Clinical Cases in Cardiology
Series Editors: Ravi V. Shah · Siddique A. Abbasi · James L. Januzzi

Ravi V. Shah · Siddique A. Abbasi *Editors*

Clinical Cases in Heart Failure

Springer

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Clinical cases are a key component in modern medical education, assisting the trainee or recertifying clinician to work through unusual cases using best practice techniques. Cardiology is a key discipline in this regard and is a highly visual subject requiring the reader to describe often very subtle differences in the presentation of patients and define accurately the diagnostic and management criteria on which to base their clinical decision-making. This series of concise practical guides is designed to facilitate the clinical decision-making process by reviewing a number of cases and defining the various diagnostic and management decisions open to clinicians. Each title will be illustrated and diverse in scope, enabling the reader to obtain relevant clinical information regarding both standard and unusual cases in a rapid, easy to digest format.

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Preface

As a common endpoint to a variety of pathologies, heart failure poses challenges from initial workup to long-term management. The clinician must be equally equipped to deal with fluctuations in hemodynamics as with the long-term care of chronic disease. Additionally, the clinician must keep up-to-date with new therapies, both medical and device-based, that hold promise but require increased vigilance.

Here, we present clinical cases that span the breadth of heart failure workup and management. These cases reflect actual or modeled patients and are intended to provide real-world context to what may be seen in modern clinical practice. Of note, *the cases and discussion herein are not a substitute for personalized clinical judgment, examination, or individual patient-centered discussions or care, and are not meant to prescribe a given avenue of therapy for any specific real patient*. Instead, we hope to provide you, the clinician, with illustrative cases and insights from practicing cardiovascular physicians as to one approach to addressing these important clinical problems.

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Chapter 1
New-Onset LV Dysfunction

Aferdita Spahillari, Olivia N. Severdija, and Donya Mohebali

Case Presentation

A 50-year-old male with a history of hypertension (treated with diuretic therapy) for >10 years and a family history of early coronary artery disease (father with myocardial infarction in his late 1930s) presents with chest discomfort, rapid heart rate, and dyspnea. He has no history of recent viral illness, endocrine disorder, or family history of cardiomyopathy. His medications include hydrochlorothiazide 25 mg daily. There are no allergies. There is no illicit drug use. He consumes 3–4 beers every 2–3 days. His physical examination is significant for a temperature of 98.5 °F, blood pressure of 90/60, heart rate 140/min irregularly irregular, and normal respirations and oxygen saturation. He has jugular venous

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distension to the angle of the mandible, with normal carotid upstrokes. Apart from an irregularly irregular heart rhythm, he has an S3 gallop. No murmur is auscultated. His pulmonary examination demonstrates rales approximately one-half up the chest. There is no hepatosplenomegaly and the remainder of the abdominal examination is normal. He has 1+ edema bilaterally and his extremities are warm.

1.1 Approach

1. *Initial assessment of etiology of left ventricular dysfunction*:

   The initial history and physical examination in new-onset LV dysfunction is aimed at (1) pinpointing underlying causes and chronicity of heart failure (HF; e.g., to differentiate an acute myocarditis from chronic HF) and (2) to delineate severity of disease. The initial physical examination should focus on the evaluation of congestion and presence of decreased or preserved peripheral perfusion to determine clinical severity of heart failure and need for more advanced therapies, including acute hemodynamic support (outside the scope of this case).

   Historical features such as antecedent or family history of cardiomyopathy, ischemic or valvular heart disease, other illnesses that predispose to heart disease (e.g., thyroid dysfunction, alcohol or illicit drug use, HIV, arrhythmias). In addition, history of modifiable conditions like hypertension, obesity, diabetes, and sleep apnea (among others) should be elicited.

   Initial diagnostic tests for determination of the etiology of new left ventricular dysfunction and HF should be obtained. These include:

   - Laboratory tests such as complete blood count to exclude anemia or infection, serum electrolytes, blood urea nitrogen, creatinine to evaluate renal function, glucose to assess for presence of diabetes, albumin, liver function tests to assess for presence of liver disease, lipid profile, thyroid-stimulating hormone to assess for

presence of thyroid disease and B-type natriuretic peptide (BNP) or N-terminal pro-B-type natriuretic peptide (NT-proBNP) to assist in diagnosis of HF and establish disease severity.

- 12-lead electrocardiogram (ECG) and chest x-ray should be obtained. ECG can demonstrate arrhythmias, such as atrial fibrillation with rapid ventricular response that can precipitate or worsen left ventricular dysfunction, ventricular premature beats, atrioventricular conduction defects, wide QRS or bundle branch block that may indicate benefit from cardiac resynchronization therapy, evidence of left ventricular hypertrophy or prior myocardial infarction.
- An important step in initial evaluation of LV dysfunction is delineating the severity of LV dysfunction, the remodeling of the ventricle, and any particular clues as to etiology of HF. In most cases, a 2-dimensional transthoracic echocardiogram (TTE) should be obtained, which in addition to left ventricular (LV) dysfunction, will quantify LV dilatation, hypertrophy (in cases of restrictive or hypertrophic cardiomyopathy), valvular dysfunction (i.e. aortic stenosis or mitral regurgitation) or regional wall motion abnormalities.
- While TTE is a portable and useful bedside modality, additional evaluation with cardiac magnetic resonance (CMR) can be helpful in some cases by adding information on left ventricular volume and function when echocardiography is technically difficult, in addition to prognostic information on presence of late gadolinium enhancement (a marker of replacement fibrosis in both ischemic and non-ischemic cardiomyopathy), perfusion, and viability.

2. *The role for ischemic testing in the evaluation of new-onset cardiomyopathy*:

Our approach to determining the underlying cause of LV dysfunction relies on a stepwise approach to excluding the most common causes. Given the high prevalence of coronary artery disease as an etiology for HF [1, 2], evaluation for coronary artery disease (CAD) should be considered. A

frequent question in the initial assessment of these patients is whether coronary angiography as a first-step is warranted. *Importantly, patients should be in a compensated hemodynamic state (e.g., not congested and with a reasonable perfusion status) before proceeding to any stress testing.*

- In individuals who do not have contraindications to exercise testing, [3] exercise stress testing may be performed as an initial strategy to evaluate for potential CAD and to assess exercise capacity (highly prognostic in HF). Of note, imaging coupled stress tests are more sensitive for the diagnosis of CAD (relative to exercise treadmill testing alone).
- Additionally, imaging tests (specifically imaging stress tests, such as nuclear or CMR stress testing) provide information not only on the location and extent of ischemic territories, but also provide an assessment of the impact of a prior infarct or ischemia on global LV and RV remodeling that can provide insights into viability, including (1) wall thickness (end-diastolic wall thickness < 5.5–6 mm being less likely to be viable); (2) infarct size (with larger infarct sizes or more transmural late gadolinium enhancement being less viable); (3) global LV dimensions and volume (with a more spherical, dilated LV being less viable), among other characteristics.
- Left-heart catheterization is indicated for patients with HF and angina, known CAD or significant ischemia diagnosed by ECG or noninvasive testing in those who are candidates for revascularization [4]. It is important to note that presence of non-severe (non-obstructive) CAD by angiography does not imply that ischemia is the cause of left ventricular dysfunction. (This is the genesis of the concept "cardiomyopathy out of proportion to CAD.").
- Increasingly, angiographic and advanced imaging modalities are complementary in the evaluation of CAD in cardiomyopathy.

3. *Revascularization options*:

   Once the diagnosis of CAD is made, consideration for revascularization should be undertaken. This is a complex decision that usually involves a HF specialist, general cardiologist, imaging experts, and cardiac surgeons versed in revascularization of individuals with cardiomyopathy. Revascularization options include coronary artery bypass grafting (CABG) or percutaneous coronary intervention (PCI). In general, standard professional society guidelines on revascularization should be applied to individuals with HF. CABG is associated with improved all-cause and cardiovascular survival in patients with reduced LV ejection fraction and high-grade CAD [5, 6], though individuals with severe LV dysfunction may require mechanical circulatory support (temporary or permanent) after CABG revascularization if the stress of bypass surgery and reperfusion of myocardium does not result in significant ventricular recovery. In general, CABG is preferred in the presence of LV dysfunction with use of arterial conduits to the left anterior descending artery or left main coronary artery. The data for PCI in patients with CAD and LV systolic dysfunction is more limited [7], though many groups consider this route in cases of high surgical risk or prohibitive ventricular dysfunction. While registry data suggest that the degree of ischemia by non-invasive testing or the presence of viability may be associated with improved survival post-revascularization, the available randomized evidence does not necessarily support viability testing in determining a role for revascularization [8].

4. *Optimal medical therapy*:

   Medical management should be initiated once an initial diagnosis of HF with reduced LV ejection fraction is made.

   - *Diuretics*: Diuretics are used for the control of congestive symptoms only. Patients with symptoms and signs of volume overload such as dyspnea, peripheral edema, and elevated jugular venous pressure benefit from

initiation of diuretics, most commonly a loop diuretic (e.g., furosemide).

Occasionally, bumetanide or torsemide (with a higher oral bioavailability) are selected in patients at risk for poor outpatient response to furosemide (e.g., severe right ventricular failure or tricuspid regurgitation). The mode of diuresis (IV versus oral; continuous infusion versus bolus for IV diuretics) remains an area of open debate. Diuretic augmentation (either via dose or addition of combination thiazide diuretics at low dose) can be used in cases of diuretic refractoriness. The presence of renal failure with volume overload is a poor prognostic feature; if this ensues, invasive assessment of filling pressure to ensure reasonable cardiac output and initiation of renal replacement can be undertaken.

- *Renin-angiotensin and neprilysin inhibition*: Activation of the renin-angiotensin-aldosterone system (RAAS) is a hallmark feature in HF with decreased LV function. Several options to achieve RAAS inhibition have been put forth, including (1) angiotensin converting enzyme inhibition (ACE-I); (2) angiotensin-II receptor blockade (ARB); (3) ARB-neprolysin inhibitor (ARNI; e.g., LCZ696) inhibitor; (4) mineralocorticoid receptor antagonist (e.g., spironolactone, eplerenone) [9]. Each of these has been shown to improve survival, with the most recent (ARNIs) medications improving survival greater than ARB alone. Common side effects of these medications include hyperkalemia, renal dysfunction, hypotension, cough, and (most seriously) angioedema. Individuals with cough on ACE-I can be switched to an ARB. Slow uptitration of these medications may reduce side effects such as hypotension and acute kidney injury. Our approach is to increase RAAS inhibition every 2 weeks with careful serial monitoring of serum electrolytes and renal function. Hypotension to RAAS inhibition or failure to tolerate even low doses of RAAS inhibitors suggest profound reliance on systemic vascular resistance to maintain blood pressure,

severe limitation in cardiac output and need for referral for advanced HF therapies.

- *Beta-blocker therapy*: While the acute hemodynamic effects of beta-blockade reduce contractility and impair LV performance, chronically, beta-blockade can improve cardiac function and structure, reduce sudden cardiac death (SCD) risk, and offers the most potent improvements in overall survival. Therefore, beta-blockade should be initiated in all patients with HF with reduced ejection fraction who do *not* have evidence of poor perfusion (e.g., cool extremities, elevated lactate, or low cardiac index) or significant bradycardia or AV block. Clinical evidence has convincingly demonstrated that beta-blockers (particularly carvedilol, metoprolol succinate and bisoprolol) have a significant mortality benefit in patients with HF with reduced ejection fraction [10]. Beta-blockade should be started at low doses, with dose augmentation at two-week intervals (similar to ACE-I titration) until the target dose is reached (carvedilol 25 mg twice daily, metoprolol succinate 200 mg daily). Occasionally, HF can clinically worsen (e.g., increased jugular venous pressure, edema, or dyspnea) during beta-blocker initation; if these symptoms are present without evidence of low cardiac output or hypotension, diuretics should be augmented briefly to eliminate congestion before beta-blocker uptitration continues.
- *Mineralocorticoid receptor antagonists (MRAs)*: MRAs such as spironolactone or eplerenone are recommended in addition to the above therapy for patients with NYHA functional class II-IV HF symptoms and LVEF $\leq$35% given the beneficial effects on mortality and HF hospitalizations [11]. As with ACE-I, renal function and serum potassium levels should be monitored closely.
- *Hydralazine/Isosorbide*: The combination of hydralazine and isosorbide dinitrate has been shown to improve survival and reduce HF hospitalizations in African-American patients who have persistent HF

symptoms despite treatment with beta-blockers and RAAS inihibitors [12]. This combination therapy should also be considered for those who cannot tolerate ACE inhibitors or ARBs due to drug intolerance, renal insufficiency or hypotension. Adherence to this therapy is challenging due to the large number of pills and three-times daily dosing; however, a combination pill is available.

- *Ivabradine*: This is a newer agent that inhibits the *If* current in the sinus node and is recommended as an adjunctive therapy for patients in sinus rhythm who have persistent HF symptoms on maximally tolerated beta-blockade and whose resting heart rate remains above 70 beats/min [13].
- *Anticoagulation*: Patients with HF with reduced ejection fraction are at increased risk for thromboembolism given their predisposition to atrial fibrillation as well as propensity to LV thrombus formation in the setting of dilated, hypokinetic heart chambers [14]. Furthermore, there are certain cardiomyopathies that are more likely to be associated with thromboembolism, such as peripartum cardiomyopathy and left ventricular noncompaction. Anticoagulation is indicated in patients with HF and a history of atrial fibrillation. Choice of anticoagulant therapy (warfarin versus direct oral anticoagulants) should be individualized based on patient preference, renal function, cost and drug interactions. Anticoagulation should also be considered in patients with LV systolic dysfunction, history of prior thromboembolic event who remain in sinus rhythm, or if LV thrombus is present. Current evidence does not support anticoagulation in patients with LV systolic dysfunction alone [15].

5. *What about device therapy and prevention of sudden cardiac death in new-onset HF?*

Sudden cardiac death (SCD) occurs approximately in one third of patients with HF with reduced ejection fraction, with life-threatening ventricular arrhythmias

accounting for a large proportion of these deaths [16]. Robust clinical trial data support the use of implantable cardioverter-defibrillator (ICD) therapy for secondary and primary prevention of SCD in selected patients with ischemic or non-ischemic cardiomyopathy. For primary prevention, current guidelines recommend ICD therapy in patients with

- A New York Heart Association (NYHA) functional class II or III with an LVEF less than or equal to 35%;
- NYHA functional class I with an LVEF less than or equal to 30%;
- With at least 40 days following an acute myocardial infarction *or* at least 3 months following revascularization.

Medical therapy should be optimized prior to ICD placement, though there are no strict criteria for the duration of optimal guideline-directed medical therapy. Importantly, given competing risks of HF pump death in patients with NYHA functional class IV and drug-refractory HF who are not candidates for transplantation, cardiac resynchronization therapy, or LV assist device placement, ICD implantation should not be routine in these patients [17, 18].

6. *Management of atrial fibrillation in heart failure*

The goal of therapy in patients with atrial fibrillation and systolic HF include symptom control, prevention of worsening LV function, and prevention of thromboembolism. While there is no current preference for rate versus rhythm control based on contemporary evidence, we favor an attempt at sinus rhythm in patients who present with rapid atrial dysrhythmias (fibrillation or flutter) alongside LV dysfunction, given (1) potential improvement in cardiac output and filling pressures with regularized rhythm (and an atrial "kick"); (2) possibility of deterioration in LV function with rapid heart rates; (3) potential for LV recovery with controlled and regularized heart rate. However, this decision varies by clinician, and factors such as potential for maintenance of sinus rhythm, ease of cardioversion,

and other relevant factors (e.g., use of anti-arrhythmic drugs) are important considerations. However, in the setting of significant HF that is unable to be decongested with rhythm control alone, or if rate control is difficult to achieve in the setting of hypotension or cardiogenic shock, we proceed with urgent attempts to restore sinus rhythm. Of note, we avoid rapid uptitration of beta blocker and non-dihydropyridine calcium channel blockers (both negative inotropes) in individuals with new onset LV dysfunction with rapid atrial fibrillation. Low dose beta-blockade and digoxin (or amiodarone in cases in which rate control is necessary in the face of hypotension) versus cardioversion (after transesophageal echocardiography excludes atrial thrombus) should be considered. In selecting anti-arrhythmic medications, we usually choose amiodarone or dofetilide (if an ICD is in place) with careful monitoring and involvement of an electrophysiologist [19].

7. *Metrics for discharge and prevention of re-hospitalization*

   Careful transition to outpatient care is needed to reduce the risk of readmissions, post discharge complications and mortality in heart failure patients. Discharge planning should address dietary sodium and fluid restriction, monitoring of body weight, electrolytes, and renal function, medication teaching as well as recommendations regarding appropriate activity levels and early and coordinated outpatient follow up. Patient education in heart failure to encourage adherence in all of the above measures is essential.

1.2 Case Resolution

ECG demonstrated atrial fibrillation without evidence of infarct or ischemia. Trasthoracic echocardiogram demonstrated a moderately dilated LV cavity and moderate-severe global hypokinesis with LVEF 30% and no significant valvular disease. Cardiac catheterization was performed and revealed non-obstructive coronary artery disease. He was diuresed with IV Lasix boluses, started on lisinopril, spironolactone and after diuresis to euvolemia, beta-blockade with carvedilol was initiated. Atrial fibrillation

persisted with heart rates of 140 bpm. Renal function was normal and he was anticoagulated with apixaban. After ensuring absence of intracardiac thrombus by transesophageal echocardiography, cardioversion was performed with successful return to sinus rhythm. He was discharged home on hospital day 10 with close outpatient follow-up in NYHA class I functional class.

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Chapter 2
Restrictive Cardiomyopathy

Aalap Chokshi and Amanda R. Vest

A 57 year-old female with a history of nonischemic cardiomyopathy was referred for management of heart failure. Five months ago, the patient was evaluated for 2 months of fevers, dyspnea on exertion and lower extremity edema. A transthoracic echocardiogram (TTE) was completed which revealed a left ventricular ejection fraction (LVEF) of 20% with global hypokinesis. A nuclear stress test was normal. A repeat TTE 1 month later showed improved LVEF to 35–40%.

Upon evaluation, the patient was limited by dyspnea on walking up any degree of incline. She was able to complete her activities of daily living. She denied chest pain, peripheral edema, orthopnea, abdominal distension and syncope. Her family history was significant for cardiomyopathy in a first degree relative. Her medications were rosuvastatin, metoprolol succinate, valsartan and furosemide.

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Her blood pressure was 96/64, heart rate 80 and oxygen saturation 98% at room air. Her physical examination was unremarkable: normal jugular venous pressure, normal S1 and S2, no murmurs, clear lungs, normal abdomen and no peripheral edema. Pertinent laboratory tests were serum creatinine of 1.04 mg/dL, BUN 2 mg/dL, BNP 1876 pg/mL and troponin I 0.17 ng/mL. Her electrocardiogram is shown in Fig. 2.1. TTE images are shown in Fig. 2.2. A left heart catheterization revealed no obstructive coronary artery disease. A cardiac MRI was also completed (Fig. 2.3).

Given the cardiac imaging findings, hematological testing was pursued. Serum protein electrophoresis (SPEP) analysis revealed elevated free lambda light chains at 751.2 mg/L, kappa light chains of 7.9 mg/L and kappa to lambda ratio of 0.01. Serum immunofixation electrophoresis identified a restricted band in the lambda region consistent with monoclonal free light chains. Serum free lambda light chains were elevated at 1294.4 mg/L. Bone marrow aspirate showed 40% lambda-restricted plasma cells, but was negative for amyloid by Congo red staining. Fat pad aspirate was also negative for Congo red staining. Urine immunofixation showed only lambda light chains.

The patient underwent a right heart catheterization which revealed a right atrial pressure of 12 mmHg, right ventricular pressure of 50/5 mmHg, pulmonary artery pressure of 49/19 mmHg, pulmonary capillary wedge pressure of 25 mmHg, Fick cardiac output of 3.7 L/m, cardiac index of 2 L/min/m^2, and pulmonary artery oxygen saturation of 56%. An endomyocardial biopsy was performed, which showed interstitial deposits of waxy amorphous material that stained positively with Congo Red, confirming its identity as amyloid.

Question 1

In a patient presenting with dyspnea on exertion, which combination of imaging and hemodynamic findings would be most suggestive of a restrictive cardiomyopathy?

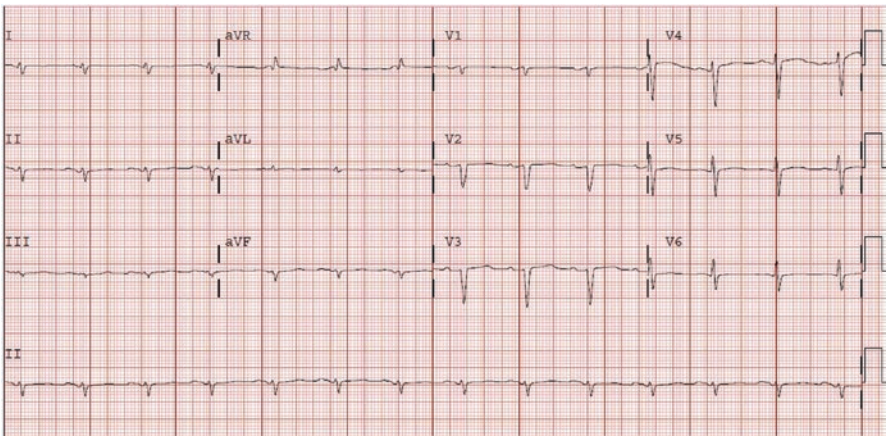

FIGURE 2.1 Electrocardiogram. Normal sinus rhythm, low voltage in the frontal leads, anterior Q waves and poor R wave progression

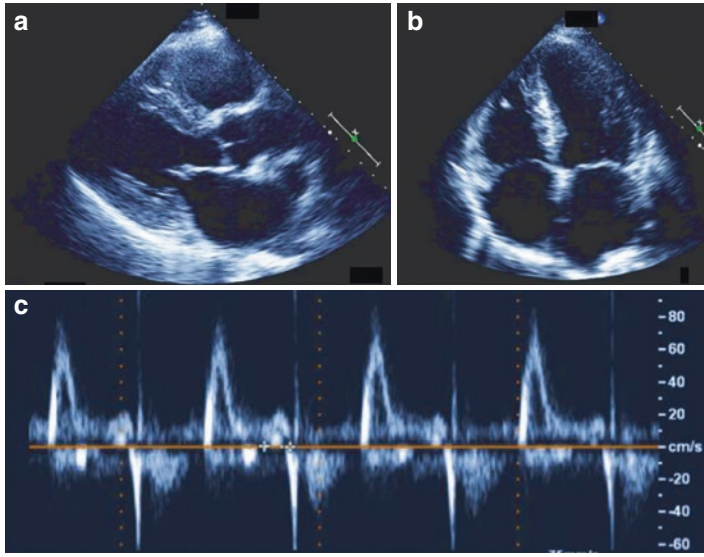

FIGURE 2.2 TTE. (**a**) Parasternal long axis view. LV EF of 30%, global hypokinesis, increased wall thickness (IVSd of 1.5 cm, LVPWd 1.5 cm, LVIDd 4.3 cm), moderately dilated right ventricle (RV), increased RV wall thickness, moderately reduced RV systolic function, no pericardial effusion. (**b**) Apical 4-chamber view. Biatrial enlargement (Left atrial (LA) volume of 78.6 ml, LA volume index of 42.8 ml/m^2), mild mitral regurgitation, mild tricuspid regurgitation, no LV thrombus. (**c**) Mitral Inflow Wave Pattern by Pulsed-wave Doppler. Mitral valve (MV) E wave velocity of 81.4 cm/s, MV A velocity of 22.5 cm/s and E/A ratio of 3.6; LV IVRT of 0.10 s (not shown, Med E' velocity 2.65 cm/s, Med E/E' 30.7, Lat E' velocity 4.13 cm/s, Lat E/e' 19.7). *IVSd* interventricular septal thickness at diastole, *LVPWd* left ventricular posterior wall thickness at diastole, *LVIDd* left ventricular diameter at diastole, *IVRT isovolumic relaxation time*

(a) Dilated right atrium, normal left atrial size, right ventricular hypertrophy, normal left ventricular end-diastolic pressure, elevated right ventricular end-diastolic pressure

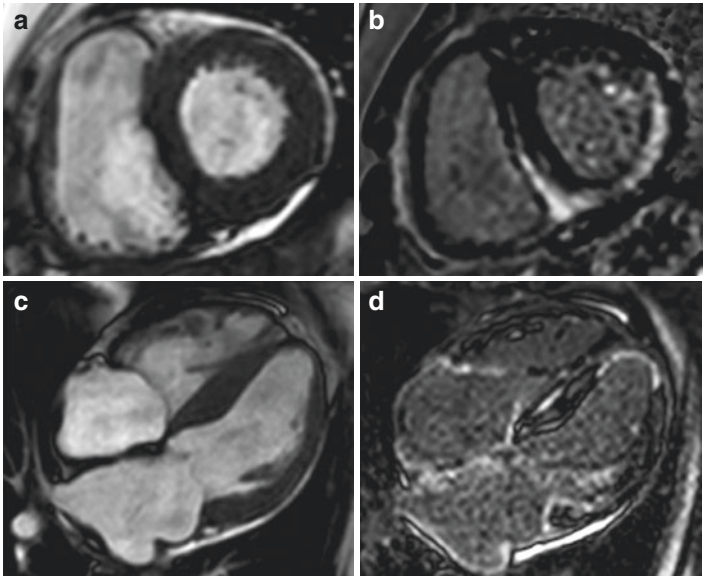

FIGURE 2.3 Cardiac MR. (**a**) T1 weighted image, short axis. Multifocal thickening of the myocardium with sparing of the anterior wall. Reduced biventricular systolic function, LVEF of 26% and RVEF of 21.1%. (**b**) Late gadolinium enhancement (LGE) image, LOOK-LOCKER sequence, short axis. Multifocal delayed hyperenhancement of the myocardium at the base with sparing of the anterior wall. (**c**) T1 weighted image, horizontal long axis. (**d**) Late gadolinium enhancement (LGE) image, LOOK-LOCKER sequence, horizontal long axis. Delayed subendocardial hyperenhancement involving the apical and apical septal walls

(b) Asymmetric septal hypertrophy, normal atrial sizes, normal left ventricular end-diastolic volume, pulmonary capillary wedge pressure 8 mmHg
(c) Biatrial dilation, increased left ventricular end-diastolic volume, severe mitral regurgitation, pulmonary capillary wedge pressure > 15 mmHg
(d) Biatrial dilation, normal left ventricular end-diastolic volume, pulmonary capillary wedge pressure > 15 mmHg,

left ventricular end-diastolic pressure greater than right ventricular end-diastolic pressure

(e) Normal atrial sizes, normal left ventricular end-diastolic volume, equalization of the left and right end-diastolic pressures, no late gadolinium enhancement and increased pericardial thickness on cardiac magnetic resonance imaging

Answer is (d)

Restrictive cardiomyopathy is usually characterized by biatrial dilation and a normal left ventricular cavity size. The pulmonary capillary wedge pressure and left ventricular end-diastolic pressure are typically elevated; the left ventricular end-diastolic pressure usually exceeds the right ventricular end-diastolic pressure in a patient with restrictive physiology as in answer (d). Occasionally, it may be necessary to challenge the patient with an intravenous volume load or exercise to reveal this hemodynamic pattern.

Conversely, a dilated right atrium, right ventricular hypertrophy and elevated right ventricular end-diastolic pressure in answer (a) is most consistent with a case of pulmonary arterial hypertension, with normal left-sided hemodynamics. Answer (b) describes a patient with asymmetric septal hypertrophy due to hypertrophic cardiomyopathy (HCM). Although there are a subset of HCM patients that display a restrictive physiology, in the absence of an elevated pulmonary capillary wedge pressure this is not the case. Answer (c) describes a patient with a dilated cardiomyopathy and severe mitral regurgitation. Answer (e) describes constrictive pericarditis with normal ventricular myocardium but a thickened pericardium causing increases in both left and right-sided end-diastolic pressures. Constrictive pericarditis classically causes equalization of filling pressures in all four cardiac chambers especially during inspiration, and ventricular interdependence. A left ventricular end-diastolic pressure that exceeds right ventricular end-diastolic pressure by $\geq$5 mmHg favors a diagnosis of cardiomyopathy (restrictive or dilated) rather than constrictive pericarditis.

2.1 Background

Restrictive cardiomyopathy is a rare myocardial disease which is principally characterized by poor diastolic filling of either or both ventricles due to wall stiffness. The left ventricle is typically non-dilated and usually non-hypertrophied, and the atria are typically dilated. This condition can be inherited or acquired, with various potential etiologies causing a similar restrictive cardiac physiology (Table 2.1).

Table 2.1 Etiologies of restrictive cardiomyopathy

Inherited	**Acquired**
Metabolic cardiomyopathies	Amyloidosis (AL, Transthyretin)
Glycogen storage diseases (Danon [LAMP-2 mutation], PRKAG2 syndrome, Pompe's)	Autoimmune
	Scleroderma
	Rheumatoid arthritis
Lysosomal storage diseases (Gaucher, Anderson-Fabry, Hunter, Hurler, Niemann-Pick)	Sarcoidosis
	Drugs
Carnitine deficiency	Anthracyclines, serotonin, methysergide, ergotamine, mercury busulfan
Kearns-Saye syndrome	
Hemochromatosis	Oncologic
Familial amyloidosis (Transthyretin, Apolipoprotein associated)	Radiation
	Metastatic cancers
Desminopathy	Carcinoid heart disease
Pseudoxanthoma elasticum	Endomyocardial
Other genetic restrictive cardiomyopathies	Hypereosinophilic syndrome
	Endomyocardial fibrosis
	Idiopathic

Amyloidosis is a rare clinical disorder characterized by local or systemic deposition of insoluble misfolded proteins in various organs [1]. The progressive accumulation of amyloid in the myocardial interstitium results in hypertrophy, diastolic dysfunction and restrictive physiology.

Local mechanisms implicated in the development of cardiomyopathy are direct toxicity of amyloid fibrils and effects of precursor and other associated soluble intermediate proteins involved in amyloid deposition [2].

There are several subtypes of amyloidosis, the most common being immunoglobulin light chain amyloidosis (AL). AL amyloidosis is a clonal plasma cell dyscrasia in which the bone marrow plasma cell count is 5–7%, far less than that seen in multiple myeloma [2]. The prevalence of lambda light chains is much higher than kappa light chains. AL amyloidosis commonly involves the heart in 50% of cases, kidneys in 50%, liver in 16% and neurologic involvement in 10% [2].

Transthyretin related (TTR) amyloidosis is the second most common type of subtype of amyloid protein deposition. It is predominantly synthesized in the liver and serves to transport thyroxine and retinol binding protein. There are greater than 100 mutations on the *TTR* gene on chromosome 18 that result in TTR amyloidosis [2]. Clinical features of mutant-type TTR (m-TTR) amyloidosis includes neuropathy, cardiomyopathy or both. The most common mutation in the United States is the substitution of valine for isoleucine in position 122 (V122I), which is exclusively present in male African Americans and results in a predominantly cardiac phenotype [3]. Although individuals with other mutations may initially present with a neurologic phenotype, they may develop cardiomyopathy later in the clinical course.

Wild-type TTR (wt-TTR), formerly known as senile systemic amyloidosis, is more common than was once thought and is often overlooked due to its phenotypic similarity to hypertensive heart disease. However, there is increasing awareness of this condition; in a large cohort of patients greater than age 80 that underwent autopsy, approximately

25% had wt-TTR amyloid deposits [1]. Bilateral carpal tunnel syndrome and biceps rupture are relatively common findings in patients with wt-TTR and may help raise clinical suspicion in a patient with cardiac disease.

2.2 Prognosis

Survival in systemic AL amyloidosis is a function of the extent of cardiac involvement. The extent of cardiac involvement and prognosis in AL amyloidosis is inferred from the magnitude of serum levels of troponin and NT-proBNP. The thresholds for positive markers are 0.035 ng/ml for troponin T and 332 pg/ml for NT-proBNP; higher stages of disease are based on none, one or both of the markers being positive [4]. In untreated, symptomatic individuals with cardiac AL amyloidosis, the median survival is six months [5]. In comparison, those without cardiac involvement of AL amyloid, the median survival is approximately four years [1].

Treatment for TTR amyloidosis is extremely limited to experimental and investigational therapies. The median survival for m-TTR and wt-TTR amyloidosis is approximately 25 and 43 months, respectively [3]. The staging system for prognosis in AL amyloid cardiomyopathy has not been validated in the the TTR amyloid population.

2.3 Clinical Presentation

Patients with systemic AL amyloidosis often present with non-cardiac symptoms such as nephrotic syndrome, autonomic neuropathy, soft tissue infiltrations and bleeding, which pertain to other organs affected by amyloidosis. However, initial presentations of progressive exercise intolerance, heart failure, syncope and arrhythmias are not uncommon and often are the symptoms that drive patients to seek medical attention.

Question 2

Which of the following imaging techniques can best differentiate AL and TTR subtypes of cardiac amyloidosis?

(a) Cardiac magnetic resonance (CMR)
(b) Myocardial strain echocardiography
(c) Pyrophosphate scintigraphy
(d) ECG-Gated cardiac computed tomography (CT)
(e) Combination of an ECG and conventional echocardiogram

Answer is (c)

Answer (c) is correct because ^{99m}Tc-pyrophosphate scintigraphy has demonstrated excellent sensitivity and specificity for distinguishing between the amyloid subtypes. A heart-to-contralateral ratio > 1.5 is consistent with diffuse myocardial tracer retention, and showed 97% sensitivity and 100% specificity for identifying TTR amyloidosis [6].

Cardiac magnetic resonance (CMR) in answer (a) is a very useful too in the diagnosis of cardiac amyloidosis, with increased ventricular wall thickness and late gadolinium enhancement (LGE) being commonly seen. However this technique cannot differentiate between the AL and TTR subtypes. Two-dimensional myocardial strain echocardiography, as in answer (b), can assist the detection of cardiac amyloidosis in a patient with left ventricular hypertrophy [7, 8]. There is a characteristic regional strain pattern characterized by apical sparing in cardiac amyloidosis, but this technique has not yet been able to differentiate between the disease subtypes. The ECG shows a characteristic picture of low QRS voltage in as many as half of patients with cardiac amyloidosis. The combination of ECG and echocardiogram in answer (e) does not have utility in distinguishing between the amyloid subtypes.

2.4 Imaging

Findings on noninvasive two dimensional (2D) echocardiography are indistinguishable for amyloid subtype. The most common features are increased ventricular wall thickness,

low ventricular volumes, biatrial enlargement and pericardial effusion. The earliest echocardiographic finding of cardiac amyloid is diastolic dysfunction [1]. A restricted diastolic filling pattern is marked by an increased diastolic flow velocity, a shortened deceleration time, prolonged isovolumetric relaxation time and decreased pulmonary vein peak systolic flow [9]. Peak systolic wall motion, medial and lateral mitral annulus velocities by tissue Doppler imaging are also significantly impaired markers of cardiac relaxation [9]. Parameters that have been associated with mortality are reduced left ventricular ejection fraction, greater wall thickness, right ventricular dilation, transmitral early filling wave deceleration time less than 150 ms and E/A ratio > 2.0 [10].

Cardiac Magnetic Resonance (CMR) accurately characterizes myocardial tissue thickness and mass in amyloid cardiomyopathy. Any type of global late gadolinium enhancement (LGE), which includes both subendocardial and either homogeneous or heterogeneous transmural patterns, is typical for cardiac amyloid [11]. Studies to date have been mixed regarding the prognostic utility of CMR LGE pattern in amyloidosis.

The gold standard for diagnosis of amyloid cardiomyopathy is endomyocardial biopsy, but is exceedingly less common due to the ability to infer a diagnosis from a combination of electrocardiography, serum and urine studies in AL amyloidosis, bone marrow biopsy, serum cardiac biomarkers, abdominal fat pad biopsy and noninvasive cardiac imaging. Biopsy requires positive staining for Congo red. However, in 85% of patients the diagnosis can be confirmed by a combination of a positive fat pad aspirate and bone marrow biopsy [2]. The diagnosis of TTR amyloidosis is often missed until very late in the disease course because of its indolent cardiac manifestation and lack of readily available serum testing for misfolded TTR.

Invasive hemodynamics typically show elevated right and left ventricular pressures, with LV pressures in excess of RV pressures – although a fluid bolus or exercise is sometimes required to reveal the expected restrictive pattern of LV end-diastolic pressure that exceeds RV end-diastolic pressure by ≥5 mmHg. Pulmonary hypertension is often present in

restrictive cardiomyopathy and the ratio of RV end diastolic pressure to RV systolic pressure is usually greater than one third. Unlike constrictive pericarditis, there is typically concordance of simultaneous systolic LV and RV pressures during respiration. Although the 'dip and plateau' or 'square root pattern' of rapid early diastolic filling and an abrupt end to late diastolic filling has been classically associated with constrictive pericarditis, may observers believe that this pattern can also be seen in restrictive cardiomyopathy.

Our patient began combination chemotherapy for systemic AL amyloidosis with stage three cardiac involvement. Her regimen was CyBorD (cyclophosphamide, bortezomib and dexamethasone). Her baseline free lambda light chains was 1294 mg/L and dropped to 68 mg/L after cycle 1, and then to 32 mg/L after cycle 4, consistent with a very good partial hematologic response. After 6 months of therapy, her free lambda light chains normalized. However, there was minimal cardiac response.

Her right heart catheterization showed right atrial pressure of 18 mmHg, pulmonary artery pressure of 57/29 mmHg, pulmonary capillary wedge pressure of 32 mmHg, pulmonary artery saturation of 44%, Fick cardiac output 2.6 L/min and cardiac index 1.5 L/min/m^2. Intravenous diuretics were initiated and milrinone was needed to maintain cardiac output. An ICD was placed with no major complications.

2.5 Treatment

When patients present with decompensated heart failure, diuretics are the mainstay of therapy. Although anecdotal, spironolactone is well tolerated and should be prescribed as renal involvement of AL amyloidosis can result in diuretic resistance [12]. Beta-blockers, ACE (angiotensin converting enzyme) inhibitors and angiotensin receptor blockers (ARB) have not been studied extensively in this population and should be used cautiously because of the possible effects of bradycardia and hypotension in the setting of autonomic

neuropathy [10]. Digoxin and calcium channel blockers are relatively contraindicated due to their affinity for amyloid fibrils.

Atrial and ventricular arrhythmias and sudden cardiac death are unfortunately common in cardiac amyloid. Standard indications for pacing apply for amyloidosis. Implantable cardioverter-defibrillators (ICD) have not been typically placed in this group of patients due to their poor 1 year prognosis, the most common cause for sudden death being electromechanical dissociation and a higher defibrillation threshold [13]. Although there is no definite survival advantage to ICDs at this time, the promise and success of therapy for systemic amyloidosis with advances in cardiac support including heart transplantation, have led some programs to develop their own criteria for ICD implantation. These include a life expectancy of at least 1 year, history of syncope, sustained VT and outpatient monitoring showing NSVT [13].

The therapeutic approach to AL amyloidosis is derived from the approach to multiple myeloma, with the mainstay of therapy being cytotoxic chemotherapy. A complete hematologic response is defined as the absence of monoclonal protein in serum and urine by immunofixation electrophoresis, normal serum free light chain ratio, and a bone marrow biopsy with less than 5% plasma cells with no clonal predominance [14]. Combination chemotherapy includes melphalen or bortezomib based regimens with cyclophosphamide and dexamethasone. High dose melphalen and autologous stem cell transplantation (ASCT) has shown the most benefit in the young, those with good performance status, no organ involvement and low level bone marrow plasma cell proliferation [15]. In individuals with organ involvement, there is an up to 15% complication rate during stem cell mobilization and collection; in addition, treatment related mortality is 2–10% [15]. NEOD001 is a promising new humanized form of monoclonal antibody that directly targets and clears light chain amyloid in affected organs; a recently completed first in human Phase I/II study proved it was safe and well tolerated [16]. Of note, a hematologic response does not equate to organ response, which is often delayed, nor a clinical response.

The only approved treatment for TTR amyloidosis is orthotopic liver transplantation. Younger individuals with the Val30Met mutation early in the disease course and those without cardiac involvement do the best [17]. The universal common problem is the deposition of TTR amyloid in the heart, resulting in increased mortality despite liver transplantation. Worldwide, approximately 60 liver transplantations are performed yearly for this particular variant of TTR amyloid and the estimated 5 year survival of 77%, with a cardiac cause of death in 39% [18]. Tafamidis meglumine and diflunisal are promising investigational therapies that stabilize TTR tetramers and prevent formation of monomers, which misfold and aggregate [19, 20]. Gene silencing RNA interference therapy (ALN-TTR01 and ALN-TTR02) has also been successfully delivered to the liver to suppress hepatic production of mutant and non-mutant transthyretin, but long term clinical efficacy studies are ongoing [21].

The patient presented with decompensated heart failure and cardiogenic shock, requiring dobutamine in addition to milrinone. During this hospitalization, she had an intra-aortic balloon pump placed. She continued to do poorly and required placement of a left ventricular assist device as a bridge to cardiac transplantation. Her post-operative hospital course was complicated by severe right heart failure and was dependent on a milrinone infusion. She underwent several attempts at weaning milrinone, which were complicated by hypotension, dyspnea and low flow alarms on the LVAD; hence she remained on milrinone for refractory RV failure.

2.6 Mechanical Circulatory Support

The intra-aortic balloon pump (IABP) is used commonly in cardiogenic shock and has been reported in patients with cardiac amyloid in addition to inotropic therapy. The IABP is often used a bridge therapy to implantation of a left ventricular assist device (LVAD) or cardiac transplantation. LVADs have been used as destination therapy in patients that are not

candidates for heart transplantation and bridge therapy for those that are. In a small series at the Mayo Clinic, 9 patients with cardiac amyloid of different types underwent LVAD implantation successfully [22]. Three of these patients died before hospital discharge and of those surviving, mean survival was 17.1 months [22]. Many of these patients developed gastrointestinal bleeding and severe right ventricular (RV) dysfunction. RV dysfunction can occur due to primary involvement of amyloid deposition, increased RV strain resulting from the augmented preload from the LVAD or pulmonary hypertension existing before LVAD implantation [22]. Further analysis of this study showed that smaller LV dimensions were associated with poor outcomes; implantation is difficult because the septum may impinge on the inflow cannula and result in fatal arrhythmias [23].

Twenty-one months after cardiac amyloidosis diagnosis, the patient undeerwent an orthotopic heart transplant. She recovered well post-operatively and was maintained on standard immunosuppressant medications and prophylactic antibiotics.

2.7 Cardiac Transplantation

The first cardiac transplantation for cardiac amyloidosis occurred in 1988. The major risk after transplantation is recurrence of amyloid in the cardiac allograft and extracardiac deposition [10]. All published studies to date report transplantation outcomes on AL amyloidosis only. The earliest data came from the United Kingdom; 24 patients with cardiac amyloid underwent orthotopic heart transplantation (OHT) with 1 year and 5 year survival of 50% and 20%, respectively [24]. Since this study, there have been major developments in chemotherapy as well as post-transplant autologous stem cell transplantation (ASCT). Multiple centers have reported small series with an estimated 1 year survival of 63–100% and 5 year survival of 65% in those undergoing sequential OHT and ASCT, with no evidence

amyloid deposition in the allograft [10, 25–27]. If ASCT occurs too soon after OHT, there is a risk of allograft rejection and if ASCT occurs too late, it allows time for amyloid to progress to other organs [25].

Our patient is doing well at 1 year post-orthotopic heart transplantation. The free lambda light chains have fallen likely in association with her immunosuppressive medications. The next step is for her to undergo melphalen induction and autologous stem cell transplantation.

2.8 Conclusion

Amyloidosis is a systemic disease that is life threatening and upon involvement of the myocardium, it has a very poor prognosis. Its accurate diagnosis requires a multidisciplinary approach between cardiology, hematology and other subspecialists who have expertise in the interpretation of electrocardiography, noninvasive imaging and specialized serum and urine tests. Management involves the design of optimal combination chemotherapies, stem cell transplantation, screening for ongoing investigational therapies, early use of mechanical circulatory support in those at highest risk and careful selection of those that would benefit from orthotopic heart transplantation.

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Chapter 3
Acute Decompensated Heart Failure

Sunit Preet Chaudhry and Siddique A. Abbasi

Case Summary

A 77 year-old male with a past medical history significant for ischemic cardiomyopathy with resultant congestive heart failure (CHF) and an ejection fraction (EF) 35%, diabetes mellitus, hypertension and dyslipidemia presented to the emergency department (ED) with shortness of breath, palpitations, increasing abdominal girth, and lower extremity edema. He states that these symptoms first began two weeks ago, at which time he was asked to increase his outpatient dose of furosemide without improvement of his symptoms. At baseline he is able to perform his activities of daily living: however, he is now becoming dyspneic even with minimal exertion. Additionally, he mentions a new three-pillow orthopnea and an 11 pound weight gain. He denies any dietary indiscretion or excess fluid intake.

Upon arrival to the emergency department, vital signs included a blood pressure (BP) of 90/78, heart rate of 142 beats/min and an oxygen saturation of 91% on 3 L of supplemental

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oxygen. On exam, he appeared mildly ill and was conversationally dyspneic. Cardiovascular exam was notable for a jugular venous pressure (JVP) of 16, an irregularly irregular rhythm, a 2/6 holosystolic murmur at the apex, and an audible S3 gallop. His lungs had crackles half way up bilaterally and his extremities were warm with 2+ pitting edema bilaterally. He mentions that he was adherent to his medications which included carvedilol, lisinopril, spironolactone, and furosemide.

3.1 What is Critical in the Initial Assessment of Acute Decompensated Heart Failure (ADHF)?

Decompensated heart failure is a complex clinical syndrome resulting from the impairment of ventricular filling or ejection associated with symptoms of dyspnea, fatigue, and peripheral and/or pulmonary edema [1]. The first step is to *evaluate the degree of hemodynamic compromise* and to *exclude acute conditions requiring emergency therapies* (e.g., acute cardiac ischemia, acute valvular insufficiency or progressive stenosis [e.g., acute mitral insufficiency from papillary muscle or chordal rupture; or progressive low-output severe aortic stenosis], or arrhythmia [e.g., VT or AF] [2]). Assessment of *perfusion* and *congestion* are the mainstay of acute hemodynamic profiling (REF), and can be used to both guide initial therapy and provide prognosis.

- *Congestion*: Patients are categorized as either "wet" (elevated right and/or left sided filling pressure) or "dry" (roughly normal filling pressures). Of note, discordance between right and left-sided filling pressure is important to note, as in these occasional cases, a normal jugular venous pressure may not reflect an elevated left sided filling pressures (or vice versa). Clinical findings suggestive of elevated filling pressures can be elicited from the history by complaints of orthopnea, paroxysmal nocturnal dyspnea, increasing dyspnea on exertion, and weight gain. Orthopnea is commonly viewed as a helpful symptom in diagnosing acute decompensated heart failure, as it is associated with

pulmonary capillary wedge pressures of over 30 mmHg [3]. Physical exam findings consistent with elevated filling pressures include an elevated JVP, an S3, edema, ascites, or the presence of hepatojugular reflux.

- *Perfusion*: This can be characterized as either "warm" (normal cardiac index) or "cold" (inadequate cardiac index). Findings suggestive of limited perfusion obtained by history include confusion and alteration in mental status. Examination findings of narrow pulse pressure, pulsus alterans, and cool extremities also suggest poor perfusion. It is important to note that in general, individuals with significant physiologic reserve (e.g., particularly young individuals) may not exhibit the same clinical signs or symptoms of poor perfusion as marginal, chronic HF patients. *A high index of suspicion is required to detect poor perfusion status in ADHF.*

This rubric (perfusion/congestion) sets up a 2 × 2 table (published initially by Nohria and Stevenson-REF) that facilitates rapid management.

- Profile A: warm and dry; standard HF management therapies indicated;
- Profile B: warm and wet; ADHF with normal systemic perfusion; standard HF management therapy indicated with intensification of diuretic therapy
- Profile C: cold and wet; poor systemic perfusion; consideration for halting beta-blockade and initiation of inotropic or vasodilator therapy, with early/urgent mechanical circulatory support.
- Profile D: rarely seen, cold and dry; optimization of filling pressures and initiation of supportive therapies (as in Profile C) if necessary

Case Summary 2

Laboratory profile was notable for sodium 128 mmEq/L, creatinine 2.3 mg/dl (baseline 0.8 mg/dl), elevated BNP and troponin, and abnormal liver function testing (ALT 180, AST 250 mIU/L, total bilirubin 2.6 mg/dl, INR 2.7). Lactic acid was

elevated. Electrocardiogram (ECG) showed atrial fibrillation with 1 mm ST depressions in the inferolateral leads. Chest x-ray revealed pulmonary edema. While in the emergency ward, he became progressively hypotensive and underwent emergent cardioversion with restoration of normal sinus rhythm and improvement in both his blood pressure and ECG. Given a marginal hemodynamic and electrical profile, he was admitted to the coronary care unit (CCU) for further care. In the CCU, he was initiated and up titrated on a continuous infusion of furosemide without substantial urine output. Repeat physical exam was notable for a BP of 105/64, increasing confusion and the development of cold extremities. Repeat labs were significant for a creatinine increase to 3.1.

3.2 How Should Patients in Profile C Be Managed?

Standard HF management is covered in another case in this series. Our patient above demonstrates evidence of hypotension with end-organ dysfunction (renal and liver), despite therapies targeted toward aggressive decongestion. In these cases, several different maneuvers should be considered, in very rapid succession to prevent hemodynamic collapse:

- Discontinuation of beta blockade may sufficiently improve perfusion and cardiac output;
- Early right heart (pulmonary artery) catheterization may be helpful in guiding clinical management, and the use of downstream mechanical and pharmacologic therapies.
- In patients where the systemic vascular resistance is high and mean arterial pressure is adequate (usually >60–70 mmHg), intravenous vasodilators can increase cardiac output and decrease filling pressures [4]. The two most commonly used intravenous vasodilators are nitroprusside and nitroglycerin.
  - Nitroprusside, a balanced arterial and venous dilator, decreases systemic vascular resistance, left and

right ventricular filling pressures, and has a resultant increase in stroke volume [5]. Its short half-life and rapidity of action make this an ideal drug in patients with HF in whom acute afterload reduction is necessary. The starting dose in heart failure is 5–10 μg/min, increased by 10 ug/min every 5–10 min as tolerated to a maximum dose of 300 μg/min. Serious adverse effects of nitroprusside to monitor for include hypotension and cyanide toxicity. Concerns over the use of nitroprusside for ischemic cardiomyopathy have not been supported in our clinical experience; while it should not be used in the setting of an acute myocardial infarction, its use in chronic ischemic cardiomyopathy may be indicated.

  - Nitroglycerin is a venous and arterial vasodilatory properties at higher doses. Initial dosing is 20 μg/min and then up titrated every 3–5 min as tolerated to a maximum dose of 400 μg/min. Side effects of nitroglycerin include headache and hypotension, and there is a risk for tachyphylaxis after 2–3 days of nitroglycerin use (mandating transition to oral vasodilator therapy or nitroprusside).
  - Other medications (e.g., nesiritide) have been used in the past, but are rarely used at present, and are not covered here.

- Alternatively, inotropes can be used in patients with poor perfusion who are unable to tolerate vasodilators secondary to hypotension or do not have an elevated systemic vascular resistance. Despite the hemodynamic improvements with inotropes, all have been associated with increased rates of myocardial infarction, both atrial and ventricular arrhythmias, and mortality [6]. Nevertheless, their use in dire circumstances (as our patient) can acutely rescue.

  - Dobutamine, the most commonly used inotropic agent during hospitalization, works primarily by activation of beta-adrenergic receptor, with a selectivity

of $\beta_1 > \beta_2$. Activation of the β_1 receptor results in an increase in cardiac output while activation of the β_2 receptor results in vasodilatation. Initial doses of dobutamine start at 2 μg/kg/min, titrated to 10 μg/kg/min.

- Dopamine works by activation of alpha, beta, and dopaminergic receptors with preference based on the dose. At low doses (between 1–3 μg/kg/min), the dominating receptor is dopaminergic with resultant renal and peripheral vasodilatation. At higher doses, there is predominantly alpha stimulation resulting in an improvement in blood pressure.
- Milrinone is a selective phosphodiesterase-3 inhibitor and results in both increase in contractility and vasodilation ("inodilator").

Case Summary 3

Given his worsening renal function and inability to decongest with a continuous diuretic infusion, he underwent right heart catheterization with the following findings: right atrial (RA) pressure: 18 mmHg; pulmonary capillary wedge pressure (PCWP): 36 mmHg; cardiac output (CO): 2.0 L/min, cardiac index (CI): 1.0 L/min/BSA; and a systemic vascular resistance (SVR): 2100 dynes. Echocardiography excluded acute valvular insufficiency or mechanical complications. Dobutamine was initiated at 2 mcg/kg/min and he continued on a furosemide infusion with improvement of his filling pressures to a RA of 6, PCWP of 12, SVR of 1080 and normalization of his creatinine and transaminases over the following 72 h. He was then started on captopril with eventual conversion to lisinopril and weaned off his dobutamine.

Despite restoration of a normal rhythm and improvement of blood pressure, our patient had worsening renal function as well as difficulty with diuresis despite the use of a continuous infusion of furosemide. A pulmonary artery (PA) line

was placed for evaluation of hemodynamics and showed elevated biventricular filling pressures and systemic vascular resistance, and an extremely depressed cardiac index, consistent with cardiogenic shock. At this time, potential options for therapy include treatment with an isolated vasodilator (such as nitroprusside) or inotropic therapy. Given his normal blood pressure and severely depressed cardiac index, it was felt that an isolated vasodilator would not provide adequate hemodynamic support, and, as a result, the remaining options included dobutamine and milrinone. Dobutamine was chosen in this case given its shorter half-life, although the use of milrinone would also be appropriate. With the addition of dobutamine, diuresis rates improved and filling pressures normalized within 72 h.

3.3 How Can Parenteral Inotropes or Vasodilators Be Weaned?

The timing of the weaning of inotropes and their replacement with oral therapies is not clearly defined. Common practice is to continue inotropic therapy until (1) congestion has resolved; (2) end-organ function (e.g., renal function) is optimal; (3) pending no inotrope-related complication (e.g., VT). Inotropes are commonly replaced with oral HF medications (e.g., ACE inhibitors, ARBs, or a combination of hydralazine/nitrates). Common practice is to initiate a short acting ACE-inhibitor such as captopril, which allows for rapid up titration with conversion to a long acting equivalent prior to discharge. Timing of initiation of beta-blockade is controversial. In individuals with extreme tenuousness, our protocol is initiation of beta-blockade (1) after maximization of oral vasodilator therapy; (2) 3–5 half-lives after inotropes have been withdrawn (and at least 24 h). In addition, we occasionally maintain right heart catheterization 12–18 h after beta-blocker initiation to monitor effects on cardiac output (which occur

before end-organ dysfunction may supervene). In general, if tolerated, this group of medications can be *initiated* while inpatient, but should be *uptitrated* as an outpatient.

In conclusion, decompensated heart failure is a complex clinical syndrome resulting from impairment of ventricular filling or ejection associated with symptoms of dyspnea, fatigue, and peripheral and/or pulmonary edema. Evaluation of these patients should first determine hemodynamic stability and once this has occurred, therapies should be tailored based on their filling pressures and perfusion status (Tables 3.1 and 3.2).

Table 3.1 Killip classification system

Class	Description	Mortality (%)
I	No clinical signs of heart failure	1
II	Rales or crackles, S3, and elevated jugular venous pressure	3.6
III	Acute pulmonary edema	5.3
IV	Cardiogenic shock or hypotension (systolic blood pressure <90, and evidence of peripheral vasoconstriction (oliguria, cyanosis, or sweating)	17.6

Flaherty JD, Bax JJ, De Luca L, et al. Acute heart failure syndromes in patients with coronary artery disease early assessment and treatment. J Am Coll Cardiol. 2009;53(3):254–263

Table 3.2 Vasodilators and inotropes

Agent name	Mechanism of action	Initial dose	Maximum dose	Time to uptitration	Oral conversion
Nitroprusside	Arterialvasodilation	5–10 mcg/min	300 mcg/min	Every 5 min	ACE inhibitors, ARB, hydralazine/ nitrates
Nitroglycerin	Venous > arterial vasodilatation	20 mcg/min	400 mcg/min	Every 3–5 min	Isosorbide mononitrate, isosorbide dinitrate
Dobutamine	$\beta_1 > \beta_2 \ggg \alpha_1$	0.5–1 mcg/kg/min	20 mcg/kg/min	As needed	–
Dopamine	α: 3–10 mcg/kg/min β: 3–10 mcg/kg/min D: 1–3 mcg/kg/min	2–10 mcg/kg/min	20 mcg/kg/min	As needed	–
Milrinone	Phosphodiesterase inhibitor	0.1–0.375 mcg/kg/ min	0.75 mcg/kg/min	As needed	–

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Chapter 4
Valvular Disease and Heart Failure: Mitral Regurgitation

Ravi V. Shah and G. William Dec

A 75-year-old female with a past medical history of type 2 diabetes mellitus, hypertension, and implantable cardioverter-defibrillator (ICD) and chronic left ventricular systolic dysfunction for over 5 years presented with increasing exertional dyspnea. Three months ago, she suffered syncope with ICD interrogation with ventricular fibrillation, and successful delivery of shock therapy. At that time, she underwent coronary angiography that demonstrated no obstructive coronary artery disease. An echocardiogram demonstrated LV ejection fraction 15% and a dilated left ventricle (end-diastolic dimension by M-mode echocardiography 81 mm) with decreased right ventricular function and severe mitral regurgitation (MR). There is no evidence of mitral valve prolapse, prior endocarditis, or other valve leaflet pathology. Of note, the MR has been present for the past 2 years, with a slow, progressive dilatation of the LV, though she has remained relatively asymptomatic (class I–II) with most daily activities.

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She is on carvedilol 12.5 mg twice a day, lisinopril 5 mg daily, and furosemide 20 mg twice a day.

Over the next 3 months, she experiences worsening exertional lightheadedness and dyspnea, limiting her to 70 m on a 6-min walk test. She is readmitted once for heart failure, thought secondary to dietary indiscretion; during that admission, she was given intravenous diuretic therapy and discharged. Her ACE inhibitor had to be discontinued and beta-blocker reduced in dose for progressive hypotension.

Cardiopulmonary physical examination shows a blood pressure 80/60, heart rate 70/min, no apparent jugular venous distension, clear lungs, a III/VI holosystolic murmur at the apex, radiating to the base of the heart, an S_3 gallop, and no peripheral edema. The extremities were cool. Electrocardiogram shows sinus rhythm with left bundle branch block.

Cardiopulmonary exercise testing shows a peak VO_2 10.0 ml/kg/min (<50% of age-, sex-, and body size-predicted), with marked elevation in V_E/VCO_2 slope (a marker of ventilatory efficiency and right ventricular-pulmonary artery coupling) and exercise oscillatory ventilation (a marker of ineffective circulation with exercise). Right heart catheterization showed central venous pressure 8 mmHg, right ventricular pressure 50/8, pulmonary artery pressure 50/30, pulmonary capillary wedge pressure 20 with *v*-waves to 40 (at rest), and a cardiac index of 1.8 L/min/m^2 (at rest).

Serum chemistries (including liver function testing) are normal except for an elevated creatinine at 2.5 mg/dl.

She presents now to your clinic for management of her heart failure and consideration of surgical or percutaneous mitral valve intervention.

Question

In general, which of the following factors influence decision making for referral for surgical (or percutaneous) mitral valve repair in advanced LV systolic dysfunction with clinical heart failure?

(A) Clinical evidence of low cardiac output with hypotension
(B) Degree of LV dilatation (e.g., LV end-diastolic dimension)
(C) Degree of RV dysfunction
(D) Use of other advanced therapies that may reduce MR (e.g., cardiac resynchronization therapy)
(E) All of the above

4.1 Discussion

Although mitral regurgitation is present in up to 50% of individuals with heart failure [1], there is no consensus on the management of "functional" MR. The etiology of MR in the setting of an advanced cardiomyopathy (both ischemic and non-ischemic) resides in remodeling of the ventricular (or atrial [2]) apparatus supporting mitral valve function (not necessarily in the mitral valve itself) [3]. These features lend the designation "functional" (rather than "anatomic") MR to this disorder. Chronic LV volume overload results in changes in myocardial architecture at the cellular level with increased cardiomyocyte hypertrophy and interstitial fibrosis over time [4], lending to a further vicious cycle of adverse ventricular remodeling and advanced heart failure. In turn, the presence and severity of functional MR are strongly linked to clinical outcomes in advanced heart failure [5]. These pathophysiologic features suggest that clinical decision making in this complex disorder relies on a comprehensive review of strategies that address underlying ventricular mechanics alongside the mitral valve itself.

There is no consensus guideline on how to best select individuals for surgical or newer percutaneous mitral valve repair. Society guidelines suggest that mitral valve repair (with chordal sparing) should be considered for individuals with advanced heart failure and symptomatic, severe MR, in order to improve symptoms (not necessarily prolong life). In our opinion, the management of these patients relies on a multi-staged approach.

4.2 Stage 1: Can My Patient Tolerate Optimal Medical Therapy? Is He/She Medically Optimized?

Once the diagnosis of severe *functional* MR is made, the cornerstone in management of functional MR in advanced heart failure is guideline-directed optimization of medical therapy, specifically directed at beta-blockade and renin-angiotensin-aldosterone axis inhibition (e.g., ACE inhibition, ARBs, or mineralocorticoid receptor antagonists). Carvedilol has been reported to improve LV function and reduce MR severity [6, 7]. Optimization of volume status with judicious use of diuretic therapy is important. Whether novel therapies (e.g., valsartan/sacubutril) are effective in this context is under investigation.

If the patient qualifies, cardiac resynchronization therapy (CRT) represents an effective mode of therapy for underlying ventricular dysfunction, with potential specific effects on MR severity [8, 9]. The current guidelines advocate consideration of CRT therapy in individuals with class II or worse heart failure, LV ejection fraction $\leq 35\%$ with QRS duration >120 ms with a left bundle-branch block morphology. (More extensive guidelines for CRT can be found in the Ref. [10].)

Assessment of underlying coronary artery disease and potential benefits of revascularization are important. Viability and ischemia testing may be useful to delineate whether restoring blood flow will be useful.

Finally, it is important to recognize individuals in whom medical therapy alone may not be enough. Evidence of low cardiac output on examination or by history (e.g., exertional fatigue, lightheadedness) with accompanying hypotension, end-organ dysfunction, or findings on exercise evaluation suggestive of low output (e.g., exercise oscillatory ventilation) prompts consideration of right heart catheterization. Advanced therapies (e.g., LV assist device and/or transplantation) should be considered in these patients alongside MR evaluation.

4.3 Step 2: My Patient Cannot Be Optimized Further. What About Surgical or Percutaneous Mitral Valve Repair? Are More Advanced Therapies Appropriate?

Current guidelines from European and American societies place mitral valve surgery as a class IIb indication in individuals who are severely symptomatic (NYHA class III–IV) after medical optimization with LV dysfunction (below LV ejection fraction 30%), in the presence of low surgical risk [11]. (Of note, in the setting of a different, non-valvular heart surgery being performed, concomitant repair of the mitral valve should be strongly considered.) Assessment of surgical risk is complex, but can be directed by a comprehensive assessment of risk factors (Table 4.1). While this list is far from exhaustive, it is important

Table 4.1 Important features to consider prior to correction of functional MR

Parameter	Optimal index
Hemodynamic and clinical profile	Normal resting blood pressure (SBP > 90)
	without evidence of vasoconstriction
	Resting cardiac index >2.1 l/min/m^2
	without need for inotropes
Cardiopulmonary exercise testing	Peak VO_2 > 14 ml/kg/min (outside ranges for transplant/VAD)
	Absence of high risk features for HF (exercise oscillatory ventilation)
Normal end-organ function	Normal renal and liver profile
Medical therapy	Ability to tolerate beta-blockers and ACE-I

(continued)

Table 4.1 (continued)

Parameter	Optimal index
Ventricular reserve	LV end-diastolic dimension <80 mm
	No clinical RV failure
CAD therapies	Revascularization possible

to note that many of the criteria that would characterize a potential patient as high-risk are equivalent to those that qualify a patient for mechanical circulatory support or transplantation.

An in-depth, fully informed discussion of the risks and potential outcomes of mitral repair should be undertaken before proceeding. Mitral valve annuloplasty (a standard procedure for correction of MR) has up to a 25% rate of recurrence at 1 year. Discussion of other procedures (ventricular restraint devices, transcatheter devices) are outside the scope of this text, and reviewed elsewhere [12]. Of note, transcatheter devices (e.g., the MitraClip) are under investigation for secondary (functional) MR.

In those cases where the decision is unclear, consultation with an advanced heart failure center and patient, surgical, and medical preparation for deployment of advanced therapies should be undertaken prior to surgery.

Answer to Question

(E) All of the above.

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Chapter 5
Valvular Disease and Heart Failure: Aortic Stenosis

Steven Gannon and Siddique A. Abbasi

Case Summary 1

A 74 year old male with a past medical history of hypertension, atrial fibrillation on warfarin and moderate aortic stenosis presented with recurrent admissions for decompensated heart failure with preserved ejection fraction. In addition to volume overload the patient complained of severe dyspnea on exertion; he denied exertional angina and syncope. He responded promptly to diuresis each hospitalization and was discharged on escalating doses of oral furosemide and beta-blockers for rate and blood pressure control. Repeat transthoracic echocardiogram demonstrated moderate concentric left ventricular (LV) hypertrophy, small LV size, LV ejection fraction of 60%, aortic valve area (AVA) of 0.5 cm^2/m^2, mean gradient of 28 mmHg, and stroke volume index of 30 ml/m^2. A dobutamine stress echocardiogram showed an increase in LV ejection fraction to 70% with stress in addition to a fixed AVA of 0.5 cm^2/m^2 and an increase in mean gradient to 32 mmHg. His aortic valve calcium score by multidetector computed tomography was 2146 AU.

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Query

Based on the above description what is the best categorization of the patient's aortic stenosis?

1. Normal-flow, high-gradient severe aortic stenosis
2. Normal-flow, high-gradient moderate aortic stenosis
3. Paradoxical low-flow, low-gradient severe aortic stenosis
4. Normal-flow, low-gradient severe aortic stenosis
5. 'Classical' low-flow, low-gradient severe aortic stenosis

Case Summary 2

Following the above evaluation the patient underwent coronary angiography which showed no significant coronary artery disease. He subsequently had a transcatheter aortic valve replacement (AVR). In follow up the patient reported improved dyspnea on exertion and required a decreased dose of oral diuretics. His atrial fibrillation became more difficult to rate control and a rhythm control strategy with amiodarone and direct current cardioversion was pursued. His final diagnosis was paradoxical low-flow, low-gradient severe aortic stenosis.

5.1 Discussion

Paradoxical low-flow, low-gradient severe aortic stenosis is a recently recognized subtype of aortic stenosis with important clinical implications [1]. This entity is defined as an aortic valve area ≤ 0.6 cm^2/m^2 in the presence of a stroke volume index of <35 ml/m^2 despite a preserved LV ejection fraction ($\geq 50\%$) [2]. Patients are typically older, more likely female, and have lower body surface areas [1]. Multiple reports have suggested a higher mortality risk compared to patients with high gradient, normal flow, severe aortic stenosis [1, 3–6]; however this finding has not been unanimous [7, 8]. In addition to a significant co morbidity burden these patients also exhibit higher afterload as reflected by exaggerated measures of valvulo-arterial impedance [1, 3–6].

Patients with this phenotype of severe aortic stenosis routinely display significant left ventricular hypertrophy and a small left ventricular cavity size [1, 3, 7]. The discrepancy between the various assessments of aortic stenosis severity may call into question the accuracy of Doppler measurements and lead to misclassified disease. In addition to considering the diagnosis of paradoxical low-flow, low-gradient severe aortic stenosis to explain these inconsistencies small body surface area and errors in measurement of the AVA or velocity gradients must be excluded [9].

The pathophysiology of paradoxical low flow, low gradient aortic stenosis is characterized by pronounced myocardial fibrosis, particularly in the subendocardium [10], and a decrease in intrinsic left ventricular function best defined by global longitudinal strain and speckle tracking [11–14]. Significant concurrent diastolic dysfunction exists in this patient population as well [1]. There is debate surrounding whether these patients represent a more advanced stage of aortic stenosis.

The recommended work up for patients with paradoxical low-flow, low-gradient severe aortic stenosis places emphasis on determining the patient's symptom burden and the likelihood that aortic stenosis is the main culprit [15]. Concurrent lung disease, arrhythmia, diastolic dysfunction and coronary artery disease should be assessed. If the patient appears asymptomatic exercise stress testing may be useful in revealing symptoms. Further evaluation includes assessment of blood pressure which should be adequately controlled, although the actual clinical benefit of blood pressure optimization has not been studied in this population. Assessing the severity of the aortic stenosis can be difficult as noted above however supplementary tools such as aortic valve computed tomography calcium scoring and cardiac magnetic resonance imaging can be useful [15]. Stress echocardiography can be used in select patients but may be inconclusive due to a largely preserved LV ejection fraction, unlike the classical form of low-flow, low-gradient aortic stenosis [16]. Determining the most likely cause of the patient's symptoms

is left to the discretion of the clinician and requires careful interpretation of the above data.

To date no large, prospective, randomized trials have been performed to answer the question of whether patients with paradoxical low-flow, low-gradient severe aortic stenosis benefit from valve procedures. The only study which compared transcatheter AVR versus medical management in a randomized fashion was the PARTNER-I trial. Post hoc analysis of the inoperable low-flow, low-gradient cohort (n = 51) showed benefit of transcatheter AVR [17]. The majority of retrospective and prospective case series and cohort studies have showed benefit of surgical or transcatheter AVR [1, 3, 5, 6, 18]. More recently Tribouilloy et al. challenged this benefit however only a total of 10 patients in the low-flow, low-gradient group underwent AVR, potentially compromising this outcome's statistical power [9, 15].

In conclusion, therapy for patients with paradoxical low-flow, low-gradient severe aortic stenosis is primarily directed at relieving the mechanical obstruction caused by the stenotic aortic valve. As noted previously blood pressure control is essential and patients with heart failure or arrhythmia should be medically optimized. Surgical or transcatheter aortic valve replacement remains controversial but appears beneficial. A number of investigators suspect that there is underutilization of surgical and transcatheter aortic valve replacement in these patients.

Key Points and Guidelines

1. Paradoxical low-flow, low-gradient aortic stenosis is defined as an AVA ≤ 0.6 cm^2/m^2 in the presence of a stroke volume index of <35 ml/m^2 despite a preserved LV ejection fraction ($\geq 50\%$).
2. In situations where the severity of aortic stenosis is in question invasive hemodynamic studies, aortic valve computed tomography calcium scoring and cardiac magnetic resonance imaging may be useful.
3. AVR is reasonable in symptomatic patients who have low-flow, low-gradient severe AS who are normotensive and have an LV ejection fraction $\geq 50\%$ if clinical, hemodynamic

and anatomic data support valve obstruction as the most likely cause of symptoms.

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Chapter 6
Low Output Heart Failure

Jeremy Robbins and Marwa A. Sabe

Case Summary 1

A 62 year-old woman with a history of dilated cardiomyopathy presents to clinic with several weeks of malaise. She notes fatigue and shortness of breath with activities such as dressing herself or bathing, whereas prior to this she was able to carry out all of her independent activities of daily living without any symptoms. She has abdominal fullness, nausea, and poor appetite but denies abdominal pain. She has been adherent to all of her medicines and consistently follows a low-sodium diet. A complete infectious review of systems is negative; she denies constitutional symptoms or chest discomfort. Review of systems is notable for palpitations. Vital signs include temperature: 98.2 °F, heart rate 96 beats/minute, regular with occasional PVCs, blood pressure 104/84 mmHg, respiratory rate 18/min, and pulse oximetry 94% saturation on room air. She appears chronically ill. She is noted to doze off twice during the physical exam, but is easily arousable and conversant. Jugular venous pressure is

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14 cm H_2O without a Kussmaul sign. Cardiac exam is notable for a laterally displaced, diffuse point of maximal impulse; consistent premature beats, S1, normally split S2, +S3, II/VI holosystolic murmurs at the apex and lower left sternal border. The lungs are clear to auscultation bilaterally. The abdomen is mildly distended but soft and non-tender. The liver edge is 3 cm below the right costal margin with a positive hepatojugular reflux. There is 2+ symmetric pitting edema to the mid-thigh. Lower extremity skin appearance is mottled and is lukewarm at the kneecaps and thighs. Pulsus alternans is present on radial pulse. Dorsalis pedis and posterior tibial arterial pulses are weak and thready.

Query

Based on just the history and physical exam, how would you describe this patient's volume status and perfusion?

1. Normal perfusion and normal filling pressures
2. Normal perfusion and high filling pressures
3. Decreased perfusion and normal filling pressures
4. Decreased perfusion and high filling pressures

Case Summary 2

She was admitted to the hospital where phlebotomy and diagnostic testing were performed, which demonstrated a sodium of 132 mEq/L, blood urea nitrogen 70 mg/dl, creatinine 2.0 mg/dl, and slightly elevated ALT/AST with a total bilirubin of 2.9 and an INR of 1.4. ECG demonstrated sinus rhythm with atrioventricular delay, right axis deviation, intraventricular conduction delay with polymorphic premature ventricular complexes (Fig. 6.1). Chest radiography revealed cardiomegaly and hilar fullness. A transthoracic echocardiogram was performed which demonstrated markedly increased biventricular cavity size (LVEDd: 7.4 cm, RVEDd: 4.8 cm) with normal wall thickness, and globally decreased biventricular function (LVEF: 10–15%, moderate global RV free wall hypokinesis); mild aortic and mitral regurgitation, moderate-severe tricuspid regurgita-

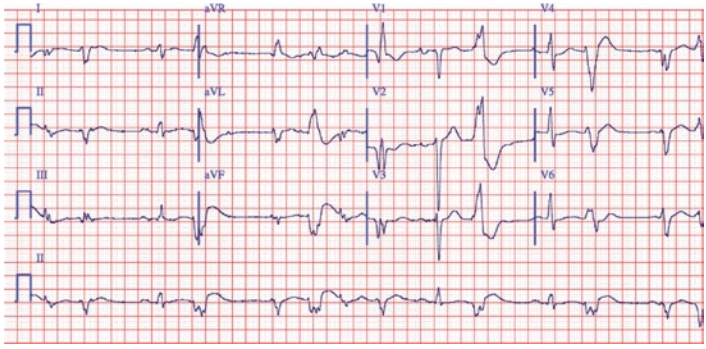

FIGURE 6.1 Electrocardiogram demonstrating sinus rhythm with AV delay, right axis deviation, intraventricular conduction delay with polymorphic premature ventricular complexes

tion; dilated inferior vena cava without collapse; and pulmonary artery systolic pressure 40 mmHg plus right atrial pressure.

Query

Which of the following would be the most appropriate diagnostic test at this point?

1. Cardiac biomarkers
2. Right-heart catheterization
3. Cardiac magnetic resonance imaging (cMRI)
4. Cardiopulmonary exercise testing (CPET)

Case Summary 3

Right heart catheterization (Fig. 6.2) showed:

Right atrial pressure [a wave/v wave, (mean)]: 17/20 (15) mmHg
Right ventricular pressure (systolic/end-diastolic): 56/17 mmHg
Pulmonary artery pressure [systolic/diastolic (mean)]: 56/24 (34) mmHg

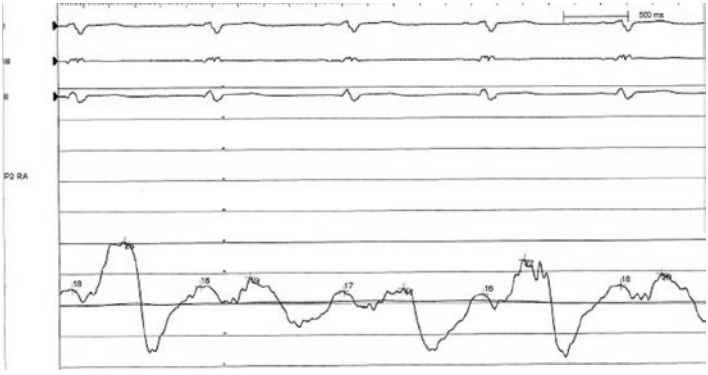

FIGURE 6.2 Right heart catheterization demonstrating right atrial waveform tracing

Pulmonary arterial wedge pressure [a wave/v wave, (mean)]: 26/29 (25) mmHg
Cardiac output (Fick): 2.21 L/min
Cardiac index (Fick): 1.14 L/min/m^2
Systemic vascular resistance: 2570 dynes/cm^2
Pulmonary vascular resistance: 326 dynes/cm^2

Query

With the results of the right heart catheterization in hand, how would you now characterize this patient's hemodynamic profile?

A. Elevated filling pressures, normal cardiac output
B. Elevated filling pressures, low cardiac output
C. Normal filling pressures, normal cardiac output
D. Normal filling pressures, low cardiac output

Query

How would you describe the pulmonary pressures in this patient?

A. Elevated pulmonary artery systolic pressure due to pre-capillary pulmonary hypertension

B. Elevated pulmonary artery systolic pressure due to post-capillary pulmonary hypertension
C. Elevated pulmonary artery systolic pressure due to a combination of pre and post-capillary hypertension
D. Normal pulmonary artery systolic pressure

Case Summary 4

The patient was initially started on nitroprusside and lasix drips with modest improvements in filling pressures and cardiac index to 1.9 L/min/m^2. Nitroprusside was transitioned to oral vasodilators and neurohormonal antagonists, namely lisinopril, hydralazine, and isosorbide dinitrate at maximum doses. She was unable to tolerate a beta-blocker, however, due to marginal cardiac index. Ultimately, she required inotropic therapy with milrinone until insertion of a left ventricular assist device as a bridge to orthotopic heart transplantation.

6.1 Discussion

The evaluation and management of acute heart failure (AHF) relies on the ability to rapidly and definitely make the diagnosis and then stratify the patient by his/her level of acuity. Central to this process is the early recognition of patients with possible cardiogenic shock, or *low-output heart failure*. Patients with low-output heart failure present with signs and symptoms of organ hypoperfusion despite sufficient preload (pulmonary capillary wedge pressure > 18 mmHg). This may manifest itself in dramatic fashion such as marked hypotension and multi-organ failure, or it may present more subtly with symptoms such as fatigue, somnolence, anorexia, presyncope, or periodic respirations (Cheynes-Stokes) in addition to more common HF symptoms.

Similarly, physical exam findings may be nuanced. Vital signs may demonstrate a resting sinus tachycardia in the absence of additional physiologic stimuli. Blood pressure may be normal or low-normal, while hypotension is strongly associated with poor outcomes in patients with AHF [1, 2]. A

narrow pulse pressure (the difference between the systolic and diastolic blood pressure) may suggest the presence of a low cardiac output state. In addition, a proportional pulse pressure [PPP = (systolic BP − diastolic BP)/systolic BP × 100)] < 25% is a very sensitive and specific marker of a cardiac index less than 2.2 L/min/m^2 [3]. General assessment of the patient may reveal pallor or a patient with altered sensorium, which may be manifest by drowsiness or a tendency to fall asleep during the history and physical exam (1). A third heart sound (S_3 gallop) is a nonspecific marker of AHF. Lower extremities may appear dusky or mottled, and lukewarm or cool to the touch, suggesting low cardiac output, increased vasoconstriction, or oftentimes both. Distal pulses may feel thready, and the presence of an alternating weak and strong pulse (pulsus alternans) has been associated with severe left ventricular dysfunction [4].

Laboratory studies may demonstrate evidence of end-organ hypoperfusion such as acute kidney injury; a transaminitis pattern on liver function testing consistent with "shock liver"; hyponatremia as a marker of advanced heart failure with poor prognosis [5] and metabolic acidosis or acidemia indicating poor tissue perfusion.

Electrocardiogram and chest radiography are often non-diagnostic in the evaluation of the patient with low-output heart failure, whereas echocardiography may help diagnose possible etiologies including: acute valvular lesions (e.g. aortic or mitral regurgitation); mechanical complications after a recent myocardial infarction such as a ventricular septal or free wall rupture; acute right ventricular systolic dysfunction in the setting of a large pulmonary embolus; or pericardial effusion leading to cardiac tamponade.

While invasive hemodynamic monitoring has fallen out of favor in the routine assessment of patients with AHF [6], it still plays an important role in the patient with low-output heart failure. Indeed, pulmonary artery catherization (PAC) provides valuable hemodynamic data including filling pressures, cardiac output, and both pulmonary and systemic vascular resistance (SVR) that allows for the tailoring of therapy. PAC monitoring remains an AHA/ACC Class I indication in

the patient with shock and unclear hemodynamic status, and class IIA with a poor response to or with persistent hypotension despite initial therapy [7].

The initial goal in the treatment of the patient with low-output heart failure is to stabilize systemic pressure and improve tissue and end-organ perfusion. This may be accomplished by either: (1) decreasing systemic vascular resistance or (2) increasing cardiac output, and oftentimes it is achieved through a combination of the two. In patients with low-output heart failure with adequate systemic pressure and primary elevation in SVR, vasodilator therapy may be a reasonable first option for pharmacotherapy. Vasodilators can be broken up into (1) mostly venodilators with predominant effects on preload; (2) mostly arterial dilators with predominant effects on afterload; and (3) mixed veno- and vasodilator therapy which acts on both. Treatment strategy depends on whether the patient is concurrently congested ("cold and wet") and would benefit from preload reduction in addition to afterload reduction with agents with agents such as intravenous nitroglycerin or nitroprusside.

Patients with evidence of poor tissue perfusion and low systemic pressures may require inotropic support. Pharmacotherapy includes agents that provide inotropic support with vasodilatory properties (e.g. dobutamine, milrinone) and those that provide vasoconstriction (moderate dose dopamine). These agents should be reserved for use when the diagnosis of low-output heart failure or cardiogenic shock has been established as a temporary bridge to support patients with hemodynamic collapse or while awaiting mechanical circulatory support given their association with increased mortality [8, 9]. There is a role for palliative inotropic therapy for a select group of patients with advanced heart failure and no options for other advanced heart failure therapies.

Pharmacotherapy with inotropes may be limited by atrial or ventricular arrhythmias, hypotension, or may precipitate or worsen myocardial ischemia in patients with coronary artery disease. In those instances and in situations where pharmacotherapy is insufficient, mechanical circulatory sup-

port with intra-aortic balloon counterpulsation or a ventricular assist device may be indicated.

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Chapter 7
Management of Stage D Heart Failure

Ian McCormick and Pablo A. Quintero

Patient Presentation

A 62 year old male with hypertension, hyperlipidemia, and ischemic cardiomyopathy with a left ventricular ejection fraction of 25% and a left ventricular end-diastolic dimension of 7 cm presented with 2 weeks of progressive weight gain, orthopnea, paroxysmal nocturnal dyspnea (PND), and dyspnea on exertion. Recent dose increase of outpatient diuretics did not provide relief of his symptoms. He was dyspneic with activities of daily living, had a poor appetite, and was frequently fatigued with occasional lightheadedness. He had no chest pain, palpitations or any other acute illnesses. He was adherent to medications, which included carvedilol, lisinopril, spironolactone, and torsemide. He underwent cardiac resynchronization therapy and defibrillator placement 2 years ago. This was his third admission to the hospital in the preceding 6 months.

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On exam, he was oriented to person and place only. BSA was 1.82 m^2. Blood pressure was 80/64 mmHg, heart rate 92 beats/min and regular. The jugular venous pressure (JVP) was 18 cm of water and there was an audible S_3. The lungs were clear to auscultation and the extremities were cool to touch with 2+ edema. Labs showed a creatinine of 1.8 (baseline 1.1), ALT 300, AST 350, total bilirubin 1.8, and lactate 2.3.

Discussion

This case describes a patient presenting with acute decompensated heart failure with reduced ejection fraction (HFrEF). History and exam suggest elevation in left- and right-heart filling pressures and a low cardiac output state. Clear lung fields are often noted in decompensated heart failure, and can belie actual filling pressures. The proportional pulse pressure [(systolic blood pressure − diastolic blood pressure)/systolic blood pressure], is 20%. A proportional pulse pressure of less than 25% often correlates with a CI of less than 2.2 l/min/m^2, which in concert with symptoms of elevated pulmonary capillary wedge pressure constitutes the hemodynamic definition of cardiogenic shock. The hemodynamic profile can be classified as "cool and wet", which carries twice the risk of death or cardiac transplantation compared to a patient with less severe decompensated heart failure, i.e. "warm and wet" [1]. The elevated lactate, creatinine, and liver function tests confirm hypoperfusion and end organ dysfunction.

Patient Presentation (Continued)

Urine output was low despite initial high dose intravenous furosemide and he was empirically started on dobutamine 2.5 mcg/kg/min and uptitrated to 5 mcg/kg/min. Urine output remained low and the transaminitis worsened despite dobutamine therapy. He was transferred to the cardiac intensive care unit for pulmonary artery catheter placement and tailored therapy.

Right heart catheterization demonstrated a mean right atrial pressure (RAP) of 18 mmHg, pulmonary artery pressure (PAP) of 50/30 mmHg, and a pulmonary capillary wedge pressure (PCWP) of 26 mmHg with a cardiac index (CI) of 1.3 L/min/m^2. Heart rate was 95 beats/min. Dobutamine was increased to 7.5 mcg/kg/min. CI remained low and milrinone 0.375 mcg/kg/min was added along with high-dose continuous infusion furosemide. After diuresis, RAP and PCWP improved to 9 and 16 mmHg, respectively. Creatinine improved to 1.2 and the transaminitis normalized.

Discussion

Initial management with diuresis and empiric low-dose empiric dobutamine proved ineffective, likely due to elevated system vascular resistance and ineffective afterload reduction. In this severely decompensated state of heart failure, the heart is more sensitive to changes in afterload than preload, with afterload reduction producing higher stroke volumes compared to the same absolute reduction in preload. However, interventions aimed to reduce preload and afterload require normotension; the patient is hypotensive upon presentation. Thus, the decision to place a pulmonary artery catheter is prudent and allows direct hemodynamic assessment and tailored therapy of preload, afterload, and contractility.

Patient Presentation (Continued)

Despite afterload optimization and significant improvement in filling pressures, attempts to wean dual inotropic support (dobutamine and milrinone) resulted in hypotension, hyponatremia, worsening urine output and a decline in renal function. He was deemed to be inotrope dependent.

An inpatient cardiac transplant evaluation was initiated given the severe biventricular systolic dysfunction, multiple recent hospitalizations, and stage D heart failure with NYHA class IV symptoms. Following the assessment by a multidisciplinary team, the patient demonstrated no absolute contraindications to heart transplantation. He was presented at the multidisciplinary transplant meeting and was listed for cardiac transplantation.

Discussion

This patient had 3 admissions in 6 months, diuretic escalation to maintain euvolemia, persistent symptoms, and had been on guideline directed medical therapy for at least a year including cardiac resynchronization therapy. He also required inotropic support to improve end organ function. Despite decongestion and medications optimization, weaning off inotropes was unsuccessful, and he is thus considered inotrope dependent. All those features should prompt rapid referral to centers with advanced heart failure capabilities.

Patient Presentation (Continued)

He was considered for durable left ventricular assist device placement for management of pump failure as a bridge to transplantation. Right ventricular function was evaluated and deemed suitable for left ventricular assist device (LVAD) placement, subsequently performed with no major complications.

Discussion

After transplantation listing, a decision needs to be made regarding circulatory support while waiting for a suitable organ donor. The use of mechanical circulatory support (MCS) with surgically implanted LVAD is rapidly evolving. Up to 40% of all listed heart transplant recipients receive MCS while awaiting a donor organ.

Patient Presentation (Continued)

He was discharged from the hospital after 12 days post-implantation. Discharge medications included aspirin, warfarin, digoxin, lisinopril, atorvastatin, and torsemide.

7.1 Case Discussion

7.1.1 Background

Patients with American College of Cardiology/American Heart Association (ACC/AHA) stage D heart failure who remain symptomatic despite optimal medical therapy are at a high risk of mortality, with ~25% survival at 1 year [2]. The treatment of choice for this patient population is cardiac transplantation, with survival rates near 90% during first year [3]. However, only a small percentage of patients are suitable candidates, and donor availability is limited, both curbing the rate of transplantation. Consequently, risk stratification for this patient population is an important step during evaluation for alternative advanced heart failure therapies. The first step is to recognize patients that might benefit from advanced heart failure interventions. There are certain clinical characteristics that can help identify this group (Table 7.1).

Prior to the current hospitalization, management of this patient has been directed by current guidelines. He was receiving optimal medical therapy, including β-blockade and inhibition of the renin-angiotensin-aldosterone system, limiting the maladaptive neurohormonal changes that are the pathologic hallmark of chronic HFrEF. Cardiac resynchronization therapy was performed, which can alleviate symptoms and improve mortality in HFrEF with left bundle branch block and widened QRS complex [1]. Despite optimal therapy, he was unable to stay out of the hospital with multiple acute heart failure exacerbation within a short period of time.

Table 7.1 Patient characteristics and clinical events associated with patients in advanced heart failure (ACCF/AHA)

Optimized on guideline-directed medical therapy
Recipient of cardiac resynchronization therapy, if indicated
Repeated >2 hospitalizations or ED visit for heart failure in the past year
Progressive deterioration in renal function
Weight loss without other cause (i.e. cardiac cachexia)
Intolerance to ACE inhibitors due to hypotension and/or worsening renal function
Intolerance to beta blockers due to worsening heart failure or hypotension
Frequent systolic blood pressure < 90 mmHg
Persistent dyspnea with dressing or bathing requiring rest
Inability to walk one block on the level ground due to dyspnea or fatigue
Recent need to escalate diuretics to maintain euvolemia
Progressive decline in serum sodium, usually to <133 mEq/L
Frequent ICD shocks

ACCF American College of Cardiology Foundation, *AHA* American Heart Association, *ED* emergency department, *ACE* angiotensin converting enzyme, *ICD* implantable cardioverter defibrillator

7.1.2 Advanced Heart Failure Assessment

General indications for heart transplantation are shown in Table 7.2. Advanced heart failure therapy options for this case are limited to cardiac transplantation, durable mechanical device support, or palliative care. In ambulatory patients, part of the evaluation includes a cardiopulmonary exercise stress (CPX) test. CPX provides an objective assessment of functional capacity in patients with heart failure and guides the decision to list a patient for cardiac

Table 7.2 Consideration for cardiac transplantation

NYHA class IIIb–IV refractory to maximally tolerated guideline-directed medial therapy
Reduced functional capacity as measured by cardiopulmonary stress testing
Malignant ventricular arrhythmias unresponsive to medical or surgical therapy
Intractable ischemic symptoms with inoperable coronary artery disease
Need for continuous inotropic support (i.e. inotrope-dependent)
Need for prolonged mechanical circulatory support

NYHA New York Heart Association

transplantation [4]. A maximal CPX test with a respiratory exchange ratio (RER) > 1.05 and achievement of anaerobic threshold with a peak Vo_2 (Vo_2max) ≤ 14 ml/kg/min or ≤12 ml/kg/min in the presence of a β-blocker can identify patients who would likely benefit of cardiac transplantation [5, 6]. In young patients (<50 years) and women, it is reasonable to consider using alternate standards in conjunction with peak Vo_2 to guide listing, including percent of predicted peak Vo_2 (≤50%). If the CPX is sub-maximal (RER < 1.05), ventilation equivalent of carbon dioxide (V_E/V_{CO2}) slope of >35 can be considered as a determinant in listing. However, listing patients based solely on the criterion of a peak oxygen consumption (Vo_2) measurement should not be performed [5].

Most patients will not be cardiac transplant candidates after evaluation. Contraindications to cardiac transplantation are shown in Table 7.3. The major hemodynamic factor that excludes cardiac transplantation is non-reversible pulmonary vascular hypertension, with pulmonary vascular resistance (PVR) > 5 Wood units, transpulmonary gradient >15 mmHg (TPG, or the mean PAP—mean PCWP), and PVR index (TPG/CI) > 6. If the pulmonary artery systolic pressure exceeds 60 mm Hg in conjunction with any 1 of the preceding

Table 7.3 Contraindications to heart transplantation

Severe irreversible pulmonary hypertension
Morbid obesity (BMI > 35 kg/m^2)
Advanced age (>70 years of age, relative)
Severe chronic obstructive pulmonary disease (F_{EV1} < 1 L/min)
Irreversible renal (eGFR <30 ml/min/1.73 m^2) or hepatic dysfunction
Uncontrolled diabetes—Associated with significant end-organ damage
Drug, tobacco or alcohol abuse currently or within the past 6 months
Non-adherence, lack of caregiver support, dementia
Active or recent malignancy
HIV/hepatitis C infection (for some centers is relative)
Severe peripheral vascular disease
Active infection

BMI body mass index, *eGFR* estimated glomerular filtration rate, *HIV* human immunodeficiency virus

3 variables, the risk of right heart failure and early death is increased.

Following the identification of pulmonary vascular hypertension, a vasodilator challenge is performed using different agents including nitroprusside, milrinone, prostacyclin or nitric oxide, among others. If the challenge is unsuccessful and PVR remains elevated, hospitalization with continuous hemodynamic monitoring may be considered, as PVR might decline after 24–48 hours of treatment with diuretics, inotropes and vasoactive agents. If PVR is still elevated, mechanical adjuncts, including intra-aortic balloon pump or left ventricular assist device (LVAD), may be considered to indicate reversibility of PVR [5].

Active malignancy and ongoing active infection are also absolute contraindications to transplantation. Recent malignancy can also be a problem and time to listing varies among centers depending on type of malignancy. Further discussion of other relative contraindications for cardiac transplantation is beyond the scope of this chapter.

7.1.3 Advanced Heart Failure Management

There are three major indications of use of LVAD: (1) as a bridge to transplantation (BTT) for patients who are "too sick" to wait for a donor, (2) as a destination therapy (DT) as a lifelong support for patients ineligible for a heart transplantation, and (3) as a bridge to decision (BTD) or bridge to recovery in circumstances when a patient presents in cardiogenic shock and it may not be possible to fully determine candidacy for transplantation or there is a need to assess neurological recovery [7].

The Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) provides a classification system used for patients being considered for MCS [8]. This patient is inotrope dependent, corresponding to INTERMACS profile 3. Table 7.4 lists each profile character-

Table 7.4 INTERMACS profiles used in MCS decisions

1. Critical cardiogenic shock, "crash and burn"
2. Progressive decline on inotropic support, "sliding on inotropes"
3. Stable but inotrope dependent, "dependent stability"
4. Resting symptoms, home on oral therapy
5. Exertion intolerant
6. Exertion limited
7. Advanced NYHA III symptoms

istic. Ideally, MCS interventions are considered and offered to a patient prior to reaching profile 1 or 2.

LVAD is one form of MCS. Other forms of MCS devices include IABP counterpulsation, Impella 2.5, 5, and CP (Abiomed, Danvers, MA, USA), and TandemHeart (Cardiac Assist Inc., Pittsburgh, PA, USA), all of which can provide hemodynamic support while a hospitalized patient is awaiting LVAD placement. Detailed discussion of MCS devices is beyond the scope of this chapter. Depict these mechanical support devices.

When considering long term MCS, patients should fulfill most of the functional, clinical, and hemodynamic criteria for transplant recipients. Special attention should be given to right ventricular function since right heart failure impacts both morbidity and mortality with device therapy [9]. In the study case, right ventricular stroke work index was 254 mmHg/ml/m^2 and the Michigan right ventricular failure risk score was 0, the former predicting increase possibility of prolonged inotropic use after LVAD [10] and the later predicting low likelihood of post-operative right ventricular failure [11]. Contraindications to left ventricular assist device implantation are shown in Table 7.5.

Table 7.5 Left ventricular assist device contraindications

Non-reversible end-organ failure (hemodialysis, hepatic cirrhosis, COPD)
Contraindication to anticoagulation
Infection
Severe right ventricular dysfunction
Comorbid disease limiting ability to rehab
Advanced cachexia and poor nutrition
Non-adherence to treatment plan
Lack of social support

COPD chronic obstructive pulmonary disease

Table 7.6 Left ventricular assist device complications

Bleeding
Infection
Stroke (ischemic and hemorrhagic)
Pump thrombosis
Aortic insufficiency
Right ventricular dysfunction

The initial LVADs implanted in the US delivered pulsatile blood flow form a volume displacement pump, driven either electrically or pneumatically. Currently, the devices most commonly used as LVADs provide continuous-flow. There are two FDA approved devices for bridge to transplantation, the HeartMate II [12] (Thoratec Corp, Pleasanton, CA, USA) and the HeartWare HVAD [13] (HeartWare Inc., Framingham, MA, USA). A comparison between both devices is seen in Table 7.6. HeartMate II is the lone LVAD approved for DT. If biventricular support is needed, the limited device options include total artificial heart (TAH) (Syncardia Systems Inc., Tucson, AZ, USA) and investigational compassionate use of HeartWare as biventricular support. Shows survival for continuous flow LVAD by pre-implant device strategy from INTERMACS.

Only about 30% of patients with continuous flow devices are free of major events (first occurrence of infection, bleeding, device malfunction, stroke or death) during the first year post implantation [14], and a clear discussion with the patient needs to address the pros-cons of such a therapy prior to LVAD placement. A list of complications is shown in Table 7.7. During the shared decision-making process of advanced heart failure management, the patient may value a more conservative approach and wish to maximize time at home at the end stages of heart failure. In this scenario, the patient's goals can be met with home inotropic therapy and palliative care.

Table 7.7 Durable continuos-flow ventricular assit devices

HeartMate II	HeartWare
Axial (continuous) flow	Centrifugal (continuous) flow
Valveless	Bearingless
Pump output 3–10 l/min	Pump output 3–10 l/min
Average speed 8600–9600 RPM	Average speed 2600–3200 RPM
Weight 0.46 pounds	Weight 0.3 pounds
Small infra-diaphragmatic pocket	Supra-diaphragmatic-intrapericardial
FDA approval BTT 2007/ DT 2009	FDA approval BTT 2012/DT 2017

RPM revolutions per minute, *FDA* Food and Drug Administration, *BTT* bridge to transplant, *DT* destination therapy

Advanced heart failure and its attendant therapeutic options represent a growing arena in cardiology. Decision-making is complex, and requires a collaborative effort amongst all health care professionals striving to improve mortality and the quality of life in patients with advanced heart failure.

Key Points

- End stage heart failure has a very high one year mortality
- Both the early identification of advanced heart failure despite maximal guideline-directed therapy and referral to advance heart failure specialist are important to improve outcomes in this patient population
- Cardiac transplantation is the treatment of choice in advanced heart failure therapy, but is limited by donor availability
- Mechanical circulatory support provides time during the clinical decision making process for cardiac transplantation listing

- Evaluation for cardiac transplant listing is complex and involves functional, clinical, and hemodynamic assessment
- Extended survival and improvement in quality of life has been achieved with new durable continuous flow left ventricular assist devices

Question 1

One of the following is NOT a complication after left ventricular assist device (LVAD) placement

A. Right heart failure
B. Infections
C. Bleeding
D. Aortic stenosis
E. Thromboembolic events

Correct Answer: D

The transition to continuous flow LVADs has been associated with a significant decline in rates of adverse events and better long-term survival. However, LVAD related complications can occur in up to 60% of patients by 6 months post implantation [15]. Right heart failure can occur in 10–40% of patients after the insertion of the LVAD [16–18]. Infections are a commons cause of morbidity. Rates of infection can range from 30–50% where driveline infections occur in approximately 19% of LVAD recipients within the first year [14]. The most common adverse event after LVAD implantation is bleeding. Several factors have been implicated including vascular dilation (arterio-venus malformation—AVM) resulting from low pulse-pressure system, vonWillebrand syndrome and anticoagulation therapy. Every LVAD patient is on anticoagulant therapy and antiplatelet [19]. This can include gastrointestinal bleeding (up to 21% first year) and bleeding into the central nervous system [20]. Aortic insufficiency (AI) and not aortic stenosis, is a frequent complication and can occur between 11% and 42% [21]. Valve incompetence can lead to worsening heart failure and

decreases pump efficiency. Thromboembolic events can include transient ischemic attacks, cerebrovascular accidents, pump thrombosis or arterial non-central nervous system embolism. Neurologic events can have an incident of 0.064–0.082 events per patient per year [22]. Pump thrombosis can cause embolic strokes and life threatening device malfunction.

Question 2

The pre-implant device strategy of the majority of left ventricular assist devices implanted in the United States is:

A. Bridge to transplantation (BTT)
B. Destination therapy (DT)
C. Bridge to decision (BTD)
D. Bridge to recovery

Correct Answer: B

About 30% patients are listed for heart transplantation at the time of device implantation. This is called bridge to transplant (BTT).

There has been a dramatic increase in the proportion of implants for destination therapy. Destination therapy (DT) refers to a long-term use of LVAD's as an alternative to transplantation in patients who are ineligible for cardiac transplantation. About 45% of LVADS are implanted as DT. Some patients might receive an LVAD prior to a final decision on their transplant eligibility and they are called bridge to decision (BTD). It is about 31% of all implants. Bridge to recovery is generally implanted as DT or BTT. If myocardial function is regained, explantation of the pump can be considered [14].

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Chapter 8
Heart Failure with Preserved Ejection Fraction

Danyaal S. Moin and Gregory Lewis

Case Summary

A 62-year old male with a history of hypertension, diabetes mellitus, and prior tobacco use is referred to the clinic for evaluation of worsening dyspnea on exertion. He has had diabetes mellitus for >10 years managed on oral agents. He is also a former 30 pack-year smoker (quit 5 years earlier). His medical regimen includes aspirin, pravastatin, lisinopril, and glyburide.

Over the course of the past year, he has noted significant shortness of breath when walking around a parking lot and climbing stairs. Six months earlier, an electrocardiogram revealed sinus rhythm with a normal QRS duration and non-specific ST-T wave changes. Echocardiography revealed a left ventricular ejection fraction of 68%, normal atrial and ventricular dimensions, and mild aortic insufficiency. Estimated right ventricular systolic pressure was 33 mmHg, and there was no left ventricular hypertrophy. Treadmill exercise tolerance testing revealed exertional dyspnea limiting further exercise at 8 min on a standard Bruce protocol with non-specific ST changes and a hypertensive response to exercise (resting 110/60, peak exercise 220/120 mmHg). Coronary angiography

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revealed no significant epicardial coronary artery disease. Given his persistent symptoms, he was referred for pulmonary function testing that revealed FEV_1 78% predicted and FVC 87% predicted. Chest radiography is normal.

On examination, he is noted to have a blood pressure of 134/68, heart rate 74/min, and oxygen saturation of 98% on room air. His jugular venous pressure is 6 cm H_2O and his cardiovascular exam reveals a normal S_1 and S_2 without abnormal heart sounds. His pulmonary exam shows clear lung fields. His serum chemistries are normal with a NT-proBNP of 392 pg/ml. His hemoglobin is 13 gm/dl (hematocrit 35%).

8.1 Step 1: What is the Cause of Exertional Dyspnea? Does My Patient Have "Heart Failure with Preserved Ejection Fraction" (HFpEF)?

While the clinical entity has been described for several years the precise definition of HFpEF remains controversial, an ongoing debate that has both research and therapeutic ramifications. The American College of Cardiology and the European Society of Cardiology have posited standard definitions of HFpEF (Table 8.1). HFpEF should be on the differential diagnosis of a patient with symptoms of heart failure, as symptoms of HFpEF broadly mirror that of patients with heart failure with reduced ejection fraction (HFrEF). Echocardiographic parameters including tissue Doppler, blood flow Doppler analysis, and biomarkers are utilized in the joint American Society of Echocardiography and European Association of Cardiovascular Imaging algorithm for diagnostic testing of diastolic dysfunction [1].

In this case, our patient has had progressive dyspnea of unclear etiology, predominantly on exertion, without any clear diagnosis (e.g., severe pulmonary or valvular heart disease, anemia, clear LV systolic dysfunction). He has had an extensive evaluation for causes of dyspnea, including chest

Table 8.1 Categorization of heart failure by left ventricular ejection fraction

LVEF (%)	Status	Description
>50 (ACC); ≥50 (ESC)	HFpEF	Traditional category of patients with HFpEF
41–49 (ACC); 40–49 (ESC)	HFpEF, borderline (ACC); HFmrEF (ESC)	Mild left ventricular dysfunction but above threshold for HFrEF (LVEF < 40%)
>40 (ACC)	HFpEF, improved	Previous patients with HFrEF with subsequent improvement in LVEF
<40 (ACC, ESC)	HFrEF	Distinct phenotype of heart failure with reduced LVEF

Adapted from American College of Cardiology Foundation/American Heart Association (ACCF/AHA) [2] and European Society of Cardiology (ESC) [3] guidelines for the diagnosis and management of heart failure. *LVEF* left ventricular ejection fraction, *HFpEF* heart failure with preserved ejection fraction, *HFrEF* heart failure with reduced ejection fraction, *HFmrEF* heart failure with mildly reduced ejection fraction

radiography, stress testing and echocardiography, pulnonary function testing, coronary angiography, and laboratory evaluation. At this point, further provocative tests to phenotype dyspnea physiology may be helpful.

Case Summary 2

He is referred for cardiopulmonary exercise testing (CPET) on a cycle ergometer with concomitant right heart catheterization to understand the etiology of his dyspnea. Representative images from his study are provided below in Figs. 8.1, 8.2, and 8.3. Baseline right heart catheterization at rest reveals a mean right atrial pressure of 4 mmHg, a pulmonary arterial pressure of 27/12 (mean 18), a pulmonary capillary wedge pressure (PCWP) of 5, and a thermodilution cardiac output of 5.0 L/min. Blood pressure was 150/77. CPET reveals a peak oxygen consumption (VO_2) of 17.3 mL/kg/min (68% predicted for

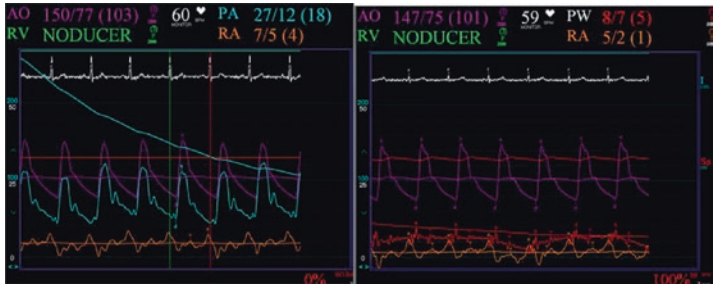

FIGURE 8.1 Baseline hemodynamics at rest

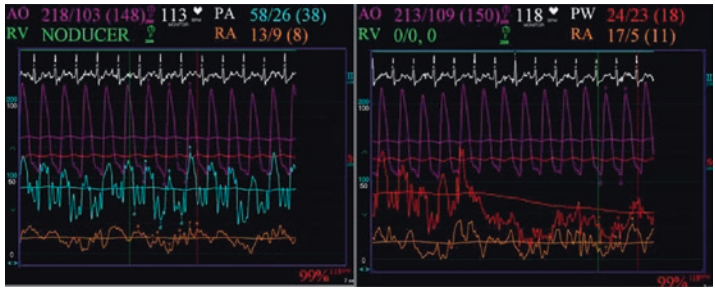

FIGURE 8.2 Right heart hemodynamics at peak exercise during CPET

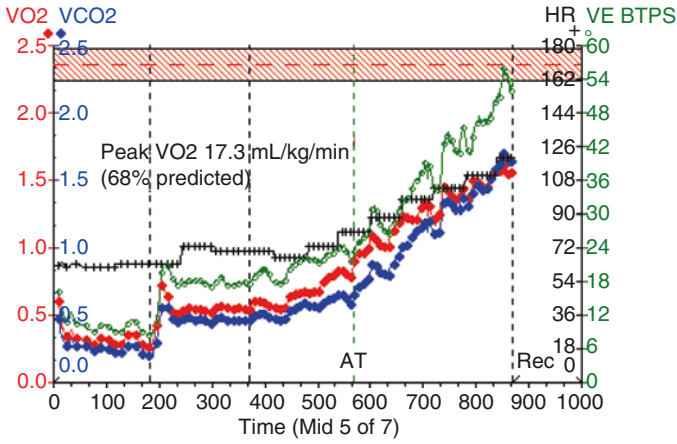

FIGURE 8.3 Changes in oxygen consumption, carbon dioxide production, and minute ventilation are demonstrated during this patient's invasive CPET testing

age/sex/body-size matched controls). During exercise, blood pressure rises to 218/103 mmHg. Mean right atrial pressure rises to 8 mmHg, pulmonary arterial pressure rises to 58/26 mmHg (mean 42), and PCWP rises to 27 mmHg with a corresponding thermodilution cardiac output of 10.7 L/min.

Query

When normal, which of the following *resting* hemodynamic parameters exclude HFpEF?

A. Right atrial pressure
B. Mean pulmonary arterial pressure
C. Pulmonary capillary wedge pressure
D. Diastolic blood pressure
E. Cardiac output
F. None of the above

8.2 Step 2: How Can Invasive Hemodynamic Testing Be Utilized in the Diagnosis of HFpEF?

Once appropriate clinical history has been obtained, the diagnostic gold-standard for HFpEF has been cardiac catheterization with use of a conductance catheter to obtain continuous left ventricular pressure and volume measurements and produce pressure/volume loops. This testing is not feasible in all patients and centers and it is reasonable that noninvasive testing is favored to establish the diagnosis of HFpEF. Echocardiographic parameters of diastolic dysfunction have been found to correlate with invasive hemodynamic measurements. Guazzi et al [4] demonstrated that E/e' (the ratio of the mitral peak early and mitral annular velocities) has been shown to correlate with peak oxygen uptake and ventilator efficiency. However, use of hemodynamics (via concomitant right heart catheterization or exercise echocardiography) may support a diagnosis of HFpEF. Early hemodynamic HFpEF studies, for example, demonstrated a blunted stroke

volume response to exercise due to a fixed end-diastolic volume in the setting of HFpEF [5]. In an invasive exercise study comparing patients with HFpEF to healthy controls, those with HFpEF stopped exercise earlier and had a higher PCWP/peak work ratio driven mainly by a lower work rate [6]. Borlaug et al [7] demonstrated that patients with HFpEF demonstrate normal or only slightly abnormal invasive hemodynamics at rest when compared to controls. These differences become significantly magnified with exercise including changes in right atrial pressure, mean pulmonary arterial pressure, pulmonary capillary wedge pressure, left ventricular end diastolic pressure (LVEDP), and cardiac index. A subsequent study reproduced these findings, showing that HFpEF patients demonstrated dynamic increases in left ventricular filling pressures and left ventricular stiffness during supine exercise [8]. These hemodynamic changes are not simply diagnostic minutiae: Dorfs and colleagues demonstrated that both PCWP in isolation and PCWP when normalized for peak work predicted long-term mortality [9].

The patient presented in this vignette is a common one that is encountered in clinical practice, specifically one that has dyspnea of uncertain etiology. In this case, *while resting hemodynamics were within a "normal range,"* comprehensive CPET exercise testing with hemodynamic assessment demonstrated that the hypertensive response to exercise and impaired aerobic capacity (peak VO_2) was accompanied by a rise in central filling pressure (PCWP and PA pressure) suggesting exercise-induced increases in LV filling pressure as a significant contributor to his symptoms.

Therapies directed at vasodilatation during exercise (e.g., nitrates) and optimal control of filling pressure were instituted with improvement in exercise capacity and symptoms.

Answer to Question

(F), none of the above

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Chapter 9
Management of Cardiogenic Shock

Robert A. Montgomery and Robb Kociol

Case Summary

A 52 year old man with no known past medical history presents to the emergency department with 24 hours of chest pain, nausea and vomiting. An initial EKG shows a right bundle branch block (RBBB) and ST elevations in anterolateral leads (Fig. 9.1). He is given intravenous heparin, prasugrel and aspirin and taken directly to the cardiac catheterization lab. Coronary angiography reveals chronic appearing 100% right coronary artery (RCA) occlusion with left to right collateralization and 100% left anterior descending (LAD) artery occlusion. Two drug-eluting stents are placed into the LAD with restoration of TIMI 3 flow (see Table 9.1 for definition). Left ventriculogram reveals diffuse hypokinesis and a left ventricular end-diastolic pressure (LVEDP) of 30–35 mmHg. The patient is confused and not following commands. An intra-aortic balloon pump is placed. Arrangements are then made to transfer to tertiary care center for further management.

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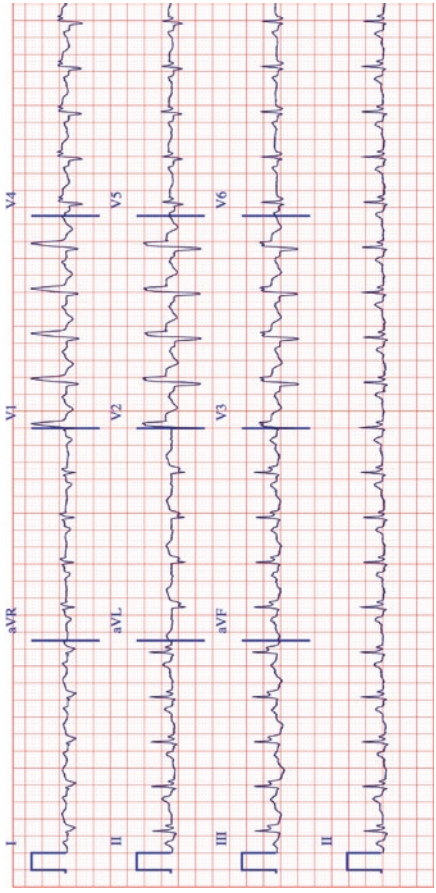

FIGURE 9.1 EKG on presentation, showing right bundle branch block (RBBB) and ST elevations in anterolateral leads

Table 9.1 Definitions of coronary blood flow in the TIMI Trial [1]

Grade 0	No flow beyond occlusion
Grade 1	Contrast passes distal to occlusion but does no fully opacify vessel
Grade 2	Contrast passes distal to occlusion and opacifies coronary artery but at diminished rate
Grade 3	Contrast passes distal to site of occlusion at normal rate

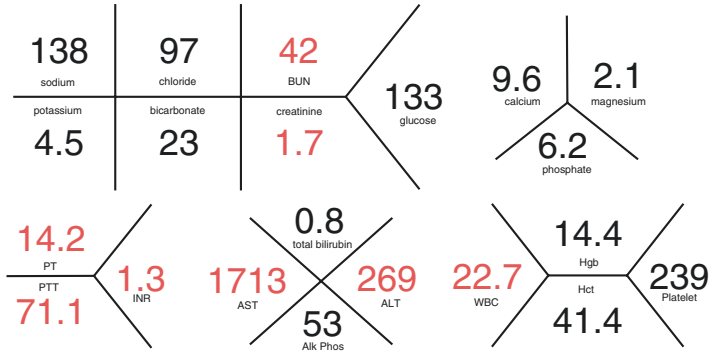

Figure 9.2 Initial Laboratory Values on Arrival to Accepting Cardiac Critical Care Unit demonstrating multi-organ system injury

On arrival to the accepting cardiac critical care unit, the patient is ill appearing with blood pressure of 102/76, heart rate of 114, respiratory rate of 24 with oxygen saturation of 96% on room air. He is tachycardic with a noted summation gallop and clear lungs sounds. His distal extremities are noted to be cool. A transthoracic echocardiogram reveals extensive regional biventricular systolic dysfunction (LVEF 10–15%) with LVEDD of 4.3 cm. Initial labs demonstrate kidney injury and hepatic injury (Fig. 9.2). Initial cardiac biomarkers are notable for CK of 13,461, CKMB 404 and Troponin-T of 24.15. As serial lactate measurements show a gradual rise despite continued intra-aortic balloon pump support, a pulmonary artery catheter is placed to guide therapy. Initial measurements reveal central venous pressure (CVP) of 9 mmHg, pulmonary artery pressure (PAP) of 30/25 mmHg, pulmonary capillary wedge pressure (PWCP) of 22 mmHg

and cardiac index (CI) of 1.4 L/min/m^2, systemic vascular resistance (SVR) 1500 dynes and mixed venous oxygen saturation (MVO) of 55%. Based on these measurements a change of management is initiated.

9.1 What is the Current Diagnosis? What are the Next Steps in Management?

This patient presents following ST elevation MI with evidence of cardiogenic shock despite percutaneous intervention with restoration of coronary perfusion. While we have limited information regarding both this patient's prior medical history and current presentation, we are able to make several inferences based on the data presented thus far. Furthermore we may be able to make some predictions about his medium to long-term outcome. With this in mind we will best determine next step in management.

There are several factors that suggest pre-existing cardiovascular disease in this patient. First, his coronary angiography shows chronic total occlusion of RCA with left to right collateralization suggesting pre-existing obstructive coronary artery disease [2]. Additionally, his initial PCWP reading is elevated but he does not have severe pulmonary edema suggesting pulmonary adaptation to elevated pulmonary vascular pressures with increased lymphatic recruitment and decreased capillary permeability [3].

We have several details which suggest a late presentation to this patient's acute myocardial infarction. First, his initial EKG (Fig. 9.1) demonstrates the natural evolution of STEMI with Q-waves developing across antero-lateral leads, consistent with a delayed presentation [4]. He has already developed hepatic injury and renal impairment indicative of prolonged shock [5]. (Fig. 9.2). Finally, his cardiac biomarkers also suggest a delayed presentation. Not only are they significantly elevated, but the trends in both CK-MB and troponin show a serial decline, which would be in keeping with a greater than 24 h delay in presentation [6]. Further

supporting this is the initial echocardiogram which showed a non-dilated left ventricle but ejection fraction of 10–15%, consistent with delayed presentation of acute anterior MI with loss of collateral flow to the inferior territory, accounting for the entire left ventricle.

Prior studies tracking the recovery of ventricular function after acute myocardial infarction would seem to provide some level of optimism for this patient's outcome as there is often a general trend toward improvement within 90 days [7]. This phenomenon of initial depression with recovery of function is often thought to be evidence for the concept of myocardial stunning, where myocytes protect themselves from ischemia by decreasing contractility until perfusion is restored. These same studies also give us reason to be pessimistic of recovery in this particular patient's case as this patient has many characteristics of patients who did not improve after MI.

Specifically, his low ejection fraction of 10–15% and impressive elevation in his cardiac biomarkers bode poorly for recovery. With this in mind, it is important to develop a treatment plan that anticipates prolonged or permanent left ventricular power failure and to initiate a workup for both durable left ventricular assist device placement and transplant evaluation.

In terms of this patient's immediate management, we have both mechanical and pharmacologic means to support this patient. The patient is already being supported by intra-aortic balloon pump counterpulsation, which is the most common mechanical support device employed in this clinical situation. While there is growing skepticism regarding the benefits of this means of mechanical support (which we will discuss later), its' use remains a Class IIa recommendation by the 2013 ACC/AHA in patients who develop cardiogenic shock after ST elevation MI despite medical therapy (level of evidence B) [8].

Given evidence of ongoing cardiogenic shock despite establishing re-perfusion and employing IABP counterpulsation, I believe that the patient requires vasoactive medica-

tions. It should be noted that this ordering of interventions runs counter to official guidelines, where IABP counterpulsation is recommended for cardiogenic shock refractory to initiation of vasoactive medications; however, this tends to be the most common ordering of interventions in practice as IABP counterpulsation is often initiated at time of revascularization [8, 9]. There is physiologic and logistical reasoning to support this ordering of interventions, as mechanical support offloads the failing ventricle and thus decreases myocardial demand whereas inotropic and vasopressor medications increase myocardial oxygen demands [10, 11]. However, clinical trials to date have not shown mechanical offloading at time of re-perfusion to be associated with measurable benefit [12].

In this situation, I believe we can use the central hemodynamic information provided by the PA catheter to guide medication selection. We now know from that this patient has a depressed cardiac index in combination with elevated system vascular resistance with a preserved mean arterial pressure (MAP) suggesting he would benefit from both inotropic and vasodilatory medications. For inotropy, it is reasonable to consider medications such as dobutamine, norepinephrine or dopamine for their beta1 activity. For afterload reduction as well as improvement in collateral blood flow, sodium nitroprusside or nitroglycerin are optimal given their short half-life and ease of titration. I would note however that often afterload reduction should be used with cautions as AMI tends to be associated with a systemic inflammatory response leading to vasodilation [13].

Case Summary

The patient is started on dobumatine for inotropic support and intravenous sodium nitroprusside for afterload reduction to target central hemodynamics of CVP 10–12 mmHg, PAD 18–20 mmHg and CI 2.2 L/min/m with MAP 65–70 mmHg which results in initial improvement in serial lactate measurements and cardiac index and normalization in mixed venous oxygen saturation measurements.

Overnight, the patient develops a fever to 101.5 and is increasingly tachycardic. Given his tenuous clinical status, he is empirically started on broad-spectrum antibiotics though no clear source is identified with chest radiography, urine and blood cultures. Over the next 12 h, his MAP falls below 65 mmHg despite weaning and eventual discontinuation of sodium nitroprusside and escalation of dobutamine. Norepinephrine is initiated with improved hemodynamic stability. After 72 h of continuous 1:1 IABP circulatory support, the couunterpulsation support is weaned to 1:2. The patient becomes hypotensive and PA catheter measurements reveal worsening hemodynamic indices. A bedside echocardiogram shows no improvement in cardiac function though preserved right ventricular function.

9.2 Why is the Patient Still Dependent on Circulatory Support? What is the Next Step in Management?

Seventy-two hours into this patient's hospitalization, we now have evidence for what we initially suspected and most feared for this patient since his initial presentation: he is proving to be dependent on mechanical circulatory support. There are several complicating factors to this patient's candidacy for durable device placement (e.g., implantable Left Ventricular Assist Device) or transplant that should be considered. First, his current clinical stability; data from the INTERMACS (Interagency Registry for Mechanically Assisted Circulatory Support) registry has shown that unstable patient's tend to have higher mortality and more postoperative complications when transitioned to a durable mechanical support device [14]. Guidelines in this population recommend transition to temporary mechanical support for stabilization prior to durable device placement in order reduce complications and mortality [15].

One other complication to this patient's candidacy for durable cardiac support or transplantation is his current

fever. Fever following MI is common development and has been described as early at 1950 as part of the Post-Myocardial Infarction Syndrome. Studies thereafter have shown that it occurs in over half of patients with myocardial infarction, and that fevers beyond the first 4 days of care were likely to be attributed to an infectious etiology [16]. Given that his fever occurred in the first 24 h of presentation, I favor a non-infectious etiology; however this is not a certainty and as such I would continue empiric antibiotics. This decision is not without trade-offs however, as any infection is a relative contra-indication to placing a durable mechanical assist device or undergoing cardiac transplantation.

In the absence of durable therapies, we would then be left to consider which intermediate-term mechanical support devices to use for this patient. There are several questions that help guide this decision. First, is the patient expected to have ventricular recovery or to be a candidate for definitive treatment in the form of cardiac transplantation (bridge to transplant) or permanent LVAD (destination LVAD)? This patient is relatively young and previously healthy and has no obvious contraindications to cardiac transplantation once stabilized. Temporary mechanical support also affords the transplant to team the ability to assess the patient's end-organ recovery following the resolution of his shock [17].

And so the next question would be "how long would this bridge support be needed until he can undergo definitive therapy?", where the relevant demarcating line is "hours to days," or "days to weeks." This is a critical question as certain devices are only approved for limited duration of use. For example, while offering less invasive percutaneous implantation, the Impella and TandemHeart devices are generally only approved for the time course of hours to days, and as such are unlikely the proper assist device for this patient [18, 19]. In patients like ours who may be able to proceed directly for transplant or may need further optimization prior to long-term LVAD placement, it makes sense to choose a support device that can be in place for days to weeks at a time.

Finally, the last question to ask is "What is the status of the right ventricle?". If there is concern for right ventricular

(RV) failure a dual LVAD and RVAD (or BiVAD) system should be employed, or at least be available. As right ventricular output is in series with left ventricular output, depressed right ventricular function can lead to ongoing cardiogenic shock despite adequate left ventricular mechanical support. This is the pathophysiologic basis for why ventricular arrhythmias may still be life-threatening in patients with LVADs. RV function is difficult assess in setting of left ventricular failure. Aside from echocardiographic findings of severe tricuspid regurgitation or left ventricular underfilling, RV failure is often intuited by elevation in CVP more pronounced than mean pulmonary artery pressure, which is not present in this patient [20]. However, perhaps a more useful metric for predicting RV failure following LVAD placement is Pulmonary Artery Pulsatility Index (PAPI), which is the PA systolic pressure minus the PA diastolic pressure over the central venous pressure [21]. In this patient his PAPI is low, which is worrisome for RV failure. Additionally, given the patient's preexisting RCA disease it would not be unreasonable to have heightened concern for RV failure as well. As such, a mechanical circulatory support system that allows biventricular support should be preferred as the next line of circulatory support in this patient.

Case Summary

On hospital day 4, the patient develops sustained atrial fibrillation with rapid ventricular response. He becomes increasingly tachypneic and hypoxic and is placed on BiPAP. A chest radiograph demonstrates marked pulmonary edema. Despite initiation of intravenous amiodarone and conversion into sinus rhythm, he has progressive respiratory distress and hypoxia and is intubated and placed on mechanical ventilation. Given his decline despite dual inotropic agents and continued IABP support, he is taken the operating room where the IABP is exchanged for a left atrial to aorta CentriMag® ventricular support system as a bridge to transplant. A right ventricular support system is considered but after implantation of LVAD, right atrial and left atrial pres-

sures equalize and there is no atrial or ventricular bowing on intra-operative transesophageal echocardriography (TEE) to suggest RV dysfunction. Radial arterial line tracings reveal limited pulsatility after the procedure with pump flow at 4.5 l/min at 4000 rpm. Over the next 10 days, the patient is able to be extubated. His fevers and hypotension gradually resolve and his markers renal dysfunction and hepatic injury all resolve. Serial echocardiograms do not reveal any myocardial recovery and a transplant workup is completed. His Centrimag® LVAD is exchanged for long-term HeartWare® LVAD on Hospital Day 12. On day 35 the patient is discharged to a cardiac rehabilitation facility. He is listed as UNOS Status 1A for cardiac transplantation.

9.3 Conclusion

This patient's presentation demonstrates many of the life threatening complications of cardiogenic shock following acute myocardial infarction. An integral part of management of patients with acute myocardial infarction is identifying cardiogenic shock and employing the proper supportive therapies. One area where the treatment of cardiogenic shock is most different than treatment of other forms of shock is the use of temporary mechanical circulatory support devices. Practice guidelines about these devices are a constantly changing subject as more devices and new trials emerge [8, 15, 22]. Table 9.2 provides a broad overview of the various mechanical circulatory devices that can be deployed in the care of critically ill patient with cardiologenic shock.

Appendix
IABP Counterpulsation

Intra-aortic balloon pump counterpulsation is the most common temporary mechanical support device and have been in use since since 1967 [23]. Intra-aortic balloon pumps (IABPs)

TABLE 9.2 Selected mechanical circulatory support devices, level of support and insertion methodology

Mechanical circulatory support device	Contra-indications	Level of support	Flow	Left ventricular unloading	Afterload reduction	RV support available	Access	Common complications
Intra-aortic balloon pump	Aortic regurgitation; aortic dissection; abdominal aortic aneurysm; chronic end-stage heart disease with no anticipation of recovery; aortic stents	Partial	Pulsatile, assist provided by inflation/ deflation of intra-thoracic balloon	Yes	Yes	No	Arterial (femoral, left axillary or left subclavian)	Infection at site of insertion; bleeding at insertion site; limb ischemia; thrombocytopenia; aortic dissection; displacement of the balloon catheter obstructing left subclavian artery or renal artery perfusion

(continued)

TABLE 9.2 (continued)

Mechanical circulatory support device	Contra-indications	Level of support	Flow	Left ventricular unloading	Afterload reduction	RV support available	Access	Common complications
Impella devices	Mechanical aortic valve; AVA < 0.6 cm^2. Moderate to severe aortic insufficiency; significant right heart failure; presence of an atrial or ventricular sepal defect; left ventricular rupture; inability to anticoagulation		Continuous via Archimedes screw impeller	Yes	No	No, unless combined with Impella RP	Arterial	Aortic valve injury; bleeding; cerebral vascular accident/ stroke; hemolysis; limb ischemia; thrombocytopenia and vascular injury
2.5	As above	Partial 2.5 L/ min	As above	Yes	No	No	Arterial	As above
CP	As above	Partial 3.0 L/ min	As above	Yes	No	No	Arterial	As above

5.0	As above	Full 5 L/min	As above	Yes	No	No	Arterial requires vascular cut down	As above
Impella RP	Mechanical tricuspid valve; severe valvular stenosis or valvular regurgitation of the tricuspid valve or pulmonary valve; mural thrombus of the right atrium or vena cava; inability to anticoagulation	Partial 4 L/min	As above	No, only RV	No	Yes	Venous (IVC to PA)	Bleeding; cerebral vascular accident/ stroke; hemolysis; limb ischemia; thrombocytopenia and vascular injury

(continued)

TABLE 9.2 (continued)

Mechanical circulatory support device	Contra-indications	Level of support	Flow	Left ventricular unloading	Afterload reduction	RV support available	Access	Common complications
Tandem heart	Severe peripheral vascular disease, atrial thrombus, inability to anticoagulation	Full 4 L/min	Continuous	No	Yes	Yes	Arterial and venous	Bleeding; cerebral vascular accident/stroke; hemolysis; limb ischemia; thrombocytopenia and vascular injury; atrial perforation, creation of ASD, migration of info cannula to right atrium or pulmonary vein
Centrimag/VA ECMO	Severe peripheral vascular disease, inability to anticoagulation, atrial thrombus (particularly right atrial)	Full 10 L/min	Continuous	No	No	Yes	Arterial and venous	Bleeding; cerebral vascular accident/stroke; hemolysis; limb ischemia; thrombocytopenia and vascular injury, pump thrombosis

are made up of two components: a double-lumen balloon positioned in the thoracic aorta via percutaneous femoral artery access, and a console that inflates and deflates the balloon with 30–60 cc of helium in synchrony with the cardiac cycle.

The devices were designed to address the central therapeutic dilemma of cardiogenic shock, namely maintaining perfusion to coronary arteries comes at the expense of increased afterload, which only increases stress and myocardial demand for a failing left ventricle. An intra-aortic balloon pump (IABP) effectively solves this issue by decoupling afterload and coronary perfusion. By inflating a balloon in the aorta during diastole, the balloon augments diastolic filling pressure to the coronary arteries. Furthermore by deflating during systole, the intra-aortic balloon is a able to decrease afterload and mechanically offload the left ventricle, decreasing myocardial demand.

Evidence

Based largely on compelling physiologic principles and the lack of other alternatives, intra-aortic balloon pumps were widely adopted in the use of cardiogenic shock, especially in case of acute myocardial infarction. Based on favorable observational studies that followed the ACC/AHA gave a Class I indication for IABP in the treatment of cardiogenic shock secondary to acute myocardial infarction [24]. However, as mentioned above there is growing skepticism regarding the role of IABP even in cardiogenic shock. Much of this has been driven by the SHOCK II trial [25], which randomized 600 patients with acute myocardial infarction with cardiogenic shock to IABP support or medical management. Using an intention to treat analysis, there was no observed statistically significant differences in 30 day all-cause mortality (39.7% and 41.3%; $p = 0.69$) or in multiple secondary end points. The authors of the trial and several commenters have raised limitations to the study, including the lower than expected mortality rate leading to underpowering, a significant number of cross-overs to IABP therapy, and lack of long term followup [9]. Based on the SHOCK-II trial and several other smaller randomized control trials which also did not

show clear benefit, the ACC/AHA revised their recommendation a Class IIa indication in patients who develop cardiogenic shock following acute MI despite medical therapy (level of evidence B) [8]. The ESC/EACTS Guidelines on Myocardial Revascularization went further and downgraded IABP use in AMI complicated by cardiogenic shock to a Class III recommendation indicating that routine use of IABP in patients with cardiogenic shock is not recommended [22]. Regardless of the equivocal current supportive data and the need for further study, IABPs remain the most common form of temporary mechanical circulatory support, and knowledge of their uses and limitations is needed for patient care.

Complications

The two most common types of complications that require troubleshooting with IABPs is ensuring proper anatomical position and proper timing of inflation and deflation. In each case, improper use cannot not only limit the effectiveness of the support but cause significant harm.

The ideal positioning of the IABP is 1–4 cm below the aortic arch, typically within 2nd rib space just above the left main bronchus and usually 2–3 cm distal take off of the subclavian artery. The tip of the IABP is radio-opaque allowing for fluoroscopic and radiographic confirmation of correct placement. An improperly positioned IABP risks occlusion of the subclavian artery proximally and renal arteries distally. With this in mind, urine output and a careful vascular exam should be monitored regularly.

Just as anatomical balloon location should be evaluated with any major change in patient position or clinical status, the console function should also be examined regularly via inspection of aortic pressure waveforms to assess for problems related to timing of inflation/deflation and under/overfilling of the balloon.

IABP inflation is triggered either by sensing cardiac electrical activity or aortic pressure sensing. In normal function, inflation is initiated when aortic valve closes and continues until the initiation of the next ventricular contraction, encompassing all of diastole. (See Fig. 9.3) Common timing malfunc-

tions include early and late activation in either inflation or deflation. The most concerning malfunctions exist when the balloon is inflated during systole as this impairs cardiac output by increasing afterload. This can be seen in early inflation or late deflation. Late inflation and early deflation are not dangerous and merely reduce the physiologic benefit of ventricular support. (See Figs. 9.3, 9.4, 9.5, 9.6, and 9.7)

Other well described complications of IABPs include anemia and thrombocytopenia from mechanical shearing, vascular injury from insertion site leading to limb ischemia, dissection, pseudo-aneurysm formation. Finally, while rare,

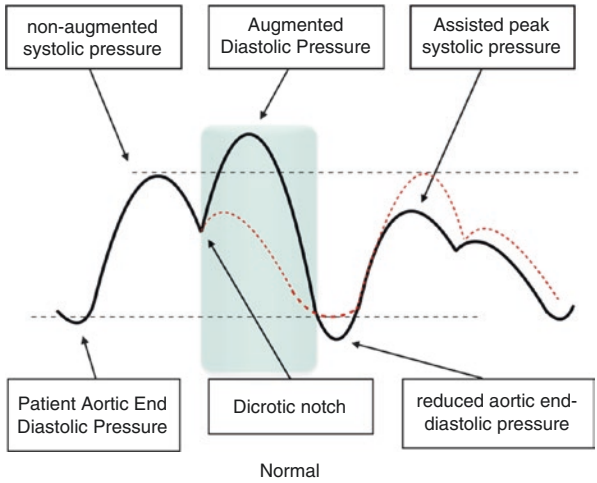

FIGURE 9.3 Analysis of IABP waveforms requires the balloon pump to be set to a 1:2 setting, which times balloon inflation to every other ventricular beat. This allows the clinician to observe both a normal and a balloon assisted cardiac cycle. An example of typical unassisted cardiac cycle followed by balloon assisted cycle is included above. The dotted horizontal lines mark unassisted systolic and diastolic blood pressures. The dotted red line is included to demonstrate a non-assisted cycle for comparison. The green box is included to illustrate timing of balloon inflation. In this example the black line represents an initial systolic waveform tracing followed by a pump generated waveform, which generates a sharp "v" appearance with increased diastolic pressures during balloon inflation) and then the systolic waveform seen following a balloon waveform with reduced systolic pressure

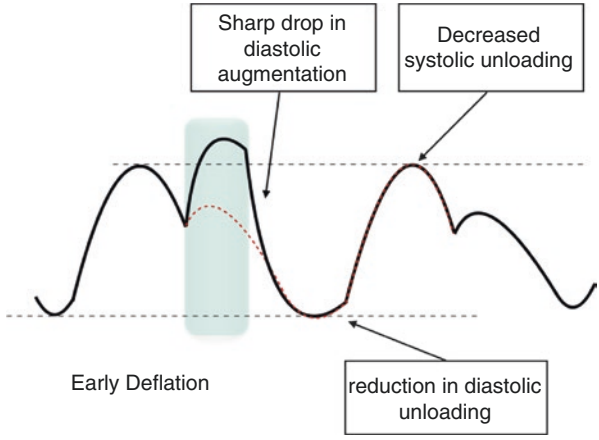

FIGURE 9.4 Earl Deflation: Optimal function of the IABP involves inflation of the IABP for the entire diastolic cycle and without inflation during the sytole. The most worrisome timing complication involves inflation of the balloon during systole as this leads impairs cardiac output. Early deflation is worrisome in that it results in the loss of afterload reduction which is the a goal of IABP therapy. Notice the sharp drop following diastolic inflation. Diastolic augmentation also becomes sub-optimal. This results in sub-optimal coronary perfusion, potential for retrograde coronary and carotid blood flow, suboptimal afterload reduction and increased myocardial oxygen demand

the balloon can rupture leading to a gas embolus. IABP are currently programmed to detect ruptures, and will attempt to aspirate helium from the aorta.

Duration of use

There is no established recommendation on how long these devices can be used. Observational data has shown that these devices can be used for as long as 20 days, though the most common duration of use is 2 days [26, 27]. These studies all show that there is a correlation between complications and duration of support. With this in mind, weaning of mechanical support should be attempted if the patient has reached a clinical stable state.

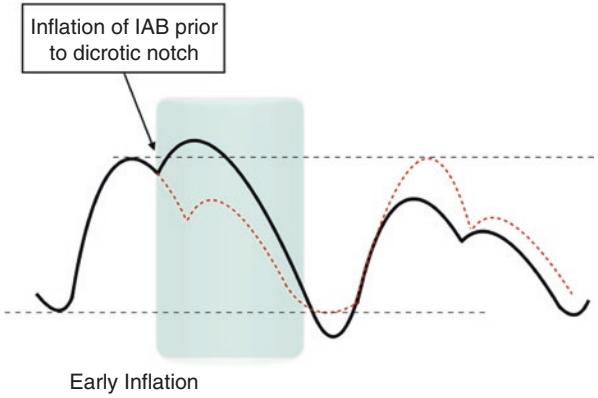

FIGURE 9.5 Early Inflation: This may result in premature closure of aortic valve, incomplete LV emptying, aortic insufficiency, increase in LVEDV and LVEDP, increased afterload, and increased myocardial oxygen demand. This requires immediate attention

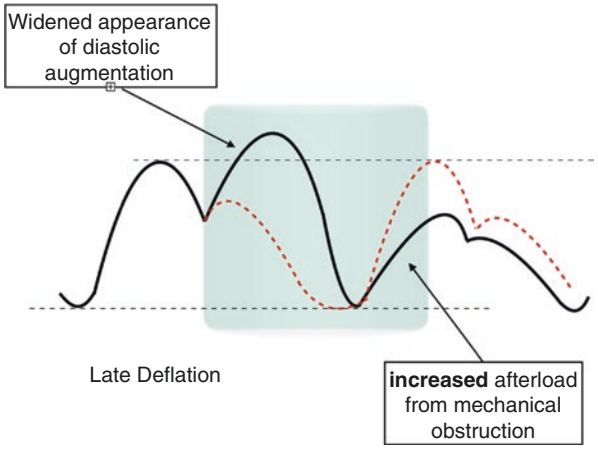

FIGURE 9.6 Late Deflation: This represents one of the most significant functional complications of intra-aortic balloon pumps. During late balloon inflation the left ventricle contracts increased afterload from an inflated balloon. This can result in increased mycoardial demand and reduced cardiac output

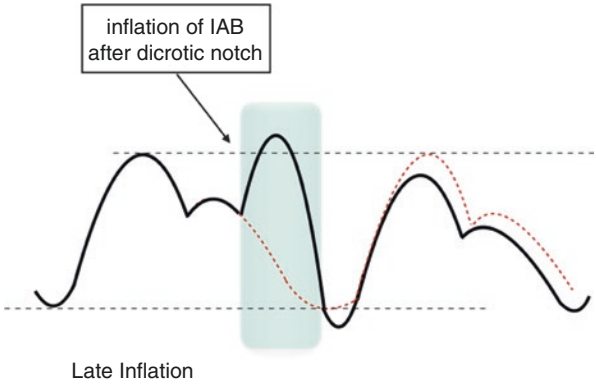

FIGURE 9.7 Late Inflation: This results in decreased augmented coronary perfusion, decreased O2 supply to coronaries and reduced overall benefit of the IABP

Contraindications

With the means of functioning and complications in mind, contraindications to IABP use are not difficult to surmise. First, the basic physiology of IABP assumes normal aortic valve function, specifically the absence of aortic regurgitation. If significant aortic regurgitation is present, it will be worsened by the diastolic inflation of the balloon pump and thus may cause vastly more harm than benefit. Other contraindications include preexisting large arterial pathologies such as aortic dissections or aneurysms that would be worsened by balloon inflation.

Temporary Ventricular Assist Devices

In patients with cardiogenic shock and need for mechanical circulatory support, consideration should also be given to percutaneous ventricular assist device (VAD) support. The most common of this type are the Impella, Tandem Heart and

Centrimag devices. It is important to be able to distinguish between these devices by their level of circulatory support, location of vascular cannulation, and durability of support.

To address the subject of evidence broadly, it is important to note that while all these devices have been approved for use as ventricular support devices, they have been approved based on demonstrating hemodynamic improvement and not based on improved survival [28–30].

Impella

The Impella 2.5 and Impella 5.0 are percutaneous, catheter-based rotary pumps that continuously pull blood from the left ventricle into the aorta via an Archimede's screw mechanism at a maximal rate of 2.5–5.0 l/min, respectively. Like the IABP, the Impella 2.5 is typically placed by interventional cardiologists into a femoral artery. It is then and guided up the aorta until it crosses the aortic valve at which point it is able to properly function. The Impella 5.0, while providing greater circulatory support, is larger and requires a vascular cut down into the femoral artery or requires open surgical access to place directly into thoracic aorta. Just as the Impella devices have different means of cannulation they also have different recommendations on level of support. The Impella 2.5 is approved for less than 6 h of circulatory support, while the Impella 5.0 has been approved for expected durations less than 6 days [31].

The Impella devices have been clinically demonstrated in several small trials to improve several important hemodynamic indices, such as increased cardiac output, elevated mean arterial pressures counterpulsation [28, 29]. The primary way these device achieve these improved hemodynamic indices is simply by providing a higher degree of hemodynamic support. Whereas an intra-aortic balloon pump may be able to augment cardiac indice by up to 0.11 L/min/m^2, an Impella 2.5 can offer greater than 0.49 L/min/m^2[28] In addition

to offering a higher level of circulatory support, Impella devices also offer the advantage of decompressing the left ventricle, which in theory lessens wall stress and myocardial oxygen demand.

Contraindications to Impella use include left ventricular and aortic valve pathologies which would predispose to calcific or thrombo-embolism, specifically, aorta stenosis (aortic valve area less than 0.6 cm^2) or LV wall thrombus. Additionally, it use to not recommended in cases of aortic regurgitation or mechanical aortic valve.

Tandem Heart

The Tandem Heart is a percutaneous support device that bypasses the left ventricle by taking oxygenated blood directly from the left atrium and shunts it to the systemic arterial circulation. It does this by using to cannulas. The inflow cannula is inserted through the venous system into the right atrium and then in the left atrium via a trans-septal puncture. Blood is then pumped from the left atrium into a magnetically driven centrifugal pump that drives blood into the systemic circulation via a femoral artery cannula.

The first data regarding the Tandem Heart was published in 2001, where its use was associated with improvements in cardiac index, MAP and concurrent reduction in markers of congestion (CVP and PWCP) [32, 33]. A randomized trial was then conducted which recruited 41 patients with cardiogenic shock following acute myocardial infarction, which found no statistically significant difference in 30 day mortality when compared to IABP counterpulsation [30]. Additionally while hemodynamic indices were improved over IABP, the Tandem Heart cohort had more episodes of severe bleeding and acute limb ischemia.

Randomized trials and observational studies have shown that duration of Tandem Heart use tends to be around 4 days though is typically recommended for as little as 6 h to as many as 30 days [30, 33].

Centrimag

The CentriMag ventricular assist device is most commonly known for being the circulatory support mechanism in very common extracorporeal membrane oxygenation (ECMO) system. The CentriMag along with a Maquet Quadrox are together able to provide full cardiopulmonary support (both hemodynamic and oxygenation of venous blood). However when pulmonary support is not needed the CentriMag device alone can be used for short term mechanical circulatory support. If pulmonary support is then needed, the oxygenator can be added to the support circuit without another procedure. The inflow and outflow cannulas for the CentriMag system can be arranged a number of combination. In cases of left ventricular failure, the inflow cannula can be surgically placed via thoracotomy in to the left ventrical and the outflow into the aorta or femoral artery. The CentriMag also affords the possibility of right ventricular support with placement of an inflow catheter into the right ventricle and outflow catheter into the pulmonary artery.

Data on the CentriMag support system is largely observational. But studies have thus far shown an acceptable safety profile with limited patient complications and device failures [34].

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