# Netherlands Institute for Continuing Cardiovascular Education (CVOI) self-assessment

In collaboration with Mediselect and supported by the company Novartis, the textbook Heart Failure, edited by Dirk Jan van Veldhuisen and Adriaan Voors, was published in Autumn 2003.

This textbook was primarily intended for the cardiology training course (OCC) in 2003. In like manner, the CVOI intends to publish textbooks on Atherosclerosis and Thrombosis in 2004 and Electrocardiography and Electrophysiology in 2005.

Following publication of the book, brief focused reviews of its chapters will be published in consecutive issues of the Netherlands Heart Journal. After each of these articles, there will be two multiple-choice questions, which can be answered in the section Questions & Answers of the website of the CVOI, www.cvoi.org. Correct answers will be honoured with 1 credit, while wrong answers to one or both questions will connect the participant to a section that presents and discusses the correct answers, after which the procedure can be repeated. Correct answers to both questions will automatically lead to registration of the CME credits in the Cardiologist Registration Accreditation System (CRAS) on the CVOI website. All textbooks contain eight chapters; participants can therefore obtain 16 credit points.

This experiment that connects CME articles to web-based self-assessment programmes and accreditation may pave the way for similar future developments and a reliable verifiable accreditation of CME articles.

# Heart failure: chapter 8 Treatment of end-stage heart failure

**N. de Jonge, P.J.M.J. Vantrimpont**

Heart failure is a lethal disorder, characterised by an initial phase of asymptomatic left ventricular dysfunction, followed by progressive deterioration.[1] The treatment options for heart failure have improved significantly over the last two decades. Especially ACE inhibitors and β-blockers have been shown to slow the progression of heart failure.[2-6] Nevertheless the prognosis of heart failure is still poor. A recent meta-analysis of the use of β-blockers in heart failure showed a 10 to 12% yearly mortality, despite the use of β-blockers.[7] The yearly mortality in the COPERNICUS trial, in patients with severe heart failure, was 20%, despite the use of ACE inhibitors as well as β-blockers.[8] In patients with end-stage heart failure, eligible for heart transplantation, yearly mortality increased to 75%.[9] It is important to note that the impressive improvement in the prognosis of heart failure, achieved by the use of ACE inhibitors and β-blockers, only translates into a modest increase in life expectancy. In the VeHeFT study this was only 0.02 year, in the SAVE study 0.3 year and with carvedilol 0.3 to 0.55 year.[10,11] These figures underline the grave prognosis of heart failure and the importance of an optimal, individualised treatment.

In all heart failure patients, potential surgical options, other than heart transplantation, have to be considered. Ischaemic heart failure patients with angina pectoris and proof of viability and contractile reserve of the myocardium should be evaluated for coronary bypass grafting, with or without aneurysm resection. Patients with heart failure due to severe aortic stenosis should be considered for aortic valve replacement, even with a compromised left ventricular function.

In all cases it is mandatory to optimise the treatment of heart failure, based on the requirements of the patient.

## General measurements

In the treatment of heart failure, the role of the compliance of the patient is often overlooked. Inadequate use of medication or excessive fluid and salt intake are important precipitating factors leading to

**N. de Jonge**
*Heart Lung Centre, University Medical Centre, Utrecht*
**P.J.M.J. Vantrimpont**
*Erasmus Medical Centre, Rotterdam*

Correspondence to: N. de Jonge
Heart Lung Centre Utrecht, UMCU, PO Box 85500, 3508 GA Utrecht
E-mail: n.dejonge@hli.azu.nl

decompensation of heart failure. In patients with advanced heart failure a total fluid intake of 1500 to 2000 ml/24 hours is advised, as well as a maximum of 2000 mg sodium (5 g NaCl) per day. All patients have to be educated about the importance of adequate drug dosing and the early detection of fluid retention by regular weighing. Some patients can be instructed to titrate the daily dose of diuretics, based on their weight. Cessation of smoking has to be stressed, as well as the use of alcohol, due to its cardiotoxic action. Obesity can add to the symptoms of dyspnoea and diminished exercise tolerance, and therefore weight reduction should be aimed for.

## Medical therapy

For the medical therapy of patients with advanced heart failure it is first and foremost important to omit medication with an adverse effect on heart and circulation. In this respect, especially NSAIDs have to be considered as they lead to fluid retention and a deterioration in kidney function in patients with heart failure, precipitating decompensation in a formerly stable heart failure patient. Antiarrhythmic medication, due to its negative inotropic effect on the heart, should be omitted. The only exception here is probably amiodarone, which has only limited negative inotropic effects.

The symptoms in most patients with advanced heart failure are related to congestion, a reflection of elevated filling pressures, as a consequence of retention of salt and water.[13,14] Left-sided congestion causes orthopnoea and dyspnoea on light exertion. Right-sided congestion results in oedema or ascites and abdominal symptoms.[15] The most important investigation for the estimation of filling pressures at physical examination is inspection of the jugular veins.[16] Right-sided filling pressures can be used accurately in most patients to estimate left-sided filling pressures.[17] These findings can be strengthened further in some patients by the presence of hepatojugular reflux and an accentuated pulmonary component of the second heart sound at auscultation.

It is very important to stress here that the absence of rales at pulmonary auscultation has no predictive value at all for the absence of elevated left-sided filling pressures.[13]

Besides estimation of the filling pressures, it is important to judge the quality of organ perfusion. For this the blood pressure can be used. A pulse pressure less than 25% [(systolic-diastolic pressure)/systolic blood pressure] is suggestive of a low cardiac output.[13] Furthermore, cold extremities, altered mental state and deterioration in renal function can be clues for a low cardiac output.[18]

Using the signs of congestion, combined with the quality of organ perfusion, four haemodynamic profiles can be recognised (cf. the 2x2 table of Stevenson).[13] Patients have either elevated or normal filling pressures (wet or dry) and adequate or limited perfusion (warm or cold). The optimal haemodynamic profile for a patient consists of normal filling pressures and adequate organ perfusion (dry and warm). Many patients admitted to hospital with advanced heart failure, however, present with signs of congestion and adequate organ perfusion (wet and warm), or with signs of congestion and limited organ perfusion (wet and cold). Treatment in patients with the 'wet and warm' profile requires drying them out with diuretics, combined with ACE inhibitors. Most of the time they do not need inotropic support. In patients already on β-blocker therapy, this may be continued if the volume balance can be easily restored. Otherwise, it should be stopped temporarily.[13]

For patients with a 'wet and cold' haemodynamic profile it is usually necessary 'to warm up in order to dry out'. In these patients β-blockers and ACE inhibitors often need to be withdrawn temporarily, combined with intravenous treatment with inotropes or vasodilators.[13]

Only a small subgroup of patients demonstrate the 'cold and dry' haemodynamic profile. Treatment options in this group are less clear. In case of low filling pressures, the dose of diuretics can be diminished cautiously. In some cases inotropic therapy can lead to temporary improvement.

The goals of therapy in patients with severe heart failure are absence of congestion and adequate organ perfusion, as determined by normal jugular venous pressure, absence of oedema, systolic blood pressure of at least 80 mmHg and a pulse pressure of at least 25% with stable renal function.[13]

## Diuretics

Diuretics result in a rapid relief of symptoms in congested patients. Apart from the increased excretion of water and sodium, loop diuretics also have vasodilatory characteristics, responsible for the rapid mode of action.[19] Several studies have demonstrated a worsening of symptoms in patients with moderate heart failure, after withdrawal of diuretics, despite replacement by an ACE inhibitor.[20-23] Patients with advanced heart failure sometimes require high-dose loop diuretics to overcome the decreased bioavailability.[24-26] Especially in patients with severe ascites, intravenous loop diuretics are more effective than oral diuretics. When using diuretics in these patients, it is important to administer them intravenously until the filling pressures have normalised. This way, patients will respond better on the re-institution of an oral regime and it will increase the chance that they will be able to continue on an outpatient basis. Instead of using very high doses of loop diuretics, it is also possible to combine a loop diuretic with a thiazide diuretic, given their different point of action in the kidney. Severe hypokalaemia, however, is a serious adverse effect of this combination.

An important misconception in the treatment of patients with advanced heart failure is that the dose of

diuretics has to be diminished in case of hyponatriaemia. The cause of hyponatriaemia in a fluid-overloaded patient with ascites and oedema, however, is too much extracellular water (dilutional hyponatriaemia). Treatment of this condition should consist of an increase in diuretic dose, combined with fluid restriction, instead of a decrease in diuretic dose.

### Beta-blockers

Despite salutary effects of β-blockers on the prognosis of heart failure, caution has to be taken in patients with end-stage heart failure. Initiation of β-blockers is not recommended for patients who are haemodynamically compromised, because of the high risk of deterioration, resulting in pulmonary oedema or cardiogenic shock.[27,28] This also applies to patients with a recent onset of heart failure who are haemodynamically unstable.

Patients on chronic β-blocker treatment who require inotropic therapy present another challenge. Pathophysiologically, the combination of β-mimetic and β-blocking agents seems illogical. Only very high doses of β-mimetic agents are able to overcome the effect of β-blockers (dobutamine 15 to 20 μg/kg/min). With hypotension and inadequate organ perfusion, β-blockers have to be stopped temporarily and the use of a phosphodiesterase blocker, such as milrinone, should be seriously considered.[28,29]

### Inotropic therapy

Inotropic therapy, such as dobutamine and dopamine, is frequently used in the management of heart failure, but lacks large randomised trials.[29] Inotropic therapy results in short-term haemodynamic benefits at the expense of acceleration of underlying disease progression, particularly in ischaemic heart disease. This may result in a vicious circle, creating 'inotropic dependency'.[29] Therefore, use of inotropes should be limited to short-term treatment for acute decompensation, refractory to diuretics and ACE inhibitors, accompanied by hypotension or renal hypoperfusion. Furthermore, inotropes can be used as a bridge to transplantation or coronary artery bypass grafting, and for palliation of severe symptoms in patients who are not candidates for heart transplantation.[29]

It should be borne in mind that inotropic therapy may mask an inadequate diuretic regimen. Therefore, it is advisable to discontinue inotropic therapy at least 48 hours before discharge from the hospital to assess if the patient will remain stable on oral therapy.[13]

Long-term inotropic therapy does not result in improvement in quality of life and increases the risk of life-threatening arrhythmias and therefore can not be recommended.[30] Besides dobutamine and dopamine, phosphodiesterase (PDE) inhibitors as mirinone and enoximone can be used, especially in patients on chronic β-blockade.[28,29,31] The use of oral dopaminergic agonists, such as ibopamine and oral PDE inhibitors, results in an increase in mortality and has therefore been abandoned.[32-34]

Of the newer drugs for the treatment of heart failure, especially nesiritide and levosimendan should be mentioned here, although both drugs are not yet available in the Netherlands.

Nesiritide is a recombinant form of human B-type natriuretic peptide with vasodilating, natriuretic and neurohormonal effects that can be administered intravenously in patients with severe heart failure. It decreases pulmonary capillary wedge pressure and improves dyspnoea and fatigue. Furthermore, it suppresses the activation of the renin-angiotensin system and prohibits the release of norepinephrine. It has no proarrhythmic effects, is usually well tolerated and appears to be effective in patients receiving concomitant β-blocker therapy.[35,36]

Levosimendan is a novel calcium sensitiser which improves myocardial contractility, without an increase in myocardial oxygen demand. A comparative study demonstrated a more effective improvement in haemodynamic performance than with dobutamine. Interestingly, β-blockade did not reduce this haemodynamic effect. Also, no proarrhythmic effects have been noted.[37]

### Heart transplantation

The first human heart transplantation in 1967 was a milestone in the treatment of patients with end-stage heart failure. The initial results, however, were very disappointing, resulting in the discontinuation of heart transplantation in most centres. Only after improvement in the early detection of acute rejection and the introduction of better immunosuppressive medication, such as ciclosporin, could the number of heart transplantations expand dramatically. More than 66,000 have been performed world-wide, accounting for ±3000 each year.[38] In the Netherlands the first heart transplantation was performed in the Erasmus Medical Centre Rotterdam in 1984,[39] followed by Utrecht University Hospital in 1985. Both centres together transplant 40 to 45 patients a year (figure 1). This low number of transplants is due to the lack of donor hearts,

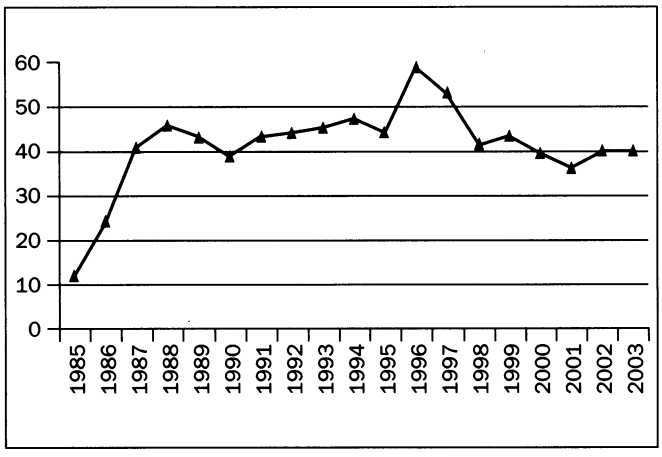


*Figure 1. The number of heart transplantations in the Netherlands.*

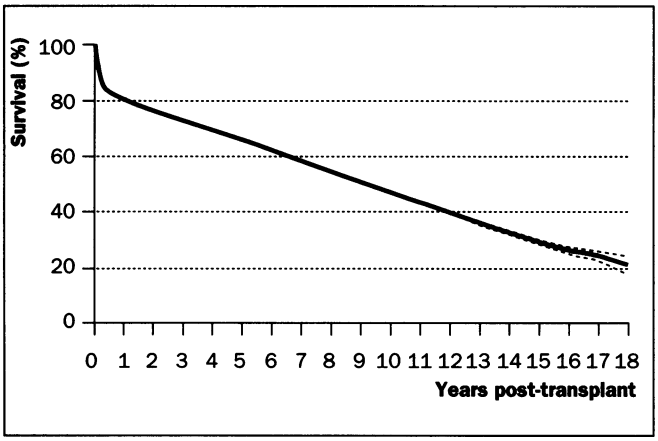


*Figure 2. Survival after heart transplantation.*

a problem which seems to increase every year. Only by accepting more and more donor hearts from older donors, potentially infected donors and more haemodynamically compromised donors is it possible to prevent the decline in the number of transplants. The introduction of the law on organ donation (WOD) some years ago has not improved this situation.

The results after heart transplantation are good. One-year survival is 80 to 85%, followed by a constant yearly decline of 4% (figure 2). Patient half-life (time to 50% survival) is 9.3 years. For patients who survive the first year this improves to 11.8 years.[38] These results are in sharp contrast with the survival data of patients with end-stage heart failure, showing a one-year mortality of 75%.[9] In the overall results of heart transplantations, also mortality on the waiting list (15 to 20%) has to be involved. Clearly, this reduces the survival chance for the individual heart failure patient, but it is still far better than the prognosis without heart transplantation.

Heart transplantation therefore remains the most effective treatment for improvement of prognosis in patients with end-stage heart failure.[41] Functional recovery after heart transplantation is impressive, with >90% reported as having no activity limitations at one, three and five years after transplantation.[38] Peak $VO_2$ at exercise testing in most patients is, however, limited to 60 to 70% of predicted values for age and sex.[42,43]

In the early period after heart transplantation the most important medical problems consist of acute rejection and infection. To prevent acute rejection, lifelong use of a combination of several immunosuppressive drugs is mandatory. Some examples are ciclosporin, tacrolimus, mycofenolate-mofetil and prednisone. For the detection of rejection, regular myocardial biopsies are used. In this way immunosuppression can be adapted according to the histological findings.

Due to the immunosuppressive medication, patients are more susceptible to infectious diseases. These include regular bacterial infections but also opportunistic infections, such as *Pneumocystis carinii, Candida* spp. *Cytomegalovirus* infection frequently occurs after organ transplantation because the virus can be transmitted by the donor organ. Medical problems later after heart transplantation include increased incidence of malignancies, renal failure and coronary artery disease. Of the malignancies especially skin tumours and a specific type of B-cell lymphomas are frequent. It is our experience that all malignancies seem to behave more aggressively, under immunosuppressive medication.

Up to 20% of patients will develop renal failure after transplantation as a result of nephrotoxic medication, such as ciclosporin and tacrolimus, requiring chronic dialysis or renal transplantation in several patients.

Progressive coronary artery disease of the donor heart is one of the major factors limiting the long-term results of heart transplantation. This specific transplant-related problem is called cardiac allograft vasculopathy (CAV), or chronic rejection due to the involvement of the immune system in its pathogenesis. It is characterised by a diffuse narrowing of the coronary arteries due to intimal hyperplasia, leading to distal vessel loss. Due to the diffuse nature of this disease, coronary angiography can underestimate severity.[44] Intravascular ultrasound (IVUS) is a very sensitive method for the detection of CAV, but is very costly. Clinical manifestations of CAV may include heart failure, myocardial infarction and sudden death. Because the transplanted heart is denervated, patients do not experience classical angina.

The diffuse nature of this process implies that coronary interventions as PTCA and CABG do not appear to improve prognosis. Currently, the only effective treatment option is retransplantation, but this is often not feasible due to the limited number of donor hearts available.

### *Selection of transplant candidates*

The limited number of donor hearts available for transplantation means that only a small group of patients with end-stage heart failure can be treated in this way. Therefore, careful selection of potential recipients is mandatory. Only patients with a prognosis worse than the prognosis after heart transplantation should be eligible. There should be no other treatment options available, and the patients should be severely limited in their activities (NYHA III-IV), despite optimal medication and compliance. Concomitant disease limiting prognosis should be absent.[45]

It is important to state here that a low ejection fraction in itself is not an indication for a heart transplantation.

One of the shortcomings in the treatment of patients with heart failure is the problem of predicting prognosis in the individual patient. No single test or measurement has enough predictive power to stratify patients.[46] Therefore, one has to rely on the com-

bination of several parameters, such as left ventricular ejection fraction, exercise tolerance, haemodynamic data, and signs of neurohormonal activation, like hyponatriaemia.[46] It is important to note that these parameters have to be evaluated in patients under optimal treatment and not during a period of decompensation.

For the estimation of exercise tolerance, peak $VO_2$ is used. A peak $VO_2$ ≤14 ml/kg/min or less than 50% of predicted for the patient during anaerobic exercise makes the patient a potential transplant candidate. Besides assessing the patient at one time point, it is also important to take into consideration the changes in time. For instance a gradual decrease in peak $VO_2$ in consecutive exercise tests, or repeated admissions in hospital for the treatment of decompensation, may also delineate transplant candidates.

Even more difficult than estimating prognosis in chronic heart failure patients is estimating prognosis in patients admitted with acute heart failure. Some patients deteriorate so rapidly that only an acute heart transplantation or mechanical support can save them. Others, however, stabilise and may show gradual improvement in the course of months or years. This is especially the case in patients with a first manifestation of a cardiomyopathy.[47] Again it should be stressed that initiation of β-blockade in these very sick patients with acute heart failure is absolutely contraindicated. Only when the patients are euvolaemic and stabilised can low-dose β-blockade be initiated cautiously. Regular consultation of a heart transplant centre to discuss therapeutic options in these difficult patients is advisable.

In the evaluation of transplant candidates several contraindications should be considered (table 1).[45] The final decision for acceptance as a transplant candidate is made in the transplant centre by a team consisting of a cardiologist, cardiothoracic surgeon, transplant nurse and a social worker. After acceptance, the patient will be listed on the national waiting list. The allocation of donor hearts is based on blood group, body size, medical urgency and waiting time. The mean waiting time at present is four to six months, but can increase in some persons to more than a year. If the medical condition of a patient on the waiting list improves, accompanied by an increase in peak $VO_2$ at exercise testing, the patient may be removed from the waiting list.

**Table 1.** Contraindications for heart transplantation.

| **Contraindications for heart transplantation** |
|---|
| Irreversible elevated pulmonary resistance (PVR >400 d/sec/cm$^5$, or transpulmonary gradient >15 mmHg) despite optimal vasodilators |
| Active infection |
| Renal insufficiency/hepatic insufficiency |
| Peripheral vascular disease |
| Diabetes with secondary damage |
| Concomitant disease limiting prognosis |
| Difficulty with treatment |

If a donor heart becomes available, the cardiologist in the donor hospital plays an important role in the assessment of donor heart function.[48] Brain death in the donor may lead to a catecholamine storm resulting in ischaemic problems of the heart and haemodynamic instability, even in young patients with a pre-existing normal heart. It is therefore important to evaluate the ECG and chest X-ray. Vital here is an echocardiographic examination, focussing on wall motion abnormalities, left ventricular hypertrophy and valvular abnormalities.[49] In donors older than 45 to 50 years coronary angiography should also be considered.[50] With the combination of these results, the transplant centre can decide if the donor heart can be used for the eligible acceptor.

One has to bare in mind that heart transplantation can only be used for a very small group of heart failure patients and that the discrepancy between the shortage of donor hearts and the increasing number of heart failure patients will only increase in the coming years. Therefore it is absolutely essential to explore other therapeutic options for patients with end-stage heart failure. Mechanical circulatory support may play an important role to help solve this problem in the near future and should be considered very carefully.

## Mechanical circulatory support

Several devices for circulatory support are currently available. Arbitrarily, they can be divided into devices meant for short-term (up to ±2 weeks) and for long-term support. Short-term devices include the intra-aortic balloon pump and external centrifugal and pneumatic devices that are mainly used in case of low cardiac output after open heart surgery or myocardial infarction. The operation time of these devices is mainly limited by thromboembolic and bleeding complications and infections.[51]

Longer support periods, as bridge to transplantation or as alternative to transplantation, require implantable devices (left ventricular assist devices; LVAD) in which the pump itself is placed abdominally and connected to the heart by two cannulas containing porcine valves (figure 3). Two examples are the Heart Mate and the Novacor. These are electrically driven pumps which only have one line penetrating the abdominal wall, necessary for power supply. Pump flow is dependent on left ventricular filling and can increase to 8 to 10 L/min while exercising. The pumps operate independently from the electrical activity of the heart, so that arrhythmias as ventricular tachycardia or fibrillation will not initially affect pump flow. Because these devices only support the left ventricle, they can not be used in patients with severely compromised

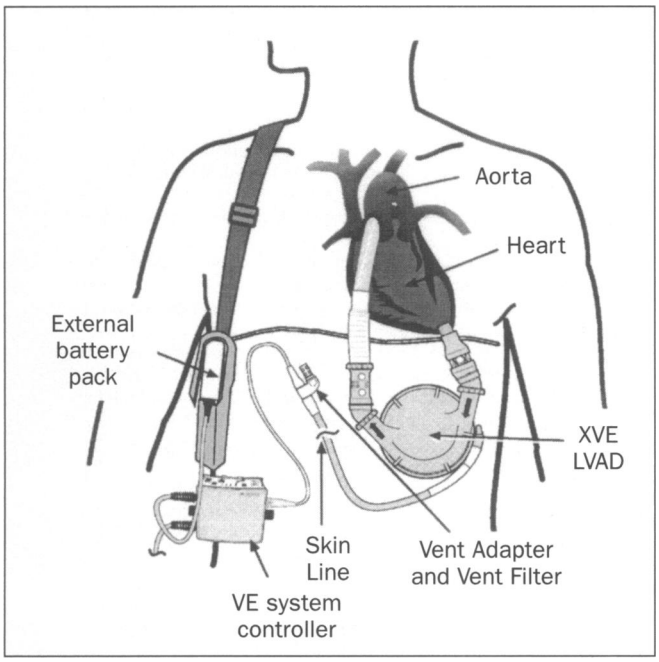


***Figure 3. Schematic drawing of a left ventricular assist device (LVAD). The inflow cannula is inserted in the left ventricular apex. The outflow cannula connects the pump with the ascending aorta.***

right ventricular function or elevated pulmonary vascular resistance.

At the moment, these devices are mainly used as a bridge to transplantation in patients at risk of imminent death. In selected patients the results are satisfactory, especially taking into consideration the dire situation at the time of implantation. Perioperative survival is 87% and 75% of the patients undergoing LVAD implantation are transplanted.[52] One of the advantages of these types of pumps is that the patients are able to move freely and that they are only hindered by the battery pack which has to be renewed every couple of hours. The exercise tolerance of these patients, while on the device, is almost as good as that of patients after a heart transplantation.[43] With several precautions and after intensive instructions, most of the patients can await their heart transplant at home.

Recently an investigation was carried out as to whether these devices can also be used as an alternative to transplantation in patients with contraindications for heart transplantation. In that study one-year survival in the patients on the device was 52%, while in the medically treated group it was 25% ($p<0.002$). Two-year survival, however, did not differ, which was mainly caused by the high percentage of mechanical problems of the pump (35% pump failure after two years).[9] It is hoped and expected that the newer devices will offer greater durability, allowing more patients to be treated as an alternative to transplantation. What the effect of this policy will be on costs has to be determined.

Alternative (surgical) modalities in patients with end-stage heart failure, such as the cardiomyoplasty and the partial left ventriculectomy (Batista procedure) have been abandoned by lack of long-term effect.[53] ■

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