß-blocker therapy.

ß-Blocker therapy is usually initiated after ACE inhibitor therapy. However, if a heart failure patient shows no fluid retention and has stable body weight, it may be reasonable to begin a ß-blocker as the first-line therapy for heart failure in that patient. This was demonstrated by the CIBIS III trial.

ß-Blocker therapy for HF is not a class effect. Only three ß-blockers have been shown to be effective in evidence-based medicine. Bucindolol and moxonidine are ineffective as demonstrated by the BEST and MOXCON trials. Results of the latter studies suggest that excessive inhibition of the sympathetic nervous system may be hazardous in patients with severe heart failure[15].

Combination Therapy

Combined inhibition of the RAS and the sympathetic nervous system results in additional risk reductions in patients with heart failure. Administration of an ACE inhibitor alone reduces relative risk rate of death by 24% in patients with heart failure, while when combined with a ß-blocker, ACE inhibitor therapy produces a 36% relative risk reduction of death. Thus, in the 2005 ACC/AHA heart failure guidelines, the recommendation is that patients with heart failure be treated with a combination of an ACE inhibitor or angiotensin II receptor blocker (ARB), a ß-blocker and a diuretic. Routine combined use of an ACEI, ARB and an aldosterone antagonist is discouraged. However, in patients with heart failure and ß-blocker intolerance, the addition of an ARB on top of an ACE inhibitor may be useful.

In RALES, administration of spironolactone in patients treated with ß-blockers produced a further reduction of mortality rate. The relative reduction of mortality produced by spironolactone in patients with and without ß-receptors was 58% and 27%, respectively. Similarly, in the EPHESUS trial, patients with myocardial infarction and heart failure derived a greater benefit from eplerenone when combined with a ß-blocker and an ACE inhibitor. In the CARE-HF trial, ß-blocker therapy in addition to cardiac resynchronization therapy resulted in a greater reduction of death and hospitalization (RR=0.59) compared to the group without ß-blockers (RR=0.72). The findings

suggest a facilitative effect of ß-blockers when combined with other therapeutic modalities.

A retrospective analysis showed that the combination of statins and ß-blockers is associated with further improvement of survival in patients with heart failure compared to either agent alone. The CORONA trial, which is ongoing, will address the effects of not only rosuvastatin alone, but also the combination of rosuvastatin and metoprolol in heart failure[16].

Ischemic Cardiomyopathy

Ischemic cardiomyopathy is a condition in which coronary heart disease results in myocardial dysfunction and heart failure. Although its clinical manifestations are often indistinguishable from those of a primary dilated cardiomyopathy, other consequences of coronary artery disease such as left ventricular aneurysm and mitral regurgitation caused by papillary muscle dysfunction may complicate ischemic cardiomyopathy and exaggerate the development of heart failure.

Coronary heart disease is the primary cause of chronic heart failure in China[17]. To combat ischemic cardiomyopathy it is important to prevent coronary artery disease[18]. In China, there are 160 million people with hypertension, 160 million with hyperlipidemia, 40 million with diabetes mellitus, and 280 million people who are overweight. As lifestyles have changed in China, the incidence of coronary artery disease has increased rapidly. To control the coronary risk factors, one should incorporate therapeutic lifestyle modification, including an exercise program, smoking cessation, and the treatment of metabolic syndrome, hypertension, diabetes, and atherosclerosis in the disease management. For patients at risk for atherosclerosis and peripheral vascular disease, carotid artery stenosis should be assessed by Doppler scans. Coronary arteriography should be considered in patients with angina or chest pain that may or may not be cardiac in origin. In patients with coronary artery disease, anti-atherosclerosis therapy should be initiated. This includes the ABCDE regimen, A) Anti-platelet/anticoagulation, ACE inhibitors; B) ß-blocker, blood pressure control; C) cholesterol, cigarette cessation; D) diabetes, diet; and E) exercise training, education.

Patients with myocardial infarction must be treated with an ACE inhibitor and a ß-blocker. Both classes of agents have been shown to reduce the mortality in patients with myocardial infarction in large-scale clinical trials, such as SAVE, AIRE, TRACE and CAPRICORN.

In the 2004 ACC/AHA STEMI guidelines and 2004 European Society of Cardiology Consensus of ß-blocker therapy, oral ß-blocker therapy is a Class I recommendation for patients with myocardial infarction, level of evidence A; intravenous ß-blocker therapy is a Class IIa recommendation, level of evidence B, for patients with acute myocardialinfarction . However, the use of intravenous ß-blockers is not without risk in acute myocardial infarction, especially in subjects with unstable hemodynamics, as evidenced by the increase in the incidence of cardiogenic shock and Killip Class II-III by intravenous ß-blockers given within the first 12 hours of myocardial infarction in the COMMIT-CCS2 trial in which 45,852 Chinese with acute myocardial infarction were enrolled. The latter study also demonstrated that although it did not reduce all-cause mortality, administration of intravenous ß-blockers followed by oral agents was effective in reducing the incidence of re-infarction and risk of ventricular fibrillation. Intravenous ß-blocker therapy also has been studied in patients with acute myocardial infarction in the ISIS-1 and MIAMI trials. In the ISIS-1 trial, intravenous injection of atenolol 5-10 mg, followed by oral atenolol 100 mg per day, reduced the cardiac mortality rate after acute myocardial infarction by 15%, but the effect was of borderline statistical significance (2P<0.4, P=0.05). The MIAMI trial compared the ß-blocker metoprolol (intravenous followed by oral) with placebo, and found similar results to those found in ISIS-1. Both of the trials were performed in the 1980s when thrombolysis therapy was not a common practice. In addition, patients studied in the ISIS-1 study were at a low risk, having only a 4% mortality rate from acute myocardial infarction. Thus, the recommendation of intravenous ß-blocker therapy for high-risk patients with acute myocardial infarction remains controversial.

For all patients with acute myocardial infarction or chronic coronary heart disease, clinical management should adhere to contemporary clinical practice guidelines.

Coronary revascularization is the most important step that can be taken to improve survival of patients with coronary heart disease or ischemic cardiomyopathy. Percutaneous coronary intervention is the revascularization of choice, and is available in most urban hospitals in China. If performed early in acute myocardial infarction, coronary revascularization may block the progression of cardiac remodeling, prevent the development of heart failure, and reduce the risk of death. The GRACE trial showed that early coronary revascularization reduced the mortality in patients with acute coronary syndrome and heart failure.

It is important to recognize hibernating myocardium in patients with ischemic cardiomyopathy.

Symptoms of heart failure may be caused by ischemic myocardial dysfunction and hibernation, diffuse fibrosis, or multiple infarctions, either alone or in combination. Hibernating myocardium is defined as impaired resting left ventricular function that can be reversed after revascularization. The return of cardiac muscle function can be partial or complete, and left ventricular systolic function may be fully restored or just somewhat improved. The functional recovery of the hibernating myocardium may occur either shortly after revascularization or delayed up to one year after revascularization. One of the goals in clinical practice is to reduce irreversible heart muscle damage by rescuing the myocardium from hibernation and protecting the heart from ischemia.

Patients with little or no viable myocardium in whom heart failure is secondary to extensive myocardial infarction and/or fibrosis should be managed in a manner similar to those with a dilated cardiomyopathy. Their prognosis is particularly poor. Cardiac transplantation may be considered.

Patients with ischemic cardiomyopathy, LVEF ≤35%, sinus rhythm, NYHA Functional Class III or ambulatory Class IV symptoms, and QRS duration >120 msec should be considered for cardiac resynchronization therapy, which is routinely performed in metropolis in China.

If a patient with ischemic heart disease is shown to have an LVEF ≤30% and NYHA Functional Class II-III symptoms more than 40 days after myocardial infarction, implantable cardioverter-defibrillator therapy should be recommended as the primary prevention to reduce sudden death. But in our country, most implantable defibrillators are implanted for secondary prevention. In fact, the most common cause of death in patients with non-ST elevation acute coronary syndromes is sudden death according to OASIS-China subgroup data[19].

For patients with left ventricular aneurysm and heart failure, coronary artery bypass surgery is frequently performed along with aneurysmectomy. In patients with severe mitral regurgitation and coronary heart disease, mitral repair or replacement should be considered along with coronary artery bypass surgery.

For patients with ischemic cardiomyopathy and heart failure, the medical therapy should include routine use of an ACE inhibitor or ARB, a ß-blocker and diuretics. In select patients, such as those in NYHA Functional Class III-IV or with a history of myocardial infarction and reduced LVEF, an aldosterone antagonist should be added. Anti-atherosclerosis therapy should be prescribed

for all patients with coronary heart failure. Digoxin should be used either with caution or not at all in patients with myocardial infarction. For patients with ischemic cardiomyopathy and angina, attempts should be made to control myocardial ischemia per contemporary guidelines. An aggressive lipid-lowing regimen is recommended for patients with coronary heart disease at very high risk, with a target LDL cholesterol level of <70 mg/dl.

Some phase I-II studies are underway for cell transplantation therapy in heart failure. Further information is needed before it can be recommended for use in patients with coronary heart disease.

We recognize that little is known of the pathophysiology of cardiac remodeling in heart failure. We do not yet fully understand the processes of cardiac remodeling and cardiac muscle regeneration at the cellular, molecular (signal-transduction system, proteins, proteomics) and genomic levels[20].

In summary, most patients with chronic heart failure have not received optimal medical therapy. We can do more to promote application of clinical guidelines for the treatment of chronic heart failure in our practice. The use of RAS inhibitors and ß-blockers is the foundation of our modern treatment of heart failure, and should be
recommended to all physicians and heart failure patients.

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