Heart Rhythm Considerations in Heart Transplant Candidates and Considerations for Ventricular Assist Devices: International Society for Heart and Lung Transplantation Guidelines for the Care of Cardiac Transplant Candidates—2006

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1. ELECTROPHYSIOLOGIC CONSIDERATIONS IN HEART TRANSPLANT CANDIDATES

1.1. Cardiac Re-synchronization Therapy With or Without Implanted Cardioverter Defibrillator as Part of Optimal Treatment

Regardless of underlying etiology, heart failure may be associated with an abnormal sequence of ventricular contractions, referred to as cardiac or ventricular dyssynchrony. This abnormality may be due to both disturbed electrical activation and regional abnormalities in contraction due to ischemia, myocardial scarring or replacement of myocardium by infiltrative diseases.[1,2] Approximately 33% of patients with systolic heart failure have evidence of abnormal electrical activation on surface electrocardiogram (ECG), seen as a QRS duration of >120 milliseconds, most commonly as a left bundle branch block (LBBB).[3] The ventricular contraction pattern associated with LBBB results in the following abnormalities[1]: abnormal ventricular septal motion with movement paradoxical to the lateral wall of the left ventricle, and thus a decrease in regional left ventricular ejection fraction (LVEF)[2]; a delay in mitral valve opening and aortic valve closure resulting in a shortened left ventricular (LV) filling time[3]; and mitral regurgitation, caused or aggravated by dyssynchronous activation of papillary muscles and the surrounding myocardium and incomplete closure of the mitral valve caused by late ventricular contraction.[2,3]

In addition to dyssynchrony resulting from underlying cardiac pathologies, some data suggest that cardiac dyssynchrony induced by a pacemaker (right ventricular [RV] or combined right atrial [RA] and RV) may increase the risk for the development of heart failure.[4] Irrespective of the underlying pathology, QRS >120 milliseconds is associated with increased mortality.[4-6]

1.2. Cardiac Re-synchronization Therapy

Recommendations for cardiac re-synchronization therapy (Class I) include:

1. Potential transplant candidates with cardiac dyssynchrony and New York Heart Association (NYHA) Class III or IV symptoms, despite maximum medical therapy, should be strongly considered for cardiac re-synchronization therapy (CRT) (*Level of Evidence: B*).
2. The use of an implantable cardioverter defibrillator (ICD), especially in patients with persistent NYHA Class III or IV symptoms, should be considered because it may further decrease mortality in this population (*Level of Evidence: B*).

CRT involves the use of pacing to specifically improve or negate the effects of cardiac dyssynchrony, usually by pacing the LV lateral wall. However, specific lead placement may depend on the underlying conduction abnormality. Early studies in the 1990s proved that the short-term use of pacing to re-synchronize the heart resulted in correction of abnormal septal motion, an increase in LV filling time, and an improvement in mitral regurgitation. Short-term animal studies showed improvement in hemodynamics and these results were also subsequently shown in human studies.[3,7]

The development of LV leads that can be reliably placed into the coronary sinus to pace the LV free wall has allowed for multiple clinical studies to evaluate the effect of CRT on hemodynamics, quality of life, NYHA class, exercise capacity and overall clinical status.[3,7-9] These early, non-controlled or non-randomized studies largely showed improvements in clinical parameters. Three large, randomized studies have since set the stage for the regulatory approval of CRT therapy and its acceptance as part of the mainstay of therapy for advanced heart failure (NYHA Class III or IV, despite maximal medical therapy).

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The first randomized, double-blind trial to evaluate CRT was the Multicenter InSync Randomized Clinical Evaluation (MIRACLE) study.[10] Conducted from 1998 through 2000, the study included 453 patients with LVEF <35% and QRS >130 milliseconds, with NYHA Class III or IV heart failure despite optimized medical therapy. These patients were randomized in a double-blind fashion to CRT therapy vs control for 6 months (all received CRT implantation, with the device turned on in only the CRT group). The success rate for device implantation was 92% (in early use the LV leads were placed via the coronary sinus). The study was not powered to show a difference in survival. However, all primary and secondary end-points significantly favored CRT therapy, including death or worsening heart failure requiring hospitalization (hazard ratio [HR] 0.60; 95% confidence limit [CL] 0.37 to 0.96; $p = 0.03$) and hospitalization for worsening heart failure (HR 0.50; 95% CL 0.28 to 0.88; $p = 0.02$). Other secondary end-points that significantly favored CRT (some evaluated in sub-studies) included improvement in quality of life (QOL) score (QOL –18 vs –9 [lower score better]; $p = 0.001$), LVEF by echocardiography (4.6% vs –0.2%; $p < 0.001$), and an improvement in clinical composite heart failure score (improved 67% vs 39%, worsened 16% vs 27%; $p < 0.001$).[11] Despite 2001 U.S. Food and Drug Administration (FDA) approval of the CRT device for use in the USA, important questions about the use of CRT, with and without an ICD, remained.[12]

The Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure (COMPANION) trial was a larger study ($N = 1,520$ patients), with a similar study population to that of the MIRACLE trial (except the QRS duration cut-off was ≥120 milliseconds), comparing optimum medical therapy to CRT, or to CRT with an ICD in a 1:2:2 randomization.[13] Randomization for the study, conducted from 2000 to 2002, was not blinded to patients or investigators. At 12 months of follow up, both CRT therapy and CRT with ICD decreased the risk of death or hospitalization for any cause (CRT: HR 0.81; 95% CL 0.69 to 0.96; $p = 0.014$; CRT with ICD: HR 0.80; 95% CL 0.68 to 0.95; $p = 0.010$). At 12 months, CRT resulted in a marginally significant reduction in death (HR 0.76; 95% CL 0.58 to 1.01; $p = 0.06$), and CRT with ICD resulted in a 36% reduction in risk of death (HR 0.64; 95% CL 0.48 to 0.86; $p = 0.003$). Thus, the effect of CRT on survival in patients was not affirmed, but suggested.

The Cardiac Re-synchronization–Heart Failure (CARE-HF) study was a randomized (CRT vs control), non-blinded study of 813 patients in NYHA Class III or IV with intraventricular dyssynchrony and LVEF ≤35% and a primary end-point of death (any cause) or unplanned hospitalization for a cardiovascular event, with death alone pre-specified as a principal secondary end-point.[14] Device placement was successful in 95% of patients in the CRT group. Death or first hospitalization was significantly reduced by 37% in the CRT group by the end of the study, with an average follow-up of 29.4 months (HR 0.63; 95% CL 0.51 to 0.77; $p < 0.001$). In addition, heart failure hospitalizations, heart failure symptoms and patient QOL were significantly improved in the CRT group. A 36% reduction in all-cause mortality was seen in the CRT group, with 82 deaths in that group, compared with 120 deaths in the control group (HR 0.64; 95% CL 0.48 to 0.85; $p < 0.002$).

Interestingly, the incidence of sudden death was unchanged in the treated arm (32%) as compared with the control arm (35%), suggesting that a defibrillator might further decrease the incidence of sudden death.

CRT has been clearly shown to improve morbidity and mortality in patients with NYHA Class III or IV heart failure, despite maximized medical therapy with evidence of ventricular dyssynchrony by surface ECG (a wide QRS).

Published studies largely assessed cardiac dyssynchrony via evidence of conduction abnormalities on the surface ECG. However, approximately 33% of patients who undergo CRT therapy receive no demonstrable improvement in morbidity. It is also clear that a wide QRS alone does not assure that ventricular dyssynchrony is present, and that mechanical ventricular dyssynchrony can be present in patients with a normal QRS duration.[15] The use of various echocardiography techniques (interventricular mechanical delay, septal-to-posterior wall motion delay, tissue Doppler imaging, strain and strain rate, tissue tracking),[16] and radionuclide angiography techniques,[17] have been evaluated in relatively small studies for the assessment of mechanical cardiac dyssynchrony, and to evaluate the effects of CRT. Further work is needed to assess optimal CRT indication and benefit.

It is important to note that severely ill patients, including those who need inotropic or device support, were largely excluded from the earlier clinical trials. These patients are today the most frequent heart transplant candidates. The risk of implantation of a CRT in an end-stage heart failure patient (Stage D), who is otherwise is a good candidate for heart transplantation, may not be warranted.

1.3. Implantable (Primary and Secondary Prevention) and Wearable External Defibrillator as a Bridge Therapy to Heart Transplantation

Recommendations for use of defibrillators include:

Class I:

1. An ICD for secondary prevention should be always considered (*Level of Evidence: A*).

2. An implanted or wearable ICD should be provided for Status 1B patients who are discharged home given that the wait for transplantation remains significant (*Level of Evidence: C*).
3. Amiodarone should be used as the agent of choice when anti-arrhythmic therapy is necessary to prevent recurrent atrial or symptomatic ventricular arrhythmias despite its numerous side effects (*Level of Evidence: A*).
4. Re-synchronization therapy in advanced heart failure patients should be considered together with a defibrillator (*Level of Evidence: B*).

Class IIa:

1. It is reasonable to consider placement of a defibrillator in patients with Stage D failure who are candidates for transplantation or LVAD destination therapy (see subsequent considerations for mechanical circulatory support device [MCSD] referral: bridge or destination) (*Level of Evidence: C*).

Patients with heart failure and reduced LVEF are at high risk for sudden death. Although ventricular tachyarrhythmias are the most common rhythms associated with sudden death, bradycardia and electromechanical dissociation are also common in patients with advanced heart failure.[18]

Appropriate heart failure therapy (β-blockers, aldosterone inhibitors) can help reduce the risk of sudden death, but the absolute frequency of sudden death remains high.[19]

Patients with heart failure and reduced LVEF are candidates for secondary prevention of sudden death from ventricular tachyarrhythmias if there is a history of previous cardiac arrest, documented sustained ventricular arrhythmias, or syncope.[19,20] These patients all have a high risk of recurrent events and are candidates for placement of an ICD.

Indications for ICD placement for primary prevention of sudden death in patients with heart failure and reduced LVEF have recently been clarified by several large trials, most notably the Multicenter Automatic Defibrillator Implantation Trial II (MADIT-II)[21] and Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT).[22] In these trials, patients were treated with optimized medical therapy and had documented, persistent severe LV dysfunction for ≥6 months. MADIT-II demonstrated that ICD, compared with standard medical therapy, decreased total mortality for patients with LVEF ≤30% after remote myocardial infarction (MI). Patients with symptomatic heart failure in this trial achieved the most benefit from ICD implantation.

The SCD-HeFT examined the benefit of ICD implantation for patients with LVEF <35%, and NYHA Class II or III heart failure symptoms from both ischemic and dilated cardiomyopathies compared with standard therapy or amiodarone. Absolute mortality was decreased only in the ICD arm. There was no improvement in survival during the first year, but at 5 years a 7.2% improvement was demonstrated.

The Defibrillators in Non-ischemic Cardiomyopathy Treatment Evaluation (DEFINITE) trial[23] compared medical therapy alone with medical therapy plus ICD in patients with non-ischemic cardiomyopathy; NYHA Class I, II or III heart failure; and LVEF <36%.

The ICD was associated with a reduction in all-cause mortality that did not reach statistical significance, but it was consistent in terms of magnitude of effect (30%) with the findings of MADIT-II and SCD-HeFT.

Other trials, such as COMPANION,[13] examined combined CRT and ICD in patients with heart failure and low LVEF, and demonstrated a survival benefit as a secondary end-point. As a result of these trials, use of defibrillators for primary prevention of sudden death is rapidly expanding in patients with NYHA Class II or III heart failure. Accordingly, by the time patients with NYHA Class II or III heart failure progress to Stage D heart failure and are transplant candidates, an ICD may already be implanted. This is particularly important as studies on primary prevention of sudden death in patients with NYHA Class IV/Stage D patients have not been performed. Generally, placement of an ICD for primary or secondary prevention of sudden death in Stage D patients is not recommended as the impact of ICD on survival is generally not seen until 1 year after implantation.

Few studies have reported the incidence of arrhythmic events in Status 1B patients. Lang et al[24] reported on data from 155 UNOS Status 1B patients, of whom 91 were discharged. Twenty-five had an implanted defibrillator and 13 wore an external device. Of those patients with defibrillators, no significant arrhythmic events were recorded. Sudden death episodes occurred in 2 patients, both of whom declined external defibrillators. Brozena et al[25] described 60 patients who were discharged to home inotropic therapy. All patients had an ICD. The average duration of participation was 160 days with 7 events that resulted in ICD firing. Six patients had an appropriate defibrillator shock for treatment of ventricular tachycardia, and 1 for supraventricular arrhythmia. These studies probably underestimate the risk for arrhythmic events given the relatively short duration of follow-up. Alternative strategies for prevention of sudden death in Stage D patients include use of amiodarone, as this anti-arrhythmic agent may be associated with neutral or positive effects in patients with heart failure and low LVEF.[26,27] In the recent SCD-HeFT investigation, administration of amiodarone to patients with symptomatic heart failure and low LVEF did not improve outcomes when compared with placebo ther-

apy.[22] However, patients with ICD and recurrent ventricular arrhythmias may require amiodarone therapy with or without catheter ablation of the arrhythmia focus.

Use of wearable defibrillators can serve as a bridge to transplant. This is particularly true for patients with systemic or device infections or in patients whose anticipated waiting time to transplant is short, such as candidates with blood types A and B. Use of the Lifecor system has been reported in 289 patients who were either awaiting placement of an implantable device (BIROAD study) or patients with heart failure and reduced ejection fraction (WEARIT study).[28] This external defibrillator system consisted of 2 gel-filled defibrillator electrodes, 4 sensing ECG electrodes, and a vibrator incorporated into a patient-worn belt. ECG signals are continuously monitored for ventricular tachycardia or fibrillation at rates programmed into the device. A series of alarms, initially vibratory then an audible tone followed by voice alarm, are activated by a detected arrhythmia. If the system is not disabled, the device delivers a shock at a pre-programmed level. In this trial, 6 successful defibrillations occurred out of 8 attempts. The 2 unsuccessful defibrillations occurred in patients who did not properly apply the defibrillator electrodes. One of these events was non-fatal as the patient was successfully cardioverted using another external device. This device has been approved for use by the FDA and is available for widespread use.

2. RELEVANT ISSUES IN HEART TRANSPLANT CANDIDATES CONSIDERED FOR MCSD THERAPY

In the decisionmaking process before MCSD implantation other cardiac, non-cardiac and technical factors must be considered. The following considerations refer to the most relevant issues in patient evaluation and management for MCSD therapy. Due to the many available devices and diverse experiences, the present statement cannot cover all the specific issues that might be encountered in patient selection and management.

Because the spectrum of uses of ventricular assist device (VAD) support includes not only bridge to transplantation but also weaning and destination therapy, the former may be changed to one of the latter two options, balancing possible advantages and disadvantages with regard to co-morbidity.[29,30]

The recommendation for MCSD therapy is based on a comparison of short- and long-term survival and QOL outcomes with conventional therapy. The following recommendations must not be viewed in isolation, but in the context of their cumulative effect on outcomes in a given patient.

2.1. Age

Class I recommendations:

1. In patients >60 years of age, a thorough evaluation for the presence of other clinical risk factors should be done *(Level of Evidence: C)*.
2. Age should not by itself be considered a contraindication to mechanical circulatory support (*Level of Evidence: C*).

Background. An inverse relationship is generally reported between ages >60 to 65 years and outcome, although encouraging results have recently been obtained in selected patients ≤70 years.[31–36]

2.2. Body Size

Class I recommendation:

1. The use of pulsatile intracorporeal devices (e.g., HeartMate XVE, Thoratec Corp., Pleasanton, CA; Novacor LVS, WorldHeart Corp., Oakland, CA) should be limited to patients with a body surface area (BSA) >1.5 m^2. For smaller individuals, the use of paracorporeal or axial-flow devices should be considered (*Level of Evidence: C*).

Background. The large size of intracorporeal pulsatile devices requires adequate thoracic and abdominal capacity. This limitation is overcome by the availability of paracorporeal, small-sized pulsatile devices or by the use of intracorporeal/intraventricular axial-flow devices.[29,34]

2.3. Renal Function

Class I recommendation:

1. All patients evaluated for MCSD therapy should have their creatinine and blood urea nitrogen (BUN) measured. Patients with a creatinine >3.0 mg/dl are at higher risk. Patients with serum creatinine above this value may be considered MCSD candidates if renal failure is acute and renal recovery is likely (e.g., acute renal failure in young patients with previously normal renal function) (*Level of Evidence: C*).

Class III recommendation:

1. Patients dependent on long-term dialysis should not be considered MCSD candidates (*Level of Evidence: C*).

Background. Renal dysfunction is a strong determinant of unsuccessful MCSD support but in many cases it recovers after adequate circulatory support.[32–34,37–40] In addition to clinically established parameters, such as serum creatinine and BUN,[41,42] pre-operative creatinine clearance has also been shown to correlate

with post-operative outcomes.[43] The Acute Physiology and Chronic Health Evaluation (APACHE) II score has been used in peri-operative renal dysfunction risk assessment.[44]

2.4. Pulmonary Function

Class I recommendation:

1. All patients evaluated for MCSD therapy should have chest X-ray and pulmonary function tests if feasible. Mechanical ventilation in the absence of significant pre-existing pulmonary dysfunction or inflammatory infiltrates is a risk factor but should not be considered an absolute contraindication to VAD support. A lung computerized tomography (CT) scan should be considered in select patients to rule out undiagnosed conditions at chest X-ray (*Level of Evidence: C*).

Class III recommendation:

1. Patients with severe pulmonary dysfunction contraindicating heart transplantation (e.g., forced expiratory volume in 1 second [FEV_1] <1) should not be considered MCSD candidates (*Level of Evidence: C*).

Background. Mechanical ventilation in cardiogenic shock is a severe risk factor for poor post-implant outcome. Recent pulmonary embolism or inflammatory parenchymal infiltrates can lead to the development of infective foci, which can be difficult to treat under mechanical circulation.[32–34,40]

2.5. Hepatic Function

Class I recommendation:

1. All patients evaluated for MCSD therapy should have liver function assessment. Patients with an alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >3-fold control values are at higher risk. Biventricular support may be considered the first option in cases of hepatic dysfunction associated with RV failure (*Level of Evidence: C*).

Class III recommendation:

1. Patients with cirrhosis and portal hypertension should be excluded from MCSD implantation (*Level of Evidence: C*).

Background. Elevated serum bilirubin and deficiency in clotting factors have a serious adverse impact on post-implant outcomes. However, because hepatic dysfunction is often a consequence of right ventricular (RV) failure, it is a strong predictor of the need for biventricular support.[32–34,37,39,40] The model for end-stage liver disease (MELD) score prognostic model is gaining increasing relevance. This score includes the logs of bilirubin (mg/dl), creatinine (mg/dl), international normalized ratio (INR) and cause of underlying disease.[45,46] Besides bilirubin, liver enzyme levels also predict survival after MCSD implantation as a bridge to transplantation.[47,48]

2.6. Coagulation Disorders

Class I recommendation:

1. All patients evaluated for MCSD therapy should have complete routine coagulation tests performed. Patients with a spontaneous INR >2.5 are at increased risk of bleeding complications (*Level of Evidence: C*).

Class III recommendation:

1. Patients with heparin-induced thrombocytopenia are generally not considered MCSD candidates (*Level of Evidence: C*).

Background. Most clinical decisions are currently guided by measurement of the INR. However, as coagulation control is crucial, measurements such as activated protein C (APC), thrombomodulin and endothelial cell protein C receptor may provide more precise guidance in the near future.[49]

2.7. Infectious Diseases and Immunoinflammatory Activation

Class I recommendation:

1. All patients evaluated for MCSD therapy should have a thorough screening for infectious foci. Any ongoing infection should be identified and adequately treated before MCSD implantation. In particular, all conditions that might enhance the risk of fungal infection should be considered and properly managed (*Level of Evidence: C*).

Class III recommendation:

1. Patients with an acute systemic infection should not be considered MCSD candidates (*Level of Evidence: C*).

Background. Sepsis is one of the most common causes of death after MCSD implantation.[29,32–34,39] In this context, an elevated white cell count (>10,000/μl) before MCSD implantation constitutes a risk factor for post-MCSD death.[31] During severe sepsis, the host defense system turns its lifesaving potential into autoaggression.[50–52] Circulating endotoxin may play an important pathogenic role.[53,54]

Fungal infection deserves special attention as MCSD patients are more prone to fungal infection and less responsive to medical treatment.[55,56]

2.8. Arrhythmias

Class I recommendation:

1. Biventricular support for recurrent sustained ventricular tachycardia or ventricular fibrillation should be considered only in the presence of untreatable arrhythmogenic pathologic substrate (e.g., giant cell myocarditis). Otherwise, appropriate medical anti-arrhythmic therapy, anti-bradycardia pacing, ICD implantation or ventricular tachycardia ablation can generally adequately control bradyarrhythmias or tachyarrhythmias during LVAD support (*Level of Evidence: C*).

Background. Ventricular tachycardia and ventricular fibrillation may resolve after adequate LVAD support except in the case of underlying pro-arrhythmic pathology. During LV MCSD support, tachyarrhythmias or bradyarrhythmias are generally tolerated in the presence of normal pulmonary resistance due to the Fontan-like circulation, and the need for biventricular support is uncommon.[32,33,57,58] In rare situations, the implantation/use of either anti-bradycardia pacing or anti-tachycardia devices may be necessary.[35]

2.9. Right Ventricular Function

Class I recommendation:

1. Evaluation of reversibility of pulmonary hypertension and RV performance should be performed before MCSD implantation. In the case of irreversible pulmonary hypertension, RV failure or multiorgan dysfunction, biventricular support should be considered. Patients >65 years of age with biventricular failure are at the highest risk for RV failure. Thus, they should be considered with great caution as MCSD candidates (*Level of Evidence: C*).

Background. RV failure constitutes one of the most powerful predictors of adverse post-MCSD outcomes.[31] The functional status of the RV and its relationship to the pulmonary circulation are of utmost importance in the decisionmaking process for MCSD implantation as is the differential indication between the use of an LVAD or biventricular assist device (BVAD).[32–34,59–61] Low RV systolic pressure coupled with elevated right atrial (RA) pressure and low systolic stroke volume indicates severe RV impairment with poor reversibility prospects.[60]

2.10. Valvular Diseases

Class I recommendations:

1. When using a completely unloading pulsatile MCSD, such as the Novacor, HeartMate I or Thoratec, the aortic valve should be sutured or replaced with a bioprostheses when more than mild aortic insufficiency is present. The replacement of a mechanical prosthesis with a bioprotheses should also be considered (*Level of Evidence: C*).
2. Anti-coagulation therapy is strongly advised when a prosthetic valve is present (*Level of Evidence: C*).
3. Severe mitral stenosis should be treated and, if weaning from MCSD is foreseen, significant mitral insufficiency should also be corrected (*Level of Evidence: C*).

Background. More than minimal aortic insufficiency can rapidly evolve to moderate/severe grades due to continuously elevated pressure in the aortic root created by the pump and not counteracted by phasic LV pressure rise. Mitral stenosis can reduce native ventricular filling and limit the output of the device. Mitral insufficiency does not interfere with MCSD function but can adversely affect future weaning and explantation. Severe tricuspid regurgitation should always be considered as an adjunctive mechanism of worsening of RV function in LVAD patients.[62] The presence of any prosthetic valve is potentially thrombogenic.[57,63–66]

Presently, a consensus does not exist on whether and how severe tricuspid regurgitation should be treated.

2.11. Neurologic Function

Class I recommendation:

1. A thorough neurologic examination should be performed to determine potential neurologic risk factors and contraindications for MCSD implantation. Specifically, post-stroke motor deficits should be assessed to determine the ability of the patient to cope with the device. In emergency cases with uncertain neurologic recovery, a short-term MCSD, such as a paracorporeal centrifugal pump, should be adopted, allowing for recovery and full evaluation of long-term MCSD candidacy. A recent or evolving stroke is considered at least a temporary contraindication (*Level of Evidence: C*).

Background. Knowledge about the neurologic status of patients referred for mechanical assistance on an emergency basis is crucial to determine the appropriateness of the procedure.[32–34]

2.12. Nutritional Status

Class IIb recommendation:

1. Cachexia should be considered a strong risk factor with regard to MCSD implantation[67] (*Level of Evidence: C*).

Background. Cardiac cachexia is a syndrome characterized by striking weight loss leading to a BMI <21 kg/m^2 in males and <19 kg/m^2 in females.[68] Heart failure patients may be characterized by the presence of

anorexia, early satiety, weight loss, weakness, anemia and edema. These features occur to a variable extent in different patients and may change in severity during the course of a patient's illness. The cachexia syndrome in advanced heart failure patients with low peak Vo_2 is a strong independent indicator of poor prognosis[69] (see Section 5: "Nurse and Social Worker Management of MCSD Candidates").

2.13. Multiorgan Failure

Class III recommendation:

1. Multiorgan failure should be considered a strong contraindication to MCSD implantation[70] (*Level of Evidence: C*).

Background. Multiorgan failure, defined as multiple, progressive, end-organ dysfunction with critical unmanageable impairment of vital functions linked to the central nervous system, kidney, liver and lung, is almost invariably associated with poor post-implant outcome for MCSD patients.

2.14. Malignancies

Class IIb recommendation:

1. Patients with potentially curable tumors may undergo MCSD implantation as a potential bridge to heart transplantation (*Level of Evidence: C*).

Background. Although active malignancies are an absolute contraindication to heart transplantation, in selected cases, mechanical support can be utilized to extend life expectancy to allow proper oncologic treatment before transplantation,[34] or as destination therapy.

2.15. Psychologic and Psychiatric Conditions

Class I recommendation:

1. A thorough psychiatric examination should be performed to determine potential psychiatric risk factors and contraindications for MCSD implantation. Specifically, patients with a significant psychiatric history, alcoholism or drug addiction should be referred to a psychiatrist or therapist as early as possible to ensure that proper treatment is initiated or optimized (*Level of Evidence: C*).

Class III recommendation:

1. Active psychiatric disease is a contraindication for MCSD implantation as many psychiatric conditions can lead to non-compliance (*Level of Evidence: C*).

For further details see Section 5, "Nurse Management and Social Worker Management of MCSD Candidates."

Background. Each patient's psychiatric history should be explored in detail. A history of depression, anxiety or suicide attempts should be documented.[71] Patients with a positive psychiatric history, or data concerning symptoms should be referred to a psychiatrist or therapist as early as possible to ensure that proper treatment is initiated or optimized.

Methods of coping with stress and illness should be discussed so that the transplant team will be able to adjust care for each patient's needs. Standardized testing, such as the Minnesota Living with Heart Failure Scale or the Sickness Impact Profile, should be administered if possible, as this may provide more objective information regarding patient coping skills. Patients and their care providers should be referred to support groups.[72–76]

An assessment should be done to determine if the patient has history of substance abuse, specifically a history of tobacco, alcohol or drug abuse.[71] If a patient is already involved in a recovery program, the continuation of this form of treatment should be highly encouraged. If the patient is not presently in recovery or in a drug rehabilitation program, this should be mandated. Referral to a substance abuse expert should be made as an adjunct to therapy.

3. RELATION BETWEEN INOTROPE THERAPY AND MCSD: IMPLANTATION AS BRIDGE TO HEART TRANSPLANTATION

Class I recommendation:

1. MCSD therapy should be considered when the patient requires incremental increases in inotropic or diuretic drug doses or additional parenteral agents, or deterioration in status occurs that includes signs of end-organ dysfunction despite these alterations (*Level of Evidence: C*).

Background. The use of inotropic therapy, specifically the use of dopamine, dobutamine and phosphodiesterase inhibitors (milrinone and enoximone), should be reserved for patients with refractory symptoms of heart failure and impending organ dysfunction as a consequence of the heart failure syndrome, typically for a low-output state. It has become increasingly clear that the use of dobutamine and milrinone/enoximone have long-term adverse effects on survival[77]; however, it is also clear that these drugs are effective in improving hemodynamics, leading to reversal of end-organ dysfunction.

It is not clear whether the elective move toward MCSD therapy in a stable heart transplant candidate awaiting transplantation on long-term inotropic therapy is indicated.

Class I recommendation:

1. Weaning from inotropes should be attempted when stable clinical conditions are achieved, but

repeated withdrawal should be avoided if dependence is well established (*Level of Evidence: C*).

Background. Most patients treated with inotropic and/or vasodilator drugs respond with an improvement in symptoms and a resolution of the end-organ effects of the low cardiac output state, specifically improvements in renal or liver function. The failure to achieve these goals may be an indication for mechanical circulatory support.

For patients responsive to inotropic therapy, a period of slow weaning from inotropes is mandatory to reduce the potential need for long-term inotropic therapy. Failure to wean from inotropes may be defined as: (a) recurrence of symptoms (shortness of breath refractory to diuretics, hypotension and/or hypoperfusion); and/or (b) declining urinary output and a progressive rise in the BUN and creatinine.

Class IIa recommendation:

1. MCSD should be considered as a useful strategy to bridge patients to heart transplantation in those patients who are otherwise not considered transplant candidates as a result of the degree and persistence of pulmonary hypertension despite inotropic therapy (*Level of Evidence: C*).

Background. High pulmonary vascular resistances limiting heart transplantation indication may persist under inotropic therapy. Completely unloading the left ventricle by MCSD implantation may lead to reversal of high-resistance pulmonary hypertension, allowing heart transplantation.[78]

Class IIa recommendations:

1. In challenging clinical cases, where it is hard to discriminate between heart failure (HF) progression and the unfavorable effect of medical therapy, it is reasonable to perform right-heart hemodynamic assessment to verify a patient's volume status and cardiac output in order to tailor inotropic drug dose if prolonged administration is being considered (*Level of Evidence: C*).
2. It is reasonable to consider right-heart hemodynamic assessment to demonstrate or to establish an association of the clinical and biochemical markers with measured hemodynamic deterioration after withdrawal of inotropic therapy (*Level of Evidence: C*).

3.1. Elective MCSD Therapy

Elective MCSD therapy has been performed with LVAD implantation in patients with severe functional impairment despite maximum medical therapy, including inotropic support, but with a relatively stable status.

This definition excludes patients receiving ventilatory support, ultrafiltration or percutaneous mechanical support or those showing signs of progressive end-organ damage or multi-organ failure due to heart failure.

There is very little information available, however, that helps determine the optimal time for recommendation of "elective" device therapy as a bridge to transplantation. Most MCSD experience was gained from implantation of devices in patients who were critically ill in the intensive care unit (ICU).

4. MCSD AS DESTINATION THERAPY

Class I recommendation:

1. Elective MCSD implant as destination therapy should be considered in non-transplant candidates who are dependent on long-term administration of intravenous inotropes to maintain a stable state (*Level of Evidence: B*).

Class IIb recommendation:

1. Despite the presence of a malignancy when a life expectancy of >2 years is foreseeable, mechanical assistance may be considered as destination therapy (*Level of Evidence: C*).

Class III recommendation:

1. Metastatic tumors should be considered an absolute contraindication to mechanical support (*Level of Evidence: C*).

Background. The relevant issues for MCSD implantation as a bridge to heart transplantation also apply to patients considered for destination therapy.

To define the non-transplant patient population that will benefit the most from elective LVAD therapy, it is important to determine the prognosis of patients with advanced, refractory heart failure. The best description of survival in this population is the analysis from the Randomized Evaluation of Mechanical Assistance in Treatment of Chronic Heart Failure (REMATCH) clinical trial, wherein patients were randomized to either medical therapy or placement of a Thoratec HeartMate I LVAD. Survival for patients on long-term inotropic therapy ($n = 91$) was only 39% and 24% vs 60% and 49% in the LVAD group, at 6 months and 12 months, respectively. In contrast, in patients with refractory heart failure who did not require long-term inotropic therapy ($n = 38$), survival at 6 and 12 months was 67% and 40%, respectively. Thus, the REMATCH data support the premise that patients with refractory heart failure, who are not on inotropic therapy, have survival similar to patients receiving LVAD support.[79] These data refer to a population older (average age 68 years) than heart transplant candidates with severe heart failure symptoms (NYHA Functional Class IV) and provide evidence from which recommendations can be made for use of an LVAD as destination therapy.

5. NURSE AND SOCIAL WORKER MANAGEMENT OF MCSD CANDIDATES

5.1. Nurse Nutritional Status

The impact of inadequate nutrition is crucial for MCSD implantation outcome.[67] Cachexia (addressed earlier) is a strong independent risk factor in patients undergoing VAD placement as a bridge to transplant.[80] In addition, implantation of an intracorporeal pump, such as the Thoratec HeartMate or Novacor LVS, can cause problems with persistent ileus and early satiety, which further limit the ability to improve nutrition. It is recommended that a thorough nutritional evaluation be undertaken pre-operatively.[81–83]

The main goals of a pre-operative nutritional plan are to promote surgical wound-healing, optimize immune function, and improve the macro- and micronutrient substrate conditions.[81] Restoration and maintenance of protein stores also facilitates management of warfarin therapy for patients on LVADs who require anti-coagulation. The following considerations should be included in a pre-operative work-up.

Nutritional assessment:

1. A thorough history should be taken of dietary habits as well as an updated assessment of bowel motility. It should be documented if patients have a history of previous abdominal surgery or malabsorption syndromes.[82]
2. Pre-albumin, albumin and transferrin should be measured with weekly follow-up until nutritional goals are reached.[82]
3. Work-up for diabetes (glycosylated hemoglobin [HbA_{1C}]) and tight control of blood sugar is recommended.[84,85]

Optimization of nutritional status:

1. Consider formal nutritional consultation for those patients who are significantly cachectic, obese, diabetic or have significant renal dysfunction.
2. Supplement of micronutrients to include multivitamin, folate, zinc sulfate and Vitamin C (the latter to facilitate wound-healing).[82]
3. Institute enteral feedings pre-operatively in selected cases.[80,81]

Other considerations:

1. Measure C-reactive protein pre-operatively and at intervals post-operatively to monitor changes in inflammatory response.[80]
2. Indirect calorimetry or other metabolic studies should be done to better define caloric needs.[82]
3. Institute parenteral nutrition if the enteral route is not feasible.[83]
4. Continued follow-up with formal nutritional consultation should be done as indicated.

5.2. Social, Family, Religious and Personal Issues Assessment

To help determine that patients receiving VAD therapy have adequate family/social support, a detailed psychosocial evaluation should be completed. This should be performed by social workers familiar with VAD therapy and the heart transplant process. Patient and family/social support should be involved in the evaluation, although the patient may be too ill to play an active role in this process.

Demographic information should be obtained, including distance from home to transplant center and emergency contacts. The names of the patient's family and social supports should be obtained. Documentation of the primary support person should be established.[86,87]

An evaluation of patient and family support and understanding of past medical history and the present medical situation should be obtained.[71] This assessment may provide insight into the patient's history of compliance.

Primary language and educational level should be established to guide teaching. Perceptions about VAD therapy and transplantation should be explored. Data gathered yield important information that will identify potential barriers and will transfer to educational goals for possible discharge home.

Marital status and personal relationships should be assessed. This should include the length and quality of the relationship.[71,88] This evaluation should also include a discussion of how difficult situations or problems were handled in the past. Additional family/support systems should be established because the primary caregiver may need assistance.[74,75]

The patient's cultural background and religious beliefs should be obtained. Beliefs/background may provide another source of social support and may also alert the team of a patient's wishes not to undergo particular treatments.

A complete assessment of the patient's financial situation should also be performed. Insurance and prescription coverage or a charity care initiative must be thoroughly established to determine whether the patient has adequate financial support to undergo VAD therapy and heart transplantation.[71]

End-of-life issues should be discussed with the patient and their social support before VAD implantation. An advanced directive or health-care proxy should be completed if possible. Assessment of patient and social support should be ongoing, as stressors may change dynamics and the willingness of family/friends to provide continued support. This should be done on a monthly basis or as needed.[71]

6. WHEN AND HOW ULTRAFILTRATION TECHNIQUES SHOULD BE USED

In patients with advanced NYHA Functional Class III and IV heart failure who are being considered or listed

for heart transplantation, the following recommendations are established:

1. Intermittent hemodialysis should not be used for removal of excess fluid because large fluid shifts in short periods of time may lead to hemodynamic instability and worsening of the overall clinical status. Intermittent hemodialysis should be instituted when patients meet criteria for end-stage renal disease, in which case the severity of intrinsic kidney disease precludes consideration for heart transplantation.
2. The role of peritoneal dialysis for short-term management of refractory heart failure is limited to situations in which extracorporeal ultrafiltration is either impossible or unavailable. However, further investigation of the efficacy and safety of this approach is needed before specific recommendations can be made on the use of peritoneal dialysis in patients with advanced heart failure.
3. Of the ultrafiltration approaches described, the most practical are veno-venous ultrafiltration techniques, in which isotonic plasma is propelled through the filter by an extracorporeal pump. These approaches avoid arterial puncture, remove a predictable amount of fluid, are not associated with significant hemodynamic instability, and, in the case of peripheral veno-venous ultrafiltration, do not require specialized dialysis personnel and can be performed in an outpatient setting.
4. Ultrafiltration techniques have been used in patients with decompensated heart failure and volume overload refractory to diuretic therapy. These patients generally have pre-existing renal insufficiency (calculated creatinine clearance 30 to 90 ml/min) and, despite daily oral diuretic doses, develop signs of pulmonary and peripheral congestion (jugular venous distention $\geq$7 cm, pulmonary rales, paroxysmal nocturnal dyspnea or orthopnea, peripheral edema [$\geq$2+], enlarged liver or ascites, sacral edema). Ultrafiltration and temporary cessation of diuretic may restore diuresis and natriuresis.
5. Based on the well-documented relationship between increases of RA pressure and reductions of glomerular filtration rate (GFR), as well as the diuretic-induced decrease of GFR, a strategy of temporarily holding diuretics and reducing volume excess with ultrafiltration may seem logical in these patients..
6. Patients should not be considered for ultrafiltration under any of the following conditions: venous access cannot be obtained; hematocrit is $\geq$40%; there is a hypercoagulable state; systolic blood pressure is $<$85 mm Hg or there are signs or symptoms of cardiogenic shock; if intravevous pressors are required to maintain an adequate blood pressure; or there is end-stage renal disease indicating the need for dialysis.

6.1. What is Ultrafiltration?

Approved therapies for congestion in acute decompensated heart failure (ADHF) are simultaneously ineffective and expensive. Mechanical fluid removal is a nonpharmacologic treatment for congestion.

Ultrafiltration is the passage of water and non–protein-bound small and medium-molecular-weight solutes through a semi-permeable membrane when hydrostatic pressure exceeds oncotic pressure. Oncotic pressure is determined by the concentration of proteins in plasma. Hydrostatic pressure is determined by the blood pressure in the filtering device, generated by either the patient's blood pressure or by an extracorporeal blood pump, plus the suction in the ultrafiltrate compartment. The sum of these pressures generates the transmembrane pressure that drives the plasma water through the membrane.

Hemofiltration is a blood-cleansing technique in which ultrafiltration occurs, but the ultrafiltrate is replaced with clean fluid, which dilutes the concentration of solute in the remaining plasma.[89]

6.2. Clinical Methods of Ultrafiltration

6.2.1. Intermittent hemodialysis. For intermittent hemodialysis, access to the circulation is achieved with either an arteriovenous fistula or with tunneled, cuffed silicone catheters inserted percutaneously into the internal jugular vein. A 4-hour hemodialysis session can lower BUN by 60%, remove 50 to 150 mEq of potassium, and remove 3 liters of ultrafiltrate.[89]

In patients with end-stage heart failure, hemodialysis is the least tolerated form of dialysis, because large fluid shifts in a short period can lead to severe hemodynamic instability.

6.2.2. Peritoneal dialysis. Peritoneal dialysis requires the delivery of a hypertonic substance (dextrose) into the peritoneal cavity. Water diffuses down its concentration gradient from the extracellular fluid spaces bathing the peritoneal cavity into the hypertonic peritoneal dialysate. This produces a net fluid loss into the dialysate.[90] The use of 2 liters of 4.25% dextrose dialysate generates an ultrafiltration rate (UFR) of 800 ml/hour. Use of less hypertonic dialysate or prolongation of dwell time decreases UFR. With the currently available peritoneal dialysis solutions, UFR of 70 to 550 ml/hour can be achieved. Peritoneal dialysis can be performed acutely or continuously for inpatients (continuous equilibration peritoneal dialysis [CEPD]) or outpatients (continuous ambulatory peritoneal dialysis

[CAPD]). Icodextrin-based solutions, which generate sustained ultrafiltration over long dwell periods, are now being studied.[91] Advantages of peritoneal dialysis include its low risk, wide availability and limited training requirements.[90] Disadvantages include unpredictable response, slow ultrafiltration, mild discomfort, hydrothorax and relative contraindications (ileus, abdominal adhesions and incisions). Complications may include respiratory compromise, impaired venous return, hypernatremia, hyperglycemia, peritonitis and abdominal wall infection.

6.2.3. Intermittent isolated ultrafiltration. With intermittent isolated ultrafiltration (IIUF), a veno-venous access is adequate because blood is pumped through an extracorporeal filter. Disadvantages include the requirement for dialysis personnel; bioincompatibility of membranes; and the risk of hemorrhage, air embolism and hypotension.[89]

During IIUF, a UFR of 500 to 1,000 ml/hour can be achieved. Hemodynamic tolerance is the limiting factor for IIUF. Slowing UFR by prolongation of therapy time improves hemodynamic tolerance.

6.2.4. Peripheral veno-venous ultrafiltration techniques. A simplified peripheral veno-venous ultrafiltration system has recently become clinically available.[92] In contrast to the ultrafiltration modalities just described and elsewhere in the text, this ultrafiltration approach does not require access to the central circulation or bed confinement, and therefore can potentially be used in the outpatient setting.

The effects of peripheral veno-venous ultrafiltration were recently evaluated in 21 fluid-overloaded patients. The removal of an average of 2,600 ml was associated with a 2.6-kg weight loss and no major adverse events.[92]

More recent studies examined the effects of early ultrafiltration in 20 patients with ADHF and diuretic resistance.[93,94] Removal of 8,654 ± 4,205 ml occurred with 2.6 ± 1.2 courses each lasting 8 hours. Twelve patients (60%) were discharged in ≤3 days. One patient was re-admitted at 30 days and 2 patients at 90 days. Weight ($p = 0.006$), Minnesota Living with Heart Failure scores ($p = 0.003$) and Global Assessment ($p = 0.00003$) were improved after ultrafiltration, at 30 and 90 days. Brain natriuretic peptide (BNP) levels were decreased after ultrafiltration (from 1,236 ± 747 to 988 ± 847 pg/ml) and at 30 days (816 ± 494 pg/ml), with $p = 0.03$. Blood pressure, renal function and medications were unchanged. These results indicate that, in heart failure patients with volume overload and diuretic resistance, ultrafiltration before intravenous diuretics may effectively and safely decrease length of stay and re-admissions. Clinical benefits persisted at 3 months after treatment.[93–105]

6.2.5. Continuous ultrafiltration techniques. Techniques for continuous ultrafiltration include slow continuous ultrafiltration (SCUF), continuous hemofiltration and continuous hemodiafiltration.[89]

The main advantages of continuous veno-venous ultrafiltration with an extracorporeal blood pump are achievement of constant blood flow and ultrafiltration rates and the hemodynamic stability afforded by isotonic ultrafiltration. Potential disadvantages include the need for central venous access or arterial puncture, the requirement for anti-coagulation, bleeding, hypovolemia and the need for specialized dialysis personnel.[89]

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