Management of Severe Heart Failure

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Patients admitted to the hospital with heart failure (HF) include those with new-onset of acute HF and those with acute exacerbation of chronic HF (CHF). In therapy for new-onset acute HF associated with acute myocardial infarction, therapy to inhibit left ventricular (LV) remodeling in the convalescent phase is required in addition to that needed to overcome the acute phase. Hitherto, CHF therapy was aimed at improving LV contractability, whereas more recently the aim has shifted to resting the heart. Most patients with HF should be routinely managed with a combination of 3 types of drugs: a diuretic, an angiotensin converting enzyme inhibitor and/or an angiotensin II receptor blocker; and a β-blocker. The administration of β-blockers is of particular importance. For HF unresponsive to medical therapy, non-pharmacological therapies are considered. When a HF patient fails to respond to all available therapies, heart transplantation becomes necessary. Of the 1,000 HF patients admitted to our hospital, two cases received heart transplants. 11 cases were indicated for heart transplantation but died before registration. It should be remembered that although in Japan the possibility of receiving a heart transplant is very low, it is by no means entirely impossible. (Circ J 2009; Suppl A: A-36–A-41)

Key Words: Acute heart failure; Chronic heart failure; Dilated cardiomyopathy; End-stage heart failure; Heart transplantation

The number of heart failure (HF) patients in Japan is increasing in parallel with the aging of society. The prognosis of HF is as poor as that of malignant neoplasms and its management and therapy continue to be problematic. Causes of the poor prognosis of HF include the high acute-phase mortality rate of severe HF and the fact that in Japan heart transplantation is rarely feasible. Here we outline the management of severe acute HF associated with high acute-phase mortality rate, and the management of refractory end-stage HF resistant to medical treatment.

Characteristics of HF Patients Admitted to Hospital

Patients admitted to hospital with HF include those with new-onset acute HF and those with acute exacerbation of chronic HF (CHF). Those with new-onset acute HF develop conditions such as acute myocardial infarction (AMI), fulminant myocarditis, acute valvular disease associated with infective endocarditis and other pathologies, as a result of which the pump function of the left ventricle abruptly declines. HF associated with AMI is the most frequent, accounting for 60–70% of such cases. Especially, since in severe cases with cardiogenic shock the acute phase mortality rate is very high, an accurate diagnosis and swift implementation of therapy are vital.

In contrast, the majority of patients admitted with HF have an acute exacerbation of CHF. In the ADHERE study, 87% of patients admitted for HF had an acute exacerbation of CHF; previously the main cause of CHF was valvular disease, while more recently coronary artery disease (CAD) has become a more frequent cause. CHF comprises HF characterized by impaired left ventricular (LV) contraction such as in dilated cardiomyopathy (DCM) and CAD, as well as that characterized by preserved LV contraction as seen in hypertensive heart disease and hypertrophic cardiomyopathy (HCM). Both types have a poor prognosis, with no significant difference noted between them with respect to the long-term outcome. In many cases, refractory end-stage HF is complicated by right-sided HF in addition to markedly impaired LV contraction.

Management of Severe Acute HF With AMI

The most important therapy in the acute phase of myocardial infarction is to initiate percutaneous coronary intervention (PCI) as swiftly as possible and thereby recanalize the occluded coronary artery. With the development of new devices, therapy for AMI has improved enormously, with the mortality rate in the acute phase showing a corresponding decline. However, since no therapy able to suppress LV remodeling adequately after myocardial infarction is yet available, the incidence of HF and post-myocardial infarction is increasing. Immediately after PCI, revascularization injury and acceleration of neurohumoral factor release help to create an environment in which LV remodeling is promoted. Thus, even if PCI is successful, these factors may subsequently accelerate LV remodeling thereby promoting the transition to CHF. Accordingly, in therapy for AMI, therapy to inhibit remodeling in the convalescent phase is required in addition to that needed to overcome the
acute phase.

In the acute phase of myocardial infarction, angiotensin converting enzyme inhibitor (ACEI), angiotensin II receptor blocker (ARB) and β-blocker administration is beneficial. In Japan, it is known that β-blockers are seldom administered in the acute phase of myocardial infarction\(^9\). Since coronary artery spasm in Asians is common, β-blockers are avoided in many cases, but in guidelines regarding the secondary prevention of myocardial infarction, their administration is recommended for post-myocardial infarction (Class of recommendation I, level of evidence A), with which we strongly concur? The β-blockers, through interfering with the action of catecholamines mediated by suppression of the sympathetic nervous system, are considered to inhibit LV remodeling. Atrial natriuretic peptide (hANP: carperitide) is also an efficacious agent for acute HF\(^6\). Carperitide, in addition to having potent diuretic and vasodilatory effects, suppresses the renin-angiotensin-aldosterone (RAA) system, anti diuretic hormone secretion and sympathetic nervous system, thereby antagonizing a variety of vessel-constricting factors. Characteristics of this agent include: (1) as a monotherapy, it quickly improves pulmonary congestion; (2) unlike agents such as nitrates and calcium channel blockers, it has no secondary sympathetic neurostimulatory effect; and (3) unlike other diuretics, it exerts no secondary stimulatory effect on the RAA system, does not worsen renal function and rarely induces electrolyte imbalances. The effect of carperitide is often considered to be solely diuretic in nature, but since its true action is to regulate neurohumoral factors, it is even worth administering even if the urinary volume does not increase. Furthermore, in the J-WIND trial, carperitide decreased the infarct size after myocardial infarction by 14.7% (P=0.016) as compared to a placebo, and improved the LV ejection fraction (LVEF) in the chronic phase by 5.1% (P=0.024)\(^11\). Although in Japan this agent is not yet covered by public medical insurance in cases of AMI, in cases complicated by HF it should definitely be used. In future, it is also holds promise as an agent to inhibit LV remodeling after AMI.

In cases developing cardiogenic shock because of AMI, inotropic agents such as dobutamine and dopamine must be administered. Inotropic agents have been proven in numerous large-scale clinical trials to worsen the long-term prognosis of CHF\(^1\)-\(^4\). However, the cohorts entered in such large-scale clinical trials have excluded those with severe disease, renal insufficiency and/or advanced age, and especially those with cardiogenic shock. Accordingly, if such evidence alone is relied on and inotropic agents not used, an opportunity will be missed to save some patients. If decreased perfusion of major organs due to hypotension is prolonged, multiple organ failure may complicate the clinical picture and increase the mortality rate. In cases in which inotropic agents do not stabilize the hemodynamic situation, intra aortic balloon pumping (IABP) and percutaneous cardio pulmonary support (PCPS) are introduced. PCPS increases the blood flow to the whole body, but in AMI with preserved right ventricular contractability, the introduction of PCPS may actually exacerbate pulmonary congestion in some cases. In such cases, a switch to a LV assist system (LVAS) is mandatory. Because LVAS increases the cardiac output without increasing the preload, it is suited to HF developing after AMI. In many severe cases, even after successful coronary artery recanalization, LV remodeling subsequently occurs and complicates the therapy for HF. When LVAS is ineffective in ameliorating cardiac function,
and signs of multiple organ failure are noted including reduced renal function and serum total bilirubin ≥2.0 mg/dl, heart transplantation is considered.\(^{15}\) When dealing with this kind of refractory HF, it is always necessary to decide on the therapeutic strategy in close cooperation with a cardiac surgeon.

Management of Refractory End-Stage HF

Recent clinical investigations have revealed multiple factors influencing the prognosis of refractory HF\(^ {15,16}\) The variables most consistently cited as independent outcome predictors are listed in Table 1\(^ {17}\) Checking for the presence/absence of these factors is useful in estimating prognosis. The underlying causes of CHF include CAD, valvular disease and DCM. The proportion of CHF cases associated with CAD is gradually increasing, and is thought likely to further increase in the future. Both a coronary artery bypass graft (CABG) and PCI should be considered in selected HF patients with CAD. Refractory end-stage CHF is characterized by markedly impaired LV contraction complicated by mitral valve regurgitation (MR), as a result of which right-sided HF supervenes. Functional tricuspid regurgitation is extremely common in refractory HF patients with biventricular dilatation, systolic dysfunction and pulmonary hypertension. Therapy is especially difficult in cases in which pulmonary congestion is mild and right-side HF is the major issue. In hypotensive patients, inotropic agents such as dobutamine and phosphodiesterase III inhibitor are administered. In our hospital, in addition to a small dose of dobutamine (1.5–3.0 μg · kg\(^{-1}\) · min\(^{-1}\)), a small dose of milrinone (0.125–0.25 μg · kg\(^{-1}\) · min\(^{-1}\)) is used in many cases. By using the 2 drugs together, their respective side effects can be kept to a minimum, while aiming to efficaciously increase cyclic AMP levels. Even in cases requiring inotropic agents, a small dose of carperitide (0.01–0.02 μg · kg\(^{-1}\) · min\(^{-1}\)) is added for cardioprotection. Also, in severe cases hypotension is frequent and, even when inotropic agents are used, an ACEI and \(\beta\)-blocker should be administered. The admin-

**Table 2. Characteristics of Therapeutic Agents for HF**

Agents that should be used only in the acute phase of HF

1. **Diuretics**
   1. Furosemide
2. **Nitrates**
   1. Isosorbide dinitrate
   2. Nitroglycerin
3. **Catecholamines**
   1. Dopamine
   2. Dobutamine
4. **Phosphodiesterase inhibitors**
   1. Milrinone
   2. Orpholine
5. Management of Refractory End-Stage HF

HF, heart failure.

Figure 1. Pharmacological therapy of refractory end-stage heart failure. Not all the drugs listed in the figure should be administered to all patients. Furosemide is administered by continuous iv. A small dose of dobutamine and small dose of milrinone are used in refractory heart failure. Even in cases requiring inotropic agents, a small dose of carperitide is added for cardioprotection. Even when inotropic agents are used, an angiotensin converting enzyme inhibitor or angiotensin II receptor blocker and \(\beta\)-blocker should be administered. In cases with poor cardiac function in which the introduction of carvedilol or bisoprolol is difficult, the introduction of a \(\beta\)-blocker during the use of pimobendan or amiodarone should be attempted. When spironolactone or eprelenone is added, the possibility of hyperkalemia must be kept in mind. When administered orally, furosemide should not be taken as a single daily dose but rather as 2 or 3 divided doses. CHF, chronic heart failure.
istration of β-blockers is of particular importance, even when the systolic blood pressure is less than 100 mmHg, and as long as urine is being produced, its dose should be increased to the largest extent possible. However, in occasional cases symptoms such as hypotension and giddiness appear and preclude the continued combined administration of an ACEI and β-blocker. In most such cases we reduce the dose or stop the ACEI entirely, and preferentially administer the β-blocker. Even though no studies have clarified which of these agents has a greater impact on improving the prognosis, we anticipate that the reverse remodeling effect of β-blockers will be of particular benefit in this context. In some cases with severe HF with hypotension, if a β-blocker can be introduced the blood pressure may rise as compared to before its introduction. In such cases, an ACEI may be re-introduced after the β-blocker. Unless contraindicated or not tolerated, the addition of a low dose of an aldosterone antagonist should be considered in these patients as well. In cases with poor cardiac function in which the introduction of carvedilol or bisoprolol is difficult, the introduction of a β-blocker during use of pimobendan or amiodarone should be attempted. Although a single failure to introduce β-blockers often results in abandoning their use altogether, various strategies should be devised to facilitate their introduction since these agents markedly improve prognosis. Therapeutic agents for HF comprise drugs that are life saving in the acute phase and those that enhance the prognosis in the convalescent phase. Please refer to Table 2 and Figure 1, which list these agents according to their timing of administration.

Recently, various innovative methods of administering diuretics have also been devised. Furosemide is essential in the treatment of HF because of its potent diuretic effect and quick onset of action. However, when injected intravenously its duration of action is short at about 2 h. After the effect of furosemide is lost, the release of neurohumoral factors shows a rebound, and sodium is retained. Accordingly, to use it most efficiently, its blood concentration should be kept at a constant level, to achieve which it is often administered by continuous iv infusion. When administered orally, furosemide should not be taken as a single daily dose but rather as 2 or 3 divided doses.

Hitherto, therapy of HF was aimed at improving LV contraction, whereas more recently the aim has shifted to restoring the heart as much as possible. In addition, recently, as determinants of prognosis in HF patients, renal dysfunction and progression of anemia have attracted increasing attention, and the concept of a cardio–renal–anemia syndrome has been proposed. Renal insufficiency and anemia are factors imposing additional stress on the heart, and their proper management will contribute to restoring the heart. To prevent any further deterioration of renal function when treating HF, potentially nephotoxic agents such as contrast media, non-steroidal anti-inflammatory drugs and antibiotics should be used at the lowest possible doses. Also, since carperitide is renoprotective, it should be administered to patients with impaired renal function.

Anemia has been consistently shown to be an independent risk factor for hospital admission and mortality. Correction of anemia has been established as routine therapy in HF. Among potential therapies, the use of erythropoietin-stimulating factor agents, usually together with iron to increase red blood cell production, represents an unproven option.

Non-Pharmacological Therapy for Refractory End-Stage HF

Some cases of severe CHF are refractory to all forms of medical therapy. Cardiac resynchronization therapy (CRT) is used to synchronize interventricular and intraventricular contraction in patients with HF in whom there is evidence of electrical dysynchrony (QRS width >120 ms). CRT with defibrillator function (CRTD) is recommended to reduce morbidity and mortality in patients in New York Heart Association (NYHA) III–IV class who are symptomatic despite optimal medical therapy, and who have a reduced LVEF (LVEF <35%) and QRS prolongation (QRS width >120 ms) (Class of recommendation I, level of evidence A). At present, in Japan, CRTD is used only in refractory end-stage HF, but since the ACC/AHA guidelines recommend its use in Stage C HF, we believe that it should be used in Stage C HF in Japan as well.

Alternate surgical and mechanical approaches for treatment of end-stage HF are under development. Clinical improvement has been reported after mitral valve repair or replacement in patients who have a clinically important degree of mitral regurgitation that is secondary to LV dilatation. MR resulting from HF enhances the release of neurohumoral factors, thereby creating a vicious cycle in the pathophysiology of HF. Mitral valve repair or replacement not only improves the MR itself but by correcting this vicious cycle is also thought to improve the underlying HF. Also, in some cases with marked LV dilatation complicated by high-grade functional MR, if left ventriculoplasty is added to mitral valve repair considerable improvement in heart function may be achieved. Our impression is that in many such cases LV contractility is relatively well preserved and the general preoperative state is also good. However, since not all cases show improvement, in cases of severe HF thorough consideration of the indications for a surgical approach is necessary. In some cases where there is no improvement, even with these therapies, IABP may be resorted to. However, given the risk of infection at the insertion site and decreased patient quality of life, it cannot be used for prolonged periods.

For HF unresponsive to all internal medical therapy, LVAS have been introduced. In Western countries, implantable LVAS are already being used, and in Japan are being evaluated at the clinical trial stage. Most clinical experience with LVAS has been derived from their use in patients as a bridge to transplantation, while the randomized evaluation of mechanical assistance for the treatment of congestive HF (REMATCH) trial investigated their use as permanent or destination therapy in selected non-transplant-eligible patients. This trial enrolled 129 patients, for whom 2-year survival was 23% in the 68 patients treated with the device in contrast to 8% in the 61 patients who received medical therapy. This trial established the efficacy of device therapy for end-stage HF.

In Japan, where heart transplantation is very difficult to undertake, LVAS will likely be relied on as a destination therapy in the near future. Improvements in the newer generation of devices will hopefully permit even further prolongation of survival.

In contrast, in some cases cardiac function improves after LVAS attachment, and weaning from the LVAS is feasible. In the future, LVAS may be used primarily with the intent of a bridge to recovery. In cases in which LVAS weaning had been impossible, Birks et al were able to raise the
weaning rate by replacing carvedilol with bisoprolol, which has marked β1 selectivity, and adding clenbuterol, which is a β2 stimulatory agent. It is anticipated that in the future the combined use of a β1 selective, β-blocker and β2 stimulatory agent will be established as one option in the pharmacotherapy of refractory HF.

When a HF patient fails to respond to all available therapies, heart transplantation becomes necessary. But despite being currently the only established surgical approach to the treatment of refractory end-stage HF, it is available to fewer than 64 patients in Japan per decade. Nonetheless, since heart transplantation is not a terribly complicated therapy, it should be kept in mind by all cardiologists. The majority of hitherto transplanted patients in Japan have used an LVAS pre-transplant, and the disease severity of patients awaiting heart transplantation in Japan is very high.

The Proportion and Outcome of HF Patients Indicated for Heart Transplantation

We investigated the proportion indicated for heart transplantation and outcome of 1,000 consecutive HF patients admitted to the Division of Cardiology, Fujita Health University from January 2000 to March 2007 (Figure 2). The 185 such cases (18.5%) aged under 60 years were identified (116 men, mean age 48.2±10.5 years). The underlying cause of HF was DCM in 47 cases (25.5%), CAD in 43 (23.2%), valvular disease in 27 (14.6%) and secondary cardiomyopathy in 27 (14.6%). Of the 185 cases, 62 (34.0%) were contraindicated for heart transplantation for reasons such as end-stage renal failure or malignancy. 61 of the remaining 123 cases responded to medical therapy and were discharged from hospital. However, in 62 cases β-blocker therapy was difficult to implement, or after its implementation readmission was necessary because of recurrent HF. The 31 of these cases were treated with pharmacotherapy alone, while 31 cases were treated non-pharmacologically. The 37 cases were indicated for HTX, 31 cases provided informed consent and 21 cases desired HTX. Two cases received HTX in Japan. Eleven cases died of exacerbated HF during the recipient registration procedure. ICD, implantable cardioverter defibrillator; CRT, cardio resynchronization therapy; CRTD, CRT with defibrillator function; IABP, intra aortic balloon pumping; PCPS, percutaneous cardiopulmonary support; LVAS, left ventricular assist system.

Figure 2. Course of therapy and prognosis of 1,000 consecutive chronic heart failure (HF) patients. The 185 such cases aged under 60 years were identified. Of the 185 cases, 62 were contraindicated for heart transplantation (HTX) for reasons such as end-stage renal failure or malignancy. In 62 cases, β-blocker therapy was difficult to implement, or after its implementation readmission was necessary because of recurrent HF. The 31 of these cases were treated with pharmacotherapy alone, while 31 cases were treated non-pharmacologically. The 37 cases were indicated for HTX, 31 cases provided informed consent and 21 cases desired HTX. Two cases received HTX in Japan. Eleven cases died of exacerbated HF during the recipient registration procedure. ICD, implantable cardioverter defibrillator; CRT, cardio resynchronization therapy; CRTD, CRT with defibrillator function; IABP, intra aortic balloon pumping; PCPS, percutaneous cardiopulmonary support; LVAS, left ventricular assist system.
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References