



Fast Facts Core Curriculum

Cardiac All

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FAST FACTS AND CONCEPTS #111
CARDIAC PACEMAKERS AT END-OF-LIFE
Harrington MD, Luebke DL, Lewis WR, Aulisio MP, Johnson NJ

Introduction

This *Fast Fact* discusses management of cardiac pacemakers at life's end. *Fast Fact* #112 discusses implantable cardioverter-defibrillators.

Background

Worldwide there are about 3 million people with pacemakers. Each year 600,000 new pacemakers are implanted, with the majority of these devices in patients over the age of 60. The primary function of pacemakers is to treat bradyarrhythmias (e.g. heart block). More recently, patients with heart failure, subvalvular stenosis and treatment resistant atrial fibrillation may qualify for pacemakers. Additionally, patients with congestive heart failure may receive biventricular pacemakers to improve symptoms.

Pacemaker Function at Time of Death

Patients and their families often make assumptions that pacemakers prolong the dying process and thus prolong suffering. However, a pacemaker is not a resuscitative device. In general, pacemakers do not keep dying patients alive, as terminal events are often due to sepsis, hemorrhage, pulmonary emboli, or arrhythmias from metabolic abnormalities associated with end-stage cancer, liver, or renal failure. At the time of death, the myocardium is usually too sick to respond to the pacemaker generated signals.

When is Pacemaker Deactivation indicated?

In patients with irreversible cognitive failure, where continued pacemaker activity is not meeting the goals of care, it may be appropriate to discuss the option of deactivation. In most other situations, deactivation is not indicated since the result is likely to be a symptomatic bradycardia, producing signs and symptoms of worsening heart failure (fatigue, dizziness, dyspnea). In contrast to popular belief, it is rare that disabling the pacemaker will result in a swift and painless death as few patients are 100% pacemaker dependant, particularly during the period of imminent death (*Fast Fact* # 3), where tachycardia is the most common rhythm. When questions arise concerning dependency on the pacemaker, consult the cardiology/pacemaker service.

Ethical/Legal issues

A patient's/surrogate's right to request withdrawal of life sustaining medical interventions, including pacemakers, is both legal and ethical. Withdrawal of a life sustaining medical intervention with the informed consent of a patient or legal surrogate is not physician-assisted suicide or euthanasia. While there may be more agreement about the deactivation of implantable cardioverter-defibrillators than of pacemakers amongst practicing clinicians, the Heart Rhythm Society issued a consensus statement in collaboration with many professional groups (including the American College of Cardiology, the American Academy of Hospice and Palliative Medicine, and the American Heart Association) which effectively erased any ethical distinction between types of implanted devices being deactivated and endorsed a patient's right to have one's pacemaker deactivated.

Summary

Initiate a discussion about pacemaker deactivation only if there is potential for patient benefit; consider the potential negative effects of deactivation before disabling the pacemaker.

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FAST FACTS AND CONCEPTS #112
IMPLANTABLE CARDIOVERTER-DEFIBRILLATORS AT END-OF-LIFE
Harrington MD, Luebke DL, Lewis WR, Aulisio MP, Johnson NJ

Background Recent clinical trials and advances in device technology have expanded the indications for implantable cardioverter-defibrillators (ICDs). At least 12,000 ICDs are implanted per month in the US and over 3 million patients in North America are eligible for an ICD. Near the end of life, however, ICD decision-making can be the source of anguish for patients, families and palliative care/hospice staff.

Current Devices ICDs are somewhat larger than pacemakers and are usually implanted in the upper chest under the clavicle. They monitor cardiac rhythm and can either cardiovert or defibrillate (electrically 'shock' a heart) when certain rapid abnormal cardiac rhythms are identified. These shocks can be painful and are inconsistent with comfort care in a dying patient. ICDs can also deliver pacing therapy. Pacing increases heart rate when slow heart rhythms are detected and can promote comfort as slow heart rhythms can cause heart failure symptoms. Finally, certain pacemakers or cardiac resynchronization therapy devices may include an ICD function all in one device. For these devices, the shocking functions of an ICD can be independently turned off and a decision to discontinue a device's ICD function should be considered separately from a decision to discontinue its pacing functions (see *Fast Fact #111*).

Indications for deactivation of ICD therapy

- Continued use of an ICD is inconsistent with patient goals.
- Withdrawal of anti-arrhythmic medications: if anti-arrhythmic medications are withdrawn consider turning off the ICD to avoid frequent shocks.
- When a patient's condition is worsening and death is anticipated.
- The patient has a DNR order. The functioning of an ICD is generally inconsistent with a 'Do-Not-Resuscitate' order since ICDs attempt to resuscitate the patient by shocking their hearts back into a life-sustaining rhythm.

Discussing deactivation of the ICD

1. Consult the clinician who manages the ICD (usually a cardiologist or associated clinician); that individual is often the person to assume responsibility for deactivation. Patients are usually followed in a device clinic and probably have an established relationship with the physician and staff. The involvement of these professionals can provide a sense of comfort and closure for the patient and family. Note: The device manufacturers will not send representatives to patient's homes for deactivation by simple reprogramming of the device.
2. Discuss expectations of "turning off" the ICD. The following should be made clear:
 - a. Turning off the ICD means that the device will no long provide life-saving therapy in the event of a ventricular tachyarrhythmia.
 - b. Turning off the ICD will not cause death.
 - c. Turning off the ICD will not be painful, nor will its failure to function cause pain.
3. Establish a plan of care that will ensure availability for addressing new questions or concerns that might arise (patient/family should not feel abandoned once the device is turned off).
4. If there are conflicts among providers or family members, consultation with a palliative care expert or ethics team can be helpful.

Emergency ICD Deactivation When patients are imminently dying, there may not be enough time for a cardiac physiologist to prevent painful shocks via ICD reprogramming. Any health care professional can temporarily deactivate the device by placing a special magnet, which are usually available at electro-physiology clinics, directly over the implant site. This stops the defibrillation function of the device, but would not disable the pacing functionality. Of note, once the magnet is

removed, the ICD will resume functionality. Hence, reprogramming of the device by a cardiac physiologist would still be required.

Ethical/Legal issues A patient's right to request withdrawal of life sustaining medical interventions, including ICDs, is both legal and ethical. Withdrawal of a life sustaining medical intervention with the informed consent of a patient or legal surrogate is not physician-assisted suicide or euthanasia.

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FAST FACTS AND CONCEPTS #144
PALLIATIVE CARE ISSUES IN HEART FAILURE

Gary M Reisfield MD and George R Wilson MD

Background The physical and psychological symptom burden in the dying heart failure (HF) patient is similar to that in the dying cancer patient. Symptom prevalence data in HF includes: pain (78%), dyspnea (61%), depression (59%), insomnia (45%), anorexia, (43%), anxiety (30%), constipation (37%), nausea/vomiting (32%), fatigue, difficulty ambulating, and edema. This *Fast Fact* reviews domains of medical management common to most end-stage HF patients.

General Symptom Management

- *Pain.* Common causes include: peripheral edema, arthritis, diabetic neuropathy, and post-herpetic neuralgia. NSAIDs are generally contraindicated because they antagonize the effects of diuretics and ACE inhibitors, promoting fluid retention while decreasing glomerular filtration and impairing renal function. Opioids are the agents of choice for nociceptive and neuropathic pain because of efficacy, rapidity of onset and potential to relieve dyspnea. See *Fast Facts* #18, 28, 53, 54, and 72.
- *Dyspnea.* Reassess/optimize HF medications and assess for reversible causes, e.g. pleural/pericardial effusions, dysrhythmias, COPD exacerbation. See *Fast Fact* #27.
- *Depression.* Short-term psychotherapy can be helpful for mild-moderate depression, but patient participation and logistical issues can be problematic. Selective serotonin reuptake inhibitors (SSRIs) are the antidepressants of choice because they preserve ejection fraction, lack hypotensive/dysrhythmogenic effects, and have few drug interactions. Sertraline in particular may be the agent of choice in HF patients. Psychostimulants (see *Fast Fact* #61) may accelerate the treatment response to SSRIs. **Note:** as there exists no data on the safety of psychostimulants in HF, therapy should be initiated with caution.

Heart Failure Pharmacotherapy Optimal drug use can improve symptoms and should be continued until the burden of administration outweighs benefits. Diuretic therapy can be crucial, but diuretic resistance is common. The following strategy can help overcome diuretic resistance:

- Optimize dose of oral loop diuretic (e.g. furosemide). Doses of up to 4000 mg/day have been found to be safe and effective.
- Change to intravenous or subcutaneous routes. IV boluses can produce symptom relief within minutes. Continuous infusions (3-200 mg/hr; 10-20 mg/hr in most patients) provide increased efficacy.
- Add a PRN oral thiazide diuretic (e.g. hydrochlorothiazide 25-100 mg/day or metolazone 5-20 mg/day). This can reestablish diuresis in a loop diuretic-resistant patient. **Note:** high dose and combination diuretics can result in electrolyte imbalances; consider electrolyte monitoring if death is not imminent.

Inotropes Intravenous inotrope therapy (dobutamine, milrinone, dopamine) has a substantial record of use but a paucity of data in the home setting. Data suggest these agents may improve symptoms, but with an increased risk of dysrhythmic death. In hospitalized inotrope-dependent HF patients, discharge on inotropes may provide the opportunity for death to occur at home if desired by patient/family.

Device therapies Decisions regarding previously implanted device therapies should be made in the context of goals of care. See *Fast Facts* #111, 112 for a discussion of implantable devices and issues surrounding deactivation; *Fast Fact* #205 discusses ventricular assist devices.

Prognostic Uncertainty Accurate prognostication is virtually impossible in HF (see *Fast Fact* #143). While this uncertainty is frustrating for physicians, it provides a basis for initiating end-of-

life discussions. The American Heart Association released a scientific statement to help Clinicians best guide their patients:

- Initiate yearly “heart failure reviews” or advance care planning discussions.
- Utilize a HF hospitalization (which triples one-year mortality) as a bridge to either optimizing medical therapy or palliative care.
- Educate patients and families about the unpredictable, but usually terminal nature of HF, and the ever present danger of sudden cardiac death (even when feeling well).
- Ascertain specific goals of care (e.g. quality of life vs. length of life, living/dying at home vs. hospital)
- Assess options for achieving these goals (e.g. initiating/handling device therapies including when and how to deactivate, hospice vs. serial hospital/critical care unit admissions).
- Assess resuscitation preferences.

Patient Resources A free advance care planning packet for HF patients is available through the Heart Failure Society of America website at: <http://www.hfsa.org/pdf/module9.pdf>.

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FAST FACTS AND CONCEPTS #143
PROGNOSTICATION IN HEART FAILURE**Gary M Reisfield MD and George R Wilson MD**

Background This *Fast Fact* reviews prognostication data in Heart Failure (HF). Although the Framingham Heart Study (1990-1999) showed a 5-year mortality rate of 50% for newly identified cases, providing accurate prognostic data for 6-12 month mortality in HF has been nearly impossible. Reasons cited include: 1) an unpredictable disease trajectory with high incidence (25-50%) of sudden death; 2) disparities in the application of evidence-based treatment guidelines; 3) inter-observer differences in New York Heart Association (NYHA) classification; and 4) heterogeneous study populations

NYHA Classification The NYHA classification remains the major gauge of disease severity. Based on data from SUPPORT, Framingham, IMPROVEMENT, and other studies, 1-year mortality estimates are:

- Class II (mild symptoms): 5-10%.
- Class III (moderate symptoms): 10-15%.
- Class IV (severe symptoms): 30-40%.

General Predictors of Shorter Prognosis:

- Cardiac hospitalization (triples 1-year mortality; nearly 1 in 10 die within 30 days of admission).
- Intolerance to neurohormonal therapy (i.e. beta-blockers or ACE-inhibitors) is associated with high 4 month mortality
- Elevated BUN (defined by upper limit of normal) and/or creatinine ≥ 1.4 mg/dl (120 μ mol/l).
- Systolic blood pressure < 100 mm Hg and/or pulse > 100 bpm (each doubles 1-year mortality).
- Decreased left ventricular ejection fraction (linearly correlated with survival at LVEF $\leq 45\%$).
- Ventricular dysrhythmias, treatment resistant.
- Anemia (each 1 g/dl reduction in hemoglobin is associated with a 16% increase in mortality).
- Hyponatremia (serum sodium ≤ 135 -137 mEq/l).
- Cachexia or reduced functional capacity.
- Orthopnea.
- Co-morbidities: diabetes, depression, COPD, cirrhosis, cerebrovascular disease, and cancer

Hospice Eligibility Guidelines The National Hospice and Palliative Care Organization's 1996 guidelines for heart disease admission criteria include: a) symptoms of recurrent HF at rest (NYHA class IV) *and* b) optimal treatment with ACE inhibitors, diuretics, and vasodilators (*contemporary optimal treatment now includes β -blockers, aldosterone antagonists, and device therapies*). The NHPCO guide indicates that an ejection fraction $\leq 20\%$ is "helpful supplemental objective evidence," but not required. The NHPCO guidelines also assert that each of the following further decreases survival: treatment resistant ventricular or supraventricular arrhythmias, history of cardiac arrest in any setting, history of unexplained syncope, cardiogenic brain embolism, and concomitant HIV disease.

Prognostic Models Since publication of the NHPCO's guidelines, several models have been developed for predicting short- and/or long-term mortality among HF patients. Two recent models purport to predict mortality among patients *hospitalized with acutely decompensated HF*. Fonarow et al (2005), using a model based on admission BUN (≥ 43 mg/dl), creatinine (≥ 2.75 mg/dl), and systolic BP (< 115 mmHg), identified in-hospital mortality rates ranging from about 2%

(0/3 risk factors) to 20% (3/3 risk factors). Lee et al (2003), using a model based on admission physiologic variables and co-morbidities (almost all from above list of indicators) identified 30-day mortality and 1-year mortality rates ranging from <1% and <10%, respectively, for the lowest risk patients to >50% and >75%, respectively, for the highest risk patients. While both models are applicable to bedside use, neither has been applied prospectively or in independent patient samples, nor do they address HF treatments as predictive variables. More recently, Levy et al (2006) developed a 24-variable risk model using the PRAISE1 ($n=1125$) database and validated it on preexisting ELITE2, ValHeFT, UW, RENAISSANCE, and IN-CHF ($n=9942$) databases. The model purports to accurately estimate mean 1-, 2-, and 3-year survival and, importantly, *dynamically* incorporates clinical and laboratory variables, HF medications, and device therapies. It awaits independent, prospective evaluation in unselected HF patients. A web-based interactive calculator can be accessed at <http://www.seattleheartfailuremodel.org>.

Bottom Line Meticulous application of medication and device therapies can and will continue to change HF prognosis. HF follows an unpredictable disease trajectory, one which is highly mutable by application of evidence-based therapies, yet still marked by a high incidence of sudden death. The 1996 NHPCO criteria are not accurate predictors of 6-month mortality. Several models have recently been developed to aid in determining short- and long-term mortality in HF patients. These models await independent, prospective validation in unselected ambulatory HF patients and will need periodic updating to control for continually evolving standards of HF care. At present, accurate prognostication remains problematic.

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FAST FACTS AND CONCEPTS #205
MECHANICAL CIRCULATORY SUPPORT IN ADVANCED HEART FAILURE

Keith M Swetz MD, MA, Daniel D Matlock MD, MPH, Heather Ferris MD, and Susan Hunt MD

***Editor's Note:** Due to rapid changes with these technologies, this Fast Fact is meant to fully replace the first edition of #205 ('Destination Ventricular Assist Devices for Heart Failure' by Heather Ferris MD and Susan Hunt MD, published August 2008).*

Introduction About 250,000 Americans have end-stage heart failure, meaning they cannot carry out any physical activities without discomfort (dyspnea or angina) and are potentially eligible for advanced therapy such as transplantation. Less than 1% of patients, however, will receive a heart transplant. The left ventricular assist device (LVAD) was initially designed as an implanted mechanical circulatory support (MCS) to extend the life of patients awaiting heart transplants ("bridge-to-transplantation" (BTT)). In 2002, the FDA approved the LVAD not only as BTT, but also as "destination therapy" (DT) where the patient would keep the device for life, with no expectation of heart transplantation.

The Technology Rapid growth in the types and numbers of MCS has occurred, including the development of the total artificial heart (see *Fast Fact # 296*) and biventricular support. Basically, an LVAD involves surgical implantation of a pump to support cardiac output. Most often, this includes a conduit implanted in the left ventricle, and another into the aorta. Blood is pulled from the left ventricle, and mechanically moved into the aorta, increasing cardiac output and reducing heart failure symptoms. First generation LVADs did this with a pumping motion (pulsatile flow), but second generation LVADs move the blood continuously (continuous or axial flow). A third conduit (the driveline) passes from the pump through the abdominal wall, and attaches to the device's battery and control system. This is of particular importance as serious life-threatening infections can result via the driveline.

Right and biventricular assist devices also exist, but are not currently approved for DT. DT patients can go home with their assist devices using a wearable battery system. Previously, to qualify for destination LVAD therapy, a patient needed to have severe, refractory Class IV heart failure including severe systolic dysfunction (ejection fraction <25%), inotrope dependence or very low peak oxygen consumption (<12 ml/kg/min), and sufficient body surface area to accommodate the LVAD. Now, patients with other situations are being considered (e.g., heart failure with preserved ejection fraction, congenital heart disease). Also, some advocate for expanding into patients who are less sick (Class IIIB) arguing that waiting to their heart failure is severe and refractory is too late, and raises their operative risk to unacceptably high levels. This hypothesis is currently being investigated.

Outcomes and Considerations

- In randomized studies, LVADs have shown significant mortality benefits, with a 2-year survival of 58% for the newer continuous-flow devices compared to 24% with pulsatile flow LVADs and 8% with optimal medical therapy alone (1,2). Observational studies demonstrate 2-year survivals of 72%, but these databases are heterogeneous and patients may be healthier than the patients enrolled in the original randomized trials (3).
- Poorer survival is predicted by poor nutritional status (hypoalbuminemia), coagulopathy, baseline renal dysfunction, right heart dysfunction, and care at a less experienced MCS center (3,4).
- Of those patients who are alive at 2 years, 79% will improve their NYHA functional class from class IV to class I, and health-related quality of life will improve by 178% (5). Readmission rates have reduced significantly as well (6).

- While markedly improved, continuous-flow LVADs have many potential complications including stroke (lifetime risk of 18%), infection (49%), sepsis (36%), bleeding requiring transfusion (81%), bleeding requiring surgery (30%), malfunctioning or thrombosed pump requiring pump replacement (10%), and readmission (94%) (2). Perioperative mortality has improved dramatically (often less than 10%) with improved patient selection and technology; however, palliative medicine providers and ICU staff often see MCS patients at their worst when critically ill or with a protracted, complicated recovery. This can be a source of moral distress, nevertheless many patients go on to perform all activities of daily living and have improved quality of life.
- MCS require a high degree of ongoing device care including daily self-care (e.g. controller self-tests, changing and maintaining power sources, and driveline exit site dressing changes), safety precautions (e.g. no immersion in water, showering with a shower kit, precautions while driving and traveling, need for a trained caregiver), and the ability to troubleshoot emergent MCS-related malfunction. Due to this, social stability and patient/family responsibility are key selection criteria when considering MCS implantation.

Discontinuing MCS and Advanced Care Planning MCS may be implanted as BTT, but later become DT if patients are no longer transplant candidates. In the rare instance of myocardial recovery, some devices can be explanted. More often, MCS is removed at cardiac transplantation or, in the case of DT, when severe complications arise (such as pump thrombosis, mechanical pump failure etc).

MCS is a surgical therapy which can prolong life and improve function in appropriately selected patients, but can associated with significant morbidity, treatment burden, and mortality. Discussions with patients and surrogates to clarify prognosis, goals, and endpoints for MCS therapy should take place before implantation. These discussions should address the quality of life below which a patient would no longer want to continue MCS, and would want to initiate comfort focused only. Having open and honest discussion regarding goals of care prior to MCS is encouraged, and a suggested process for these discussions will be in a future *Fast Fact*. Practical aspects of discontinuing an LVAD in a dying patient are discussed in *Fast Fact* #269.

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FAST FACTS AND CONCEPTS #209 MALIGNANT PERICARDIAL EFFUSIONS

Vincent Thai MD

Introduction Malignant pericardial effusions (MPEs) are a rare complication of advanced cancer, but are associated with high morbidity and mortality. This *Fast Fact* discusses the diagnosis and management of MPEs.

Epidemiology and Prognosis Approximately 10% of patients with cancer develop cardiac metastases, with ~75% of these affecting the epicardium (1, 2). Only a third of these, however, will develop clinically significant MPEs (1). Lung and breast cancers are the most common causes. MPEs are associated with a poor prognosis. Studies suggest a *median* survival of 2-3 months after a MPE is diagnosed, with a *mean* survival of 5 months for solid tumors and 20 months for hematologic malignancies (3, 4).

Physiology and Symptoms The pericardial space is normally filled with <50 ml of serous fluid. As this volume increases due to epicardial or pericardial metastases or lymphatic obstruction, both right and left ventricular failure can occur due to inadequate filling. Signs and symptoms include peripheral and pulmonary edema, chest discomfort, cough, shortness of breath, and orthopnea. Severity of symptoms depends on the volume of the MPE as well as the rapidity of its accumulation; severe cases can present with cardiac tamponade and shock. An echocardiogram is indicated whenever a MPE is suspected. Not only does it confirm the presence of an effusion, but its findings can dictate whether or not urgent treatment is indicated (e.g. if signs of tamponade are evident). A diagnostic pericardiocentesis or pericardial biopsy is sometimes needed to confirm the cause of the effusion.

Treatment Options

- *Systemic chemotherapy or radiotherapy* are effective for chemo- or radio-sensitive tumors such as previously untreated breast cancer and many lymphomas. Reaccumulation rates for both modalities are about 1/3 overall, depending on the patient's overall course and response to therapy (5).
- *Pericardiocentesis* results in immediate symptom relief in most patients, however the effusion may re-accumulate, requiring repeat pericardiocentesis (within 1-2 weeks in some series) (6).
- *Pericardial sclerosis* involves instilling a sclerosing agent with the intention of scarring the pericardium to the epicardium, preventing reaccumulation of the MPE (similar to pleural effusions – see *Fast Fact #157*). Multiple agents have been studied including doxycycline, minocycline, and bleomycin. Success rates (no reaccumulation at 30 days) are about 70-90% (7, 8). Longer term success rates are undefined due to the poor survival of study patients. The major side effect is chest pain (50-70%), cardiac arrhythmias, and fever (8, 9, 10). In head to head comparisons with doxycycline, bleomycin has been shown to have fewer side effects and to lead to shorter hospitalizations (10, 11, 12).
- *Surgical decompression* therapies range from less invasive (balloon pericardiotomy, subxiphoid or thorascopic pericardiostomy) to more extensive (open thoracotomy with pericardial stripping). A pericardial 'window' (which allows ongoing drainage of fluid externally or internally such as into the pleural cavity) is often created. Case series have suggested reaccumulation rates with surgical therapies are low (less than 15% up to 10 months out) (13, 14, 15).

Decision-Making The treatment of MPEs depends on how urgently treatment is needed, the likelihood of the tumor responding to anti-neoplastic treatments, and the anticipated survival of the patient. A multidisciplinary approach to decision-making, involving input from medical and radiation oncology, cardiology, and thoracic surgery is recommended. Simple pericardiocentesis may be appropriate for patients with short prognoses (<1 month), particularly if their MPE is not expected to re-accumulate in their remaining life-span. A symptomatic patient with no signs of tamponade and a chemotherapy-sensitive tumor such as untreated breast cancer may receive a

lasting response from a pericardiocentesis for symptom relief, followed by chemotherapy. Patients with longer prognoses (>1 month) who are expected to re-accumulate their MPEs will likely benefit most from sclerosis or surgical decompression; there is no clear evidence currently suggesting one strategy is superior to the other. Symptom directed care without specific intervention for the MPE is an appropriate option for patients with very short prognoses and for those who decline more invasive treatments.

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FAST FACTS AND CONCEPTS #283
USE OF HOME INOTROPES IN PATIENTS NEAR THE END OF LIFE

Mallory Strickland Ciuksza MD, Randy Hebert MD, and George Sokos DO

Background Some patients with end-stage heart failure causing symptoms at rest are placed on continuous infusions of cardiac inotropes in an attempt to improve symptoms and avoid hospitalizations. Among end-stage heart failure patients who are ineligible for advanced cardiac therapies (such as heart transplant or a ventricular assist device), mean life expectancy with inotrope-dependent medical therapy is estimated at 9.4 months, with 26% surviving to 1 year. Hence, the home use of continuous inotrope therapy may be commonly encountered by clinicians who care for the seriously ill.

Pharmacology Both major classes of inotropic agents, adrenergic agonists (i.e. dopamine and dobutamine) and phosphodiesterase inhibitors (i.e. milrinone), increase contractility by increasing available calcium levels within myocardial tissue via cAMP regulation (2).

Patient Selection Patients on maximal medical therapy who continue to have refractory symptoms at rest (New York Heart Association Class IV) may benefit from home IV inotrope therapy. Eligible patients must have either failed a trial of weaning inotropic support in the inpatient setting or been too ill to attempt weaning (3,4). Patients should not receive home inotropic therapy if they are not maximized on their oral medications, unable or unwilling to utilize an infusion pump and central line, unwilling to undergo appropriate monitoring, or have refractory ventricular tachycardia or life threatening arrhythmias (5).

Outcomes and Risks Available data assess the number of hospitalizations, symptom control, mortality, and quality of life (6-13). Unfortunately, the strength of the data is relatively weak and the outcomes are mixed as very few studies utilize the same methods or measure the same outcomes. The prevailing literature suggests trends of hastened death with dobutamine and milrinone administration largely due to arrhythmias (10,11, 14-18). However, the majority of this data is based on data from small trials on oral and intermittent IV inotropes (not continuous therapy), and, importantly, are from an era in which prophylactic ICD implantation was not the standard of care. The most recent guidelines advocate against the use of intermittent therapy altogether. Despite these risks, if the patient's goal is to be at home, there is evidence that *continuous* outpatient inotrope infusion may shift the remaining survival time to a home setting through marked improvements in symptom control and therefore may be an excellent treatment for the well selected patient (9).

Practical Concerns Inotropes are started during an inpatient hospitalization. This typically occurs in the setting of the intensive care unit where doses can be titrated to allow for a weaning trial if the patient is clinically stable enough to do so. Patients will require a PICC line or Hickman catheter for infusion with regular, high quality line care to prevent infections. Patients on home inotropes require ongoing care by an adequately trained home care team and an experienced physician (typically a cardiologist) so that their medications can be adjusted as needed. The most common side effects are hypotension and arrhythmias. For this reason electrolytes should be regularly followed, as well as renal function through regular serum creatinine monitoring in order to anticipate dosing changes that may be necessary if changes in creatinine clearance should occur.

Medicare Coverage Requirements: Medicare has strict coverage guidelines for home inotropes, which greatly affect how they are used in the US. Below are the criteria that need to be met in order for inotrope therapy to be covered (5).

- Symptoms must be uncontrolled; specifically, **dyspnea at rest** must be present despite maximum tolerated doses of digoxin, loop diuretics, ACEIs, or other vasodilators.
- **Hemodynamic studies** must be performed within six months prior to initiation of home

inotropic therapy that show both:

- o Cardiac index of 2.2 L/min/m² (maximum) and/or pulmonary capillary wedge pressure of 20 mmHg before infusions while on maximum tolerated oral medications.
- o A 20% increase in cardiac index, and/or at least a 20% decrease in pulmonary capillary wedge pressure during inotrope infusion.
- **Improvement in patient “well-being”** (i.e., decreased dyspnea, increased diuresis, improved renal function, or reduction in weight) must be shown with the absence of dyspnea at rest at the time of discharge and with outpatient follow up.
- There must be **documented deterioration** with attempts to discontinue/wean the patient from inotropes while in the hospital.
- Any life-threatening **arrhythmia must be controlled** and addressed prior to discharge. Some evidence suggests that oral amiodarone may benefit these patients who experience ectopy but are still benefiting from inotrope therapy (17,19).
- Covered inotrope dosing must be within the following **ranges**:
 - o Dobutamine 2.5-10 mcg/kg/min.
 - o Milrinone 0.375-0.75 mcg/kg/min.
 - o Dopamine may also be used at a rate of 2 mcg/kg/min.
- Efforts to maintain the patient on the **lowest practical dose** must be made and documented during the first three months of therapy.

Cost Cost of these therapies varies significantly depending on choice of drug and insurance type. Milrinone cost per month ranges between \$4500-\$21,000 and dobutamine between \$1140-\$2790 (estimates are based on a 75 kg patient with infusions of 0.5 mcg/kg/min and 5mcg/kg/min for milrinone and dobutamine respectively) (20). Medicare will reimburse for these therapies and for associated equipment such as infusion pumps, however nursing visits are not included in these estimates.

Home Care and Hospice Many hospices will not accept inotrope-dependent patients given the cost and need for advanced training (12). Some communities have specialized home-care agencies or programs for patients on home inotropes, which may or may not be part of a hospice program.

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**FAST FACTS AND CONCEPTS # 296
TOTAL ARTIFICIAL HEART**

Sara E. Wordingham MD, Rachel M. Kasten, MSN, APRN, CNP, and Keith M. Swetz MD, MA

Background With a limited supply of donor organs, mechanical circulatory support (MCS) has played a key role in advanced heart failure (1). While left ventricular assist devices (LVADs) can be used as a bridge to transplantation, recovery, or as destination therapy (refer to Fast Fact #205), a total artificial heart (TAH) is only approved as a bridge to transplantation. Approximately 100 TAHs are implanted annually in the U.S (2,3). This *Fast Fact* explores practical and ethical considerations with TAH therapy.

The Technology The TAH is a pulsatile pneumatic pump that orthotopically replaces both native cardiac ventricles and all heart valves and is attached to the remnant native atria. It can deliver a cardiac output of 9.5 L/min and is used in patients when LVAD is contraindicated -- biventricular failure or refractory arrhythmias. While a 400-lb machine was previously required to operate a TAH, smaller "suitcase-sized" drivers are available in the hospital setting. In the U.S., patients with a TAH require hospital care unless part of a clinical trial. A portable "backpack-sized" driver which can support patients outside of the hospital is under investigation in the U.S (approved for use in Europe).

Outcomes Almost 80% of patients with a TAH go on to receive cardiac transplantation (4). For the remaining 20% who become transplant-ineligible or die awaiting a suitable organ, data are limited regarding best practices for the disease-directed and supportive care for when the TAH has become *de facto* destination therapy. Classic symptoms of heart failure -- dyspnea, anxiety, pain, and debility -- can remain problematic for patients with a TAH; a sense of confinement in the hospital setting, sleep disturbance and anxiety from the sound of the pneumatic pump can negatively impact quality of life. The longest reported time a patient has been supported with a TAH prior to receiving a transplant is 3.5 years (2). Bleeding in the immediate postoperative period and infection are the most common complications. When infections occur, they are unlikely to cause death or delay transplantation. TAHs have a low risk of device malfunction or thromboembolic events (5). In a small cohort, mortality with TAH *in situ* was usually from multiorgan failure followed by procedural or technical complications (6).

Ethical/Legal Issues It is ethically permissible to discontinue life-sustaining treatments as patients maintain a right to refuse intervention. Legal rulings have asserted no difference between withholding or withdrawing such therapies (See Fast Fact #56,#111,#112,#159). Some raise concern as to whether the considerations are different with TAH compared with an LVAD since the native heart's valves and ventricles are surgically removed (7). Regardless, many ethicists, cardiologists, and palliative care clinicians support TAH deactivation if it no longer meets a patient's goals of care or if the burdens of the TAH outweighs its benefits (8). Considering that 20% who receive a TAH do not go on to transplantation, informing patients prior to TAH implantation that an iatrogenic condition is being created that can alter their end-of-life experience is prudent (8).

Palliative Care Specialist Services Supportive care and symptom management of patients can be provided in parallel, similar to LVADs (See Fast Fact #269). Palliative care teams are often instrumental in assuring symptom management, and providing psychosocial support to patients and families when transplantation is no longer an option. Common palliative medications which can prolong the QT interval (i.e. haloperidol or ondansetron) are acceptable as the ventricles are surgically absent and hence ventricular arrhythmias are not an issue.

Discontinuing TAHs Most TAH deactivations take place in the hospital setting, although deactivation elsewhere has been reported. Following informed consent from the patient or surrogate and discussion with key stakeholders—including cardiothoracic surgery, cardiology, MCS coordinators, and social work—deactivation can be planned. Unlike discontinuation of other

cardiac therapies where survival can be variable, death after TAH deactivation occurs within minutes due to absence of cardiac output and is confirmed by apnea. Care should be taken to ensure that effective symptom management and that loved ones are fully supported during this time; see related *Fast Facts* that explore discontinuation of other life-sustaining therapies (See Fast Fact #33,#34,#35,#269). Patients may also progress to clinical death (i.e. respiratory arrest or brain death) with the TAH functioning, necessitating post-mortem pump deactivation. Providers can be trained by perfusionists to deactivate the TAH in a manner with minimal alarms. TAHs, like LVADs, do not require explantation prior to cremation whereas pacemakers and defibrillators do as they have an internal battery (See Fast Fact #111,#112,#269).

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FAST FACTS AND CONCEPTS #339
EXTRACORPOREAL MEMBRANE OXYGENATION IN ADULTS
Edward Feinstein MD, Jeffrey Rubins MD, Drew A Rosielle MD

Introduction Use of extracorporeal membrane oxygenation (ECMO) (sometimes called extracorporeal life-support) is increasing in many countries. This *Fast Fact* will review the role of palliative care teams in caring for adults on ECMO, and their families.

The Technology The technology is fundamentally the same as a ‘heart-lung bypass machine’ used in some cardiac surgeries, although ECMO can be used for weeks instead of hours. Central venous blood is removed from the patient and pumped through a gas exchange membrane where it is oxygenated and carbon dioxide is removed. In venovenous (VV) ECMO the blood is then reinfused into the right-sided circulation where the patient’s own heart circulates it. In venoarterial (VA) ECMO, the oxygenated blood is reinfused under arterial pressure into the aorta for circulation. Therefore, VV ECMO ‘replaces’ lung function (gas exchange); VA ECMO ‘replaces’ both heart (pump) and lung function. Initiating and providing ECMO requires specialized teams and currently is only offered at specific referral centers.

VV ECMO: VV ECMO is used for severe hypoxemic respiratory failure; typically the acute respiratory distress syndrome – ARDS.

- The best available data comes from the CESAR Trial (2009) – a randomized study showing improved disability-free survival at 6 months with ECMO (63%) vs. usual ICU care (47%) (1). There are also observational data suggesting improved survival from ARDS during influenza pandemics (2).
- In the Extracorporeal Life Support Organization’s (ELSO) international ECMO database, 57% of patients receiving VV ECMO survive to hospital discharge (disability rates unknown) (3).
- VV ECMO has seen a 10-fold increase between 2005 and 2015 from ~150 cases to ~1900 cases (4).

VA ECMO: VA ECMO is used for severe cardiogenic shock such as after a massive pulmonary embolus, ST- elevation myocardial infarction, or cardiac surgery.

- Data supporting VA ECMO are less clear than VV ECMO on whether it improves outcomes compared with other advanced technologies for cardiogenic shock (e.g. ventricular-assist devices, intra-aortic balloon pumps, etc.) (5).
- The ELSO database reports hospital survival for VA ECMO is ~40% (disability rates unknown) (3).
- VA ECMO is also used for sudden cardiac death patients who do not have return of spontaneous circulation after CPR. This use is called “E-CPR”. Patients are rapidly transported to an ECMO center where ECMO is initiated in an attempt to perfuse the brain and other organs while the cause of the arrest is treated. The efficacy of E-CPR has not been evaluated yet in high quality trials.

Patient Experience & Complications ECMO requires large caliber vascular catheters, placed in the groin or neck. Initially patients are intubated, sedated, and paralyzed. Patients who are on ECMO for many days sometimes can be awoken, and even have limited mobility such sitting up in a chair or engaging in physical therapy (6,7). Continuous anticoagulation is required during ECMO to prevent thrombus formation in the circuit. Bleeding (including intracranial, gastrointestinal, and pulmonary) is the most serious complication (30-50%) and can be life-threatening (4,8). Other complications include thromboembolism, infections, acute kidney injury, and limb ischemia.

Patient Trajectories Apart from the survival statistics above, little has been written about what happens to patients receiving ECMO. Our experience is that most patients fall into 1 of 6 categories.

1. The underlying illness recovers sufficiently for ECMO to be discontinued. These patients can have a full recovery or remain chronically critically ill, albeit off ECMO.
2. No recovery occurs, but an alternative intervention is available such as heart or lung transplantation or ventricular assist device, allowing ECMO to be discontinued.
3. The patient dies while receiving ECMO, for instance from massive intracranial bleeding.
4. ECMO is discontinued with the intent of allowing the patient to die, due to the identification of a poor functional or survival prognosis (e.g. anoxic brain injury).
5. The ECMO circuit fails (for instance, it clots off). This can lead to urgent intervention to replace the catheters and ECMO devices versus a decision to allow the patient to die. For patients with a poor underlying chance of recovery, ECMO circuit failure should trigger frank conversations about prognosis and goals, and if it is in the patient's best interest to replace the failing ECMO system.
6. A patient becomes "stuck" on ECMO, without recovery of the underlying illness or available alternative intervention, and little chance of ever surviving without ECMO. This can cause ethical and resource utilization dilemmas if the patient/family do not agree to discontinue ECMO. There is no arbitrary time-limit to ECMO use, however its use in one patient may prevent it being used in another due to the limitation on the number of ECMO machines and personnel (9).

Palliative and End-of-Life Care Fundamentally, palliative care teams can support ECMO patients/families as they would any other critically ill patient at high risk of dying: assess and clarify patient/family understanding, provide emotional and spiritual care, support patient-centered goals of care discussions, and help provide comfort care to dying patients. Educating families and preparing them early on for the possibility that a patient will not recover and ECMO will need to be discontinued is advisable. Clinicians should be prepared that most families will have no knowledge of ECMO, unlike other ICU treatments such as mechanical ventilation. Different institutions will have different protocols for discontinuing ECMO in a patient who is expected to die. The approach to symptom management in patients expected to die after ECMO discontinuation is similar to the removal of any other advanced life-support technology such as a ventilator or LVAD. It is particularly important to ensure patients are comfortable and have adequate circulating levels of symptom medications *prior* to discontinuing ECMO due to the probability of rapid circulatory collapse (see *Fast Facts* #33, 34, 269).

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Ryan Jozwiak MD and Sean Marks MD

Background Diuretics are a mainstay of treating symptomatic volume overload in heart failure (HF), including at the end-of-life. For some patients, bowel edema from HF-related congestion can diminish the absorption and effectiveness of oral diuretics. Intravenous diuretics, however, are difficult to administer in an outpatient or hospice setting, which likely contributes to the frequent emergency department visits and hospitalizations in HF, even near the end-of-life (1). In this context, subcutaneous (SC) furosemide can be helpful. This *Fast Fact* reviews its use.

Clinical Context Although thiazide diuretics (e.g. hydrochlorothiazide, chlorthalidone, or metolazone) and potassium sparing diuretics (e.g. spironolactone) are established therapies for chronic HF, loop diuretics such as furosemide or bumetanide are the mainstay for acute or severe HF (2,3). Loop diuretics work via two mechanisms: an immediate veno-dilator effect as well as diuresis of fluid and electrolytes (2). Some HF patients enrolled in hospice develop refractory dyspnea, and swelling with resultant anxiety despite the use of opioids or benzodiazepines (4-6). SC furosemide, which is more easily administered at home than IV, has been proposed to help these patients.

Pharmacology Bumetanide has not been established as safe and/or effective subcutaneously, thus furosemide is the preferred SC diuretic. Typically, the IV furosemide formulation is given via a SC clysis line for continuous subcutaneous infusions (CSCI) or a SC butterfly needle for intermittent dosing. Hence, SC and IV costs are essentially equivalent. For patients with an indwelling IV catheter, there is little rationale to utilize SC over IV. Furosemide formulations come in 20 to 50 mL syringes with concentrations of 10 mg/mL. Current daily dose limits are based on available commercial syringes and are approximately 200-300 mg daily. This may change as the market for SC medications change (7).

- Onset of diuresis is 1-1.5 hours for oral; 30 minutes for SC; 5 minutes for IV furosemide. Therefore, if there is minimal urine output 1-2 hours after oral administration of furosemide, it is reasonable to consider a dose of parenteral furosemide in the setting of symptomatic dyspnea from HF (8).
- Diuretic effect is 6-8 hours for oral; 4 hours for SC; 2 hours for IV furosemide (9).
- For intermittent SC dosing, many experts recommend starting with an equivalent oral dose. For CSCI dosing, calculate the initial hourly dose from the previous daily oral dose (10, 11). E.g., someone receiving 100 mg/day of oral furosemide should receive 100 mg SC in 24 hours or 4 mg/hr CSCI.

Outcomes A human, pre-clinical, placebo-controlled trial demonstrated that furosemide has diuretic activity when administered SC (9). The clinical evidence for SC furosemide otherwise is in a handful of case reports and series. In a series of 43 consecutive end-stage HF patients prescribed CSCI by palliative care or hospice clinicians, CSCI was associated with a median weight loss of 5.6 kg and most patients avoided hospital admission and terminal breathlessness (10). A case series of HF patients who received intermittent SC furosemide demonstrated a prompt resolution of weight gain, breathlessness, and peripheral edema (4).

Side Effects & Safety Diuretics can cause intravascular volume depletion and kidney injury. Furosemide promotes diuresis of sodium, potassium, magnesium, and chloride which can lead to significant electrolyte abnormalities and subsequent risk for cardiac arrhythmia (7). Furosemide infusions have been associated with ototoxicity when used at doses >1600 mg daily or when used concurrently with a medication associated with ototoxicity (e.g. vancomycin) (7,12). Self-resolving dermatologic site reactions involving stinging/burning at the site of injection may occur in up to 23% receiving CSCI (9).

Controversies Clinicians should be cognizant of several unresolved clinical questions regarding the appropriate use of SC furosemide (11).

- In general, the data supporting the efficacy of SC furosemide is less robust than other SC palliative-based medications, e.g. SC use of opioids (11).

- Clinical debate remains regarding the need for serum monitoring of renal function and electrolyte abnormalities for dying HF patients receiving SC furosemide to prevent sentinel iatrogenic events such as renal failure or cardiac arrhythmias. When prognosis is anticipated to be less than a month and goals of care are comfort, the rationale for serum lab monitoring may be less compelling.
- For patients who can still safely swallow oral medications, adjuvant oral diuretics such as chlorthalidone and metolazone may augment the effectiveness of SC furosemide (5,13).
- While empiric oral potassium supplementation has been associated with prolonged survival in those initiating furosemide use (14), there is no current literature supporting or arguing against the use of oral potassium in standard end-of-life diuretic use and supplementation may depend on goals of care.
- It remains unclear whether the optimal approach to utilizing SC is as a rescue therapy when clear signs of acute HF are apparent – e.g. breathlessness, peripheral edema – versus a preventative approach wherein intermittent SC furosemide doses are given in response to weight gain.

Conclusion In the setting of end-of-life HF management, there appears to be a role for the use of SC furosemide when oral treatment fails. While further research is needed, small clinical investigations have demonstrated effective diuresis and prevention of hospital admissions and hospice de-enrollment without significant adverse effects from SC furosemide.

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