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Review Article

Heart Failure: Mechanisms, Treatment, and Anesthesia Management

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ABSTRACT

Aim of review: To update our understanding of the pathogenesis and mechanisms of heart failure with reduced ejection fraction (HFrEF), treatment, and issues pertaining to the perioperative care of these patients.

Methods: We conducted a comprehensive review of the current literature, including both original basic and clinical studies on HFrEF from basic mechanisms of its development to clinical treatments. We used PubMed as the main database. We found over 5000 publications with the keyword "heart failure with reduced ejection fraction," including original research, meta-analyses, and review studies. We selected recent reviews, recent original studies (basic and clinical), and past landmark original studies (basic and clinical) over the past 10 years. We also reviewed the literature on some specific issues regarding the perioperative care of patients with heart failure.

Recent findings: HFrEF presents perioperative challenges to anesthesiologists. It is characterized by chamber dilatation with low contractility and altered cardiac excitation-contraction coupling processes. Treatments for HFrEF consist of angiotensin-converting enzyme inhibitors and/or angiotensin II receptor blockers and β blockers at early stages, and device therapies and heart transplantation at more advanced stages. Novel therapies are being investigated as well. Specific perioperative care for patients with HFrEF includes preoperative optimization, maximization of myocardial protection, minimization of myocardial injury, appropriate use of positive inotropic agents, proper fluid management, and management of device therapies.

Summary: The pathophysiology of heart failure involves activation of multiple signaling pathways and significant alterations in excitation-contraction coupling. Perioperative care of patients with heart failure is challenging and requires an understanding of the basic mechanisms of heart failure. Moreover, practitioners should be able to stratify and minimize risk, optimize and manage compromised patients, and prevent the worsening of symptoms and complications. (Funded by the American Heart Association.)

Patients with heart failure (HF) present increasing challenges to anesthesiologists during various procedures. Recent clinical studies have found that HF patients have high rates of perioperative mortality and morbidity (1, 2), as much as two - to three-fold higher than for patients with coronary artery disease (CAD) (3, 4). The high incidence of morbidity and mortality is due to complications such as heart attack, worsening HF, and other organ failures (5, 6). Clinical-

Table 1. Characteristics of Patients with HFpEF and HFrEF.

Characteristic	HFpEF	HFrEF
Percent of patients	30–50%	50–70%
Ejection fraction	>40–50%	<40–50%
Age at diagnosis, years	71–78	70–71
Predominant sex	Female (62%)	Male (>62%)
African American	10–17%	13–25%
Cardiovascular comorbidities	Hypertension (55-100%) Atrial fibrillation (21-41%) Left ventricular hypertrophy?	CAD (ischemia) (50-70%)
Non-cardiovascular comorbidities	31-34%	27%
COPD	26-52%	25-52%
Renal insufficiency	22-33%	14-28%
Anemia	24-45%	22-40%
Diabetes mellitus	35-51%	25-35%
Obesity	79.9%	78.5%

CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction.

ly, the worsened cardiac contractility of patients under general anesthesia is often treated with conventional positive inotropic agents or vasopressors. However, these agents are potentially deleterious to the failing myocardium: Ca2 + overload can be worsened by positive inotropic agents, which elevate intracellular Ca2 + , and by vasopressors, which reduce cardiac output further via increases in afterload. Inhalational anesthetics have been shown to have powerful myocardial protective properties in both basic and clinical research studies (7, 8). In addition, they are associated with less occurrence of intraoperative awareness (9). These unique attributes of inhalational agents, however, are overshadowed by their inhibitory effects on myocardial contraction.

As patients with hypertension and CAD survive longer, owing to the better treatments available to them, the number of HF patients has increased (10). It is expected that we, the anesthesiologists, will encounter increasing numbers of HF patients at various stages for both cardiac and non-cardiac procedures. Understanding the mechanisms and management strategies of HF is essential to our ability to manage these patients safely and effectively during the perioperative period. This review will focus on current understanding of the mechanism(s) underlying HF, current treatments for HF, and issues related to the perioperative care of HF patients who require anesthesia.

Pathogenesis of HF

What is HF?

HF occurs when the heart cannot pump enough blood to adequately meet all of the body's needs. Chronic HF develops over time after the injured heart undergoes extensive pathological remodeling, as opposed to acute HF, which develops abruptly as a result of acute myocardial ischemia, acute myocardial traumatic injury, acute myocardial infection, etc. Here, we will discuss chronic HF. There are two types of patients with chronic HF: 1) patients who have HF with reduced ejection fraction (or HFrEF), in which the contractility of the heart (best represented by ejection fraction (EF) (11) is reduced and 2) patients who have HF with preserved ejection fraction (or HFpEF) and HF syndromes (such as dyspnea, fatigue, and edema). Diastolic HF is the prominent feature of HFpEF. Nearly half of HF patients have HFpEF (12). Table 1 compares the two forms of HF. Currently, clinical management of

HFpEF is similar to that of HFrEF. In this review, we will focus on HFrEF given its clearer implications to our clinical practice.

Mechanism and Pathophysiology of HFrEF

Development of HF is chronic and complex (Figure 1) (13-15). Any insult to the heart (ischemia, infection, toxins, etc.) will activate an array of compensating mechanisms, including the sympathetic system and release of cytokines and neurohormones. Renal hypoperfusion activates the renin-angiotensin-aldosterone system (RAAS). Consequently, levels of epinephrine, norepinephrine, renin, angiotensin I and II, aldosterone, natriuretic peptides, prostaglandins, and nitric oxide (NO), etc. are increased. These compensatory changes tend to restore contractility to maintain normal cardiac output and organ perfusion (11). However, the persistence of these insults will eventually lead to persistent activation of these mechanisms such that they become maladaptive (i. e., causing harm). Other changes that occur include increases in inflammatory factors such as cytokines, IL-6 family, and TNF-α; altered interstitial proteins; altered Ca2+ regulatory proteins; altered gene expression; and increased apoptosis and necrosis. The heart becomes chronically maladaptive and undergoes extensive remodeling. As a result, the heart develops hypertrophy followed by ventricular wall thinning and chamber dilation, and loses its power during the contraction—HFrEF manifests itself clinically.

At the cellular level, HFrEF is the result of an altered excitation-contraction coupling (ECC) process (Figure 2). Prolongation of membrane action potential accompanied by early after-depolarizations and delayed after-depolarizations are the hallmarks of the failing heart (16, 17). These are usually (but not always) caused by decreased functional expression of membrane potassium channel Ito, by the increased opening of voltage-gated Ca2+ channel Cav1.2, and by the prolonged opening of membrane sodium channel Nav1.5. Action potential prolongation and the dynamics of action potential changes can lead to cardiac arrhythmias, including ventricular tachycardia and fibrillation.

Altered Ca2+ metabolism/regulation by the sarcoplasmic reticulum (SR) is central to the development of HFrEF (17, 18). Decreased expression and function of SERCA2a, as well as decreased phosphorylation of phospholamban, reduce Ca2+ uptake by the SR. Phosphorylation of SR ryanodine Ca2+ release channel anchoring protein FKBP12.6 promotes Ca2+ leak from the SR. These alterations result in decreased contractility because less activator Ca2+ is released from the SR. Additionally, the heart is prone to arrhythmias because diastolic Ca2+ levels increase.

Myofilament dysfunction can also compromise cardiac contractility in patients with HFrEF (19, 20). For example, altered phosphorylation of troponin (Tn) and other myofilament proteins causes changes in myofilament Ca2+ responsiveness and thus alters force development in the failing heart/myocardium (21, 22). Oxidation of tropomyosin and actin also has been linked to contractile dysfunction in ischemic and failing myocardium (23, 24). Myosin and some regulatory proteins (TnI and TnT) have been found to revert to fetal phenotypes.

Mitochondrial dysfunction, decreased biogenesis, and thus decreased energy production are evident in HFrEF (25). One main mechanism for mitochondrial dysfunction is mitochondrial Ca2+ overload caused by cytosolic Ca2+ overload. In addition, opening mitochondrial Ca2+ uniporter worsens mitochondrial Ca2+ overload. Mitochondrial production of reactive oxygen species thus increases significantly, impairing ATP production and causing cell death. Changes in metabolism also negatively affect energy production and promote HF development (26).

Treatments

The past 30 years have witnessed significant advances in treatment for patients with HFrEF, leading to a decline in age-adjusted death rate and prolonged life. Treatments depend on the stage of HFrEF (Table 2) (27, 28). Clearly, treatment should integrate multiple approaches, from risk reduction to social support, from drug therapy to device therapy, and from treating comorbidities to comfort care. Here, we review briefly drug therapy and device therapy, which have been the mainstay therapies for HFrEF.

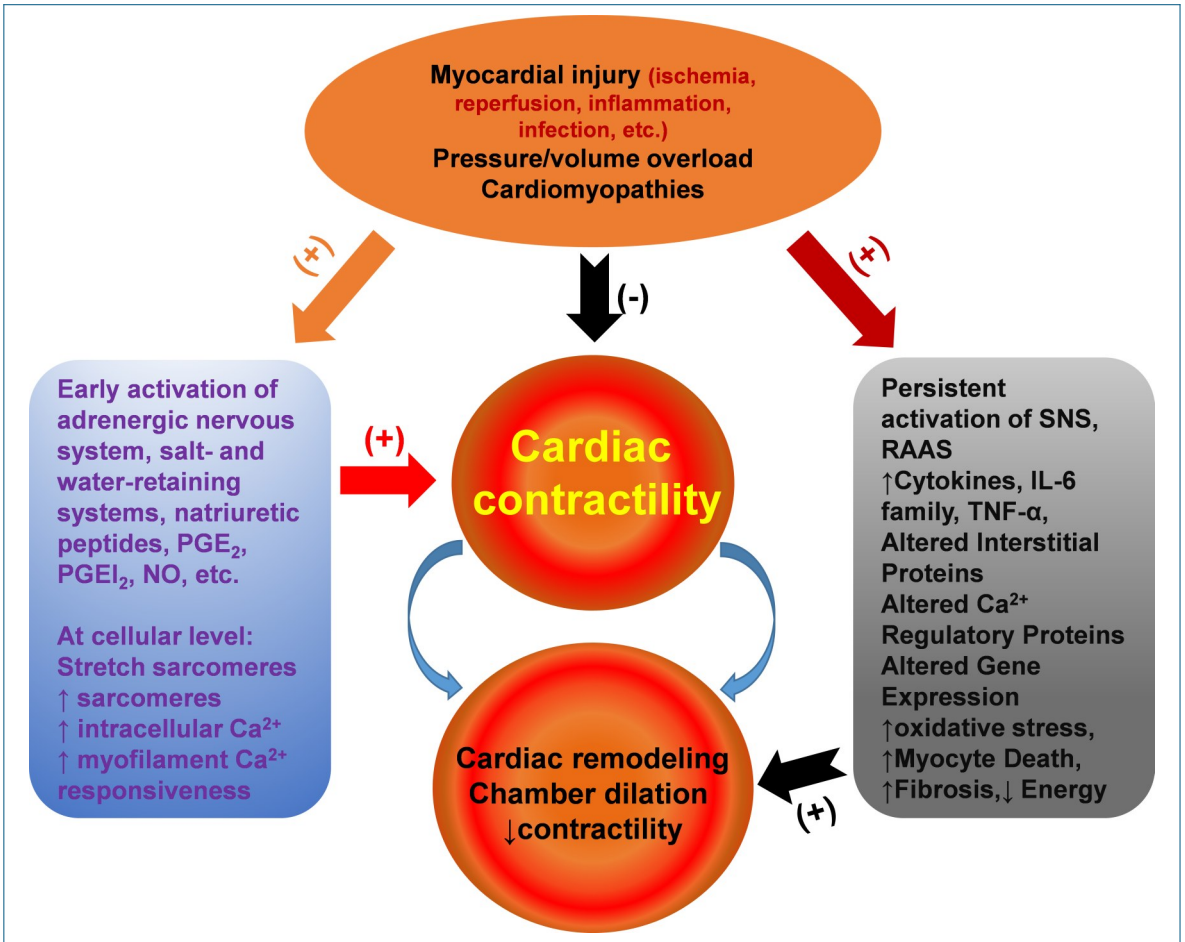

Figure 1. Diagram Illustrating Development of Heart Failure with Reduced Ejection Fraction (HFrEF).
IL-6, interleukin 6; NO, nitric oxide; PGE, prostaglandin E; RAAS, renin-angiotensin-aldosterone system; SNS, sympathetic nervous system.

Drug Therapies

RAAS antagonists

Currently, all guidelines regarding HFrEF management recommend RAAS blockade. Many clinical trials have established that RAAS blockade improves survival by modifying the natural history of HFrEF progression (29). Recently two new developments have occurred in RAAS blockade for management of HFrEF. i) Aggressive aldosterone receptor antagonism, especially in New York Health Association class II HF patients with EF < 30%, since eplerenone, a mineralocorticoid receptor antagonist, significantly reduced the risk of cardiovascular death and hospitalization (by 27%) (30). However, because of its potential to cause hyperkalemia and renal dysfunction, mineralocorticoid receptor antagonists are currently underutilized. ii) Direct plasma renin inhibitors are being increasingly used to treat HFrEF patients because conventional RAAS inhibitors can induce an increase in plasma renin activity. Renin inhibitors include direct angiotensin receptor type 1 inhibitors and drugs that prevent the breakdown of atrial natriuretic peptide and brain natriuretic peptide (neprilysin inhibitors) (31, 32).

β-Adrenergic blockers

Because abnormal activation of adrenergic receptors has profound negative effects on cardiac

structure and function in the development of HF, β-adrenergic blockers are recommended for disease management (33). Today, the β-receptor blockade has become a standard component of therapy for HFrEF because of its effectiveness in inhibiting the pathological remodeling process and reducing mortality. β-Blockers are beneficial because of their antiarrhythmic effects and their ability to decrease heart rate, slow detrimental remodeling, and decrease myocyte death from catecholamine-induced necrosis. It is important that patients on β-blockers reach their targeted doses as soon as possible to achieve maximal benefits. They should begin therapy early and use more than one β-blocker (34).

New Medical Therapies

New knowledge about the pathogenesis of HFrEF from basic research has stimulated translation of new findings to clinical research. As a result, some novel therapies are emerging and being tested in clinical trials (35).

Gene therapy to boost SERCA2a activity

HFrEF is associated with deficiencies in SR ATPase activity (or SERCA2a). A few preclinical studies have shown that increased expression of SERCA2a restores cardiac function. Based on these results, investigators have attempted SERCA2a gene delivery to HFrEF patients and shown promising clinical benefits (The Calcium Upregulation by Percutaneous Administration of Gene Therapy in Cardiac Disease (CUPID I) Phase IIa Study) (36). However, a recent follow-up trial, CUPID II, failed to show any benefits of SERCA2a gene delivery (37). Thus, gene therapy for HFrEF has been met with great challenges for now.

Ca2+ sensitizers

HFrEF is characterized by low contractility. But positive inotropic agents, which increase cardiac contractility, have failed to reduce mortality (in fact they have increased it) (38) because they lead to Ca2+ overload. To circumvent this problem, a new class of positive inotropic agents has been developed. Levosimendan (Simdax, Orion Corp., Espoo, Finland) was reported to promote Ca2 + binding to TnC, increase contractility without additional increases in Ca2 +, and improve patient survival (39). However, a later trial in the US (the SURVIVE trial) did not find any differences between levosimendan and dobutamine (40). Therefore, levosimendan has not been approved by the FDA, but has been used widely in Europe. Recently, omecamtiv mecarbil, which binds directly to the myosin head catalytic domain and promotes the transition to and stabilization of strong, force-generating cross-bridges (41), has undergone two phase-II clinical trials. In the ATOMIC-HF (Acute Treatment With Omecamtiv Mecarbil to Increase Contractility in Acute Heart Failure) study (42), 606 HF patients (EF ⩽ 40%) received 48 hours of drug infusion (three sequential, escalating-dose cohorts). The patients tolerated the drug well and showed greater dyspnea relief through 5 days of high-dose treatment as compared with low doses. In the COSMIC-HF (Chronic Oral Study of Myosin Activation to Increase Contractility in Heart Failure) trial (43), 150 HF patient (EF <40%) were treated orally for 20 weeks, and showed improved cardiac function with no side effects. Thus, omecamtiv mecarbil showed promising results in these two trials, and a larger phase-III trial is being planned.

Cell regeneration therapy

Cell regeneration therapy has garnered great interest in recent years because of its potential to provide new myocytes in place of dead or dying ones to recover cardiac contractility (44). Many clinical trials have utilized a variety of stem cells. However, a recent Cochrane review (45) found "low-quality evidence that treatment with bone marrow-derived stem / progenitor cells reduces mortality and improves left ventricular ejection fraction over short - and long-term follow-up and may reduce the incidence of non-fatal myocardial infarction and improve New York Heart Association (NYHA) Functional Classification in people with chronic ischaemic heart disease and congestive heart failure." Nevertheless, another review of 1520 patients from 32 trials found that blood levels of BNP/NT-proBNP decreased, 6-minute walk distance increased, and quality of life improved (46). In addition, the treatment improved EF and NYHA class at both short-term (< 12 months) and long-term (>12 months) follow-up and reduced rehospitalization and mortality. A larger, well-designed clinical trial with robust

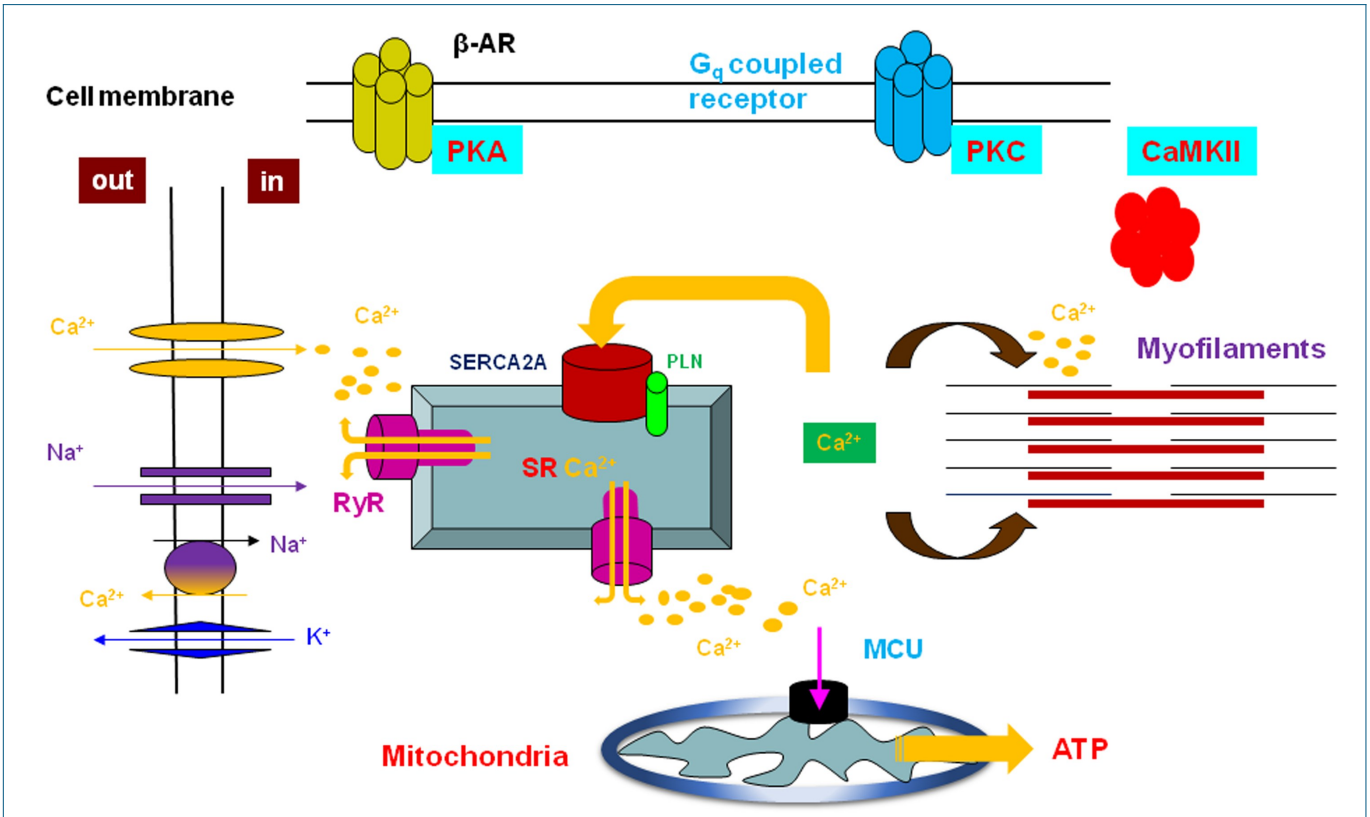

Figure 2. Schematic Representation of Simplified Cardiac Excitation-Contraction Coupling (ECC). (1) Electric pulses activate membrane-bound ion channels such as Na+, Ca2+, and K+ channels to produce action potential allowing Ca2+ entry into the cell. In HFrEF, this excitation process is altered such that action potential duration is prolonged. (2) Ca2+ entry from outside triggers more Ca2+ release from the sarcoplasmic reticulum (SR). Multiple changes in this process occur in HFrEF: decreased SR ATPase function, abnormal function of SR release channels (i.e., ryanodine channels, RyR), and altered phosphorylation of phospholamban and RyR. SR Ca2+ content is reduced leading to decreased SR Ca2+ release. (3) Contractile force is reduced because of decreased Ca2+ release from the SR, decreased myofilament responsiveness to Ca2+, and loss of myocytes. (4) Mitochondrial energy production is altered because of Ca2+ overload and increased reactive oxygen species production. (5) Altered function of membrane G-protein-coupled receptors and intracellular calmodulin-dependent kinase II (CaMKII) affects all aspects of the ECC process. β-AR, beta-adrenergic receptor; MCU, mitochondrial Ca2+ uniporter; PKA, protein kinase A; PKC, protein kinase C; PLN, phospholamban.

results is still needed to justify the use of cell regeneration therapy.

Others

Soluble guanylate cyclase (sGC) activation by NO is impaired in patients with HFrEF because of dysfunctional endothelial cells. Thus, direct stimulation of sGC offers a novel new target to treat HFrEF. Vericiguat, an sGC stimulator, has been shown to reduce levels of NT-proBNP at 12 weeks and improve EF in HFrEF patients (47), but larger trials are needed to confirm these results. Ivabradine, a specific sinus node inhibitor, has been shown to reduce cardiac decompensation and mortality, especially in HF patients with high heart rate (48).

Device Therapy

Chronic resynchronization therapy (CRT)

CRT, known as biventricular pacing, involves simultaneous pacing of the right and left ventricles. Two pacing electrodes (a right ventricular endocardial lead and a coronary sinus lead) are controlled by a minicomputer device that is inserted

into the chest wall and delivers electric pulses to each ventricle. The goal of CRT is to restore left ventricular synchrony in patients with dilated cardiomyopathy and a widened QRS, which results predominantly from left bundle branch block, in order to improve the mechanical functioning and cardiac output of the left ventricle.

In the early 2000s, the MIRACLE trial showed a significant reduction in worsening and hospitalization, and improvement of survival, in NYHA class III or IV HF patients with EF 35% and QRS >130 ms (49, 50). Later, larger clinical trials all showed benefits of CRT in HFrEF patients (51). By eliminating mechanical dyssynchrony (i. e., intraventricular, interventricular, and atrioventricular), CRT is one of the most successful HFrEF therapies to date. However, approximately one-third of patients do not respond to CRT therapy, especially those with QRS 130 ms. The remaining task is to identify these patients and develop alternative therapies.

Left ventricular assist device (LVAD)

As an alternative to heart transplantation for patients with end-stage HF, an LVAD is a surgically implanted mechanical pump that is attached to the heart and assists the left ventricle to pump more blood with less work. A few types of LVAD are available, but HeartMate II (Thoratec Corporation, Pleasanton, CA, USA) is most commonly used for patients with chronic HF. HeartMate II is a small portable LVAD with an inner rotary pump that provides continuous axial flow. It has two cannulas (inflow and outflow) without valves. The inflow cannula connects to the apex of the left ventricle and the outflow cannula connects to the ascending aorta distal to the aortic valve. HeartMate II has several advantages: low risk of infection, easy implantation, few moving parts, and few blood-contacting surfaces (important to reduce destruction of blood components). The device also has low energy requirements, is reliable, produces little noise, and has low thrombogenicity and low thromboembolic risk.

Treatment of HF patients with LVAD began almost two decades ago. The landmark 2001 study, the REMATCH trial, showed long-term benefit of LVAD (HeartMate VE, pulsatile flow) over optimal medical therapy at 2 years in NYAH IV end-stage HF patients who were not candidates for the heart transplant (52). In 2007, HeartMate II was implanted in HF patients waiting for heart transplantation (53). At 6 months, 100 of 133 had undergone transplantation, had cardiac recovery, or had ongoing mechanical support while waiting for transplantation. The survival rate was 75% at 6 months and 68% at 1 year. In addition, patients experienced significant improvements in functional status and quality of life. Since then, significant progress has been made in LVAD therapy, both technologically and clinically. Pulsatile LVADs have been replaced with pulseless ones, and devices have become much smaller, with a significant reduction in noise. Clinically, the duration of LVAD has increased, and now LVAD implantation has become a destination therapy for patients with HFrEF (the FDA approved HeartMate II as a destination therapy in 2010). It appears that LVAD is becoming the future "cure" for end-stage HFrEF given the limited availability of donor hearts (35, 54). In addition, accumulating evidence shows that some patients with an LVAD have a significant recovery of their (native) heart function (55). It is also beneficial to continue drug therapy after LVAD implantation because of the additional structural and functional improvements (56). Two future trends include i) trials of smaller, more durable, quieter, and safer LVADs (HeartMate III (57) and HeartWare (58)) and ii) optimizing medical therapy such that patients can recover (bridge-to-recovery).

Anesthesia Management

Patients with HFrEF present a challenge to anesthesiologists when they come to the operating room (OR) for surgeries and procedures. Unfortunately, there are no formal clinical guidelines on the perioperative management of patients with HF. Perioperative care of HF patients includes careful routine preoperative evaluation (especially the status of organs affected) and preparation, appropriate intraoperative monitoring and management, and well-planned postoperative discharge (Table 3). Additionally, several specific issues pertain to anesthesia management and warrant further discussion. This section will consider these issues.

Table 2. Stages of HFrEF and Their Treatments (27, 28).

HF Stage (NYHA class)	Description	Treatments
A (NYHA I)	High risk, no symptoms	Risk factor reduction; patient and family education; treat hypertension, diabetes mellitus, coronary artery disease, and dyslipidemia; use ACEIs or ARBs
B (NYHA II)	Evidence of structural heart disease, no symptoms	ACEIs, ARBs, beta blockers in select patients
C (NYHA III – early NYHA IV)	Presence of structural disease, clinical symptoms	Diuretics if volume overload; mineralocorticoid receptor antagonist; refer for cardiac rehabilitation; evaluate for iron deficiency; hydralazine-nitrates in African Americans; consider sacubitril/valsartan (LCZ696); consider ivabradine; consider implantable monitoring device; assess biomarkers; evaluate risk. Ventricular assist device; heart transplant;
D (NYHA IV)	Refractory symptoms, requires special treatments	end-of-life discussions; palliative care

ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; HF, heart failure; HFrEF, heart failure with reduced ejection fraction; NYHA, New York Heart Association.

Preoperative Medical Management

Preoperative assessment and risk stratification

HFrEF has long been recognized as an important independent risk factor for negative perioperative outcomes (59). As mentioned earlier, perioperative mortality and morbidity are higher in these patients than in those with CAD. Because patients have already been diagnosed with HF before they arrive for surgery, the focus of preoperative evaluation should be on a patient's functional capacities and the involvement of other organs, as outlined in published guidelines (60, 61). The assessment is needed to stratify the risk of these patients, in particular to identify patients with potential exacerbations of HF. The cardiopulmonary exercise test is the best way to assess a patient's functional capacity, and a decrease in O_2 consumption suggests increased risk (61). Measurement of blood levels of natriuretic peptides is also recommended to enhance risk stratification, as these levels are strongly correlated with HF prognosis and perioperative outcome (61). For HF patients with acute exacerbations, elective surgeries should be deferred to a later date, preferably to 3 months if managed as new onset of HF. The goal of this delay is to allow time for improvement in left ventricular function, resolution of fluid overload, stabilization of blood pressure, and optimization of organ perfusion (61).

Preoperative optimization of all HF patients

Preoperative optimization of patients with HF requires teamwork. The cardiologist, not the anesthesiologist, should optimize the patient before he/she comes to the OR for elective surgeries. The goal of optimization is usually to improve or stabilize symptoms, minimize risks, and enhance communication with caregivers.

One reliable sign of medical optimization is if patients are on RAAS inhibitors, β-blockers, or both. According to the AHA/ACC practice guideline for high cardiovascular risk (CAD) patients, use of β-blockers is II with the level of evidence B for all surgeries (60). The guideline also recommends the preoperative use of β-blockers (both short- and long-term) in patients with cardiac ischemia risks (remember: HFrEF patients are always ischemic) based on clinical trials which showed reduced perioperative cardiac events and improved postoperative survival. A recent review of randomized controlled clinical trials on perioperative use of β-blockers have revealed two major findings (62): i) If given <1 day before surgery, β-blockers decreased incidence of myocardial infarction but increased risk of postoperative death, stroke, hypotension, and bradycardia; ii) It is not known if starting β-blockers 2 or more days prior to surgery is harmful or beneficial. To date, there are no studies that specifically investigate the effect of perioperative β-blockade in patients with HF. However, given the proven benefits of β-blockade in preventing disease progression and pathological remodeling, all patients with HFrEF should be on β-blockers unless there is a contradiction to them.

In early clinical trials (SOLVED(treat) (63), V-HeFT (64), CONSENSUS (65), SOLVED(prevent) (66), SAVE (67), and GISSI-4 (68)), angiotensin-converting enzyme inhibitors (ACEIs) were shown to be very effective at reducing the risk of mortality in both symptomatic and asymptomatic HF patients (class II-IV). Angiotensin II receptor blockers (ARBs) are usually alternatives to ACEIs if patients cannot tolerate their side effects (69, 70). Current guidelines for management of patients with HFrEF recommend starting at least one RAAS inhibitor (see section above). A recent meta-analysis found that ACEIs, but not ARBs, reduced cardiovascular events and all-cause mortality in HFrEF patients with EF ⩽ 35-40% (71). In general, HFrEF patients should be on RAAS inhibitor(s) as well.

Preoperative withholding versus continuing RAAS inhibitors

Whether to continue or stop ACEI or ARB therapy is an ongoing debate (72, 73). At present, no data address whether or not to hold RAAS inhibitors in HFrEF patients preoperatively. For patients who have CAD and take ACEIs or ARBs, AHA / ACC guidelines recommend continuing these medicines into the preoperative period (60) before non-cardiac surgeries. However, this recommendation is based largely on clinical studies with small sample sizes. A recent study that analyzed 4,802 patients who were taking ACEIs/ARBs from a cohort 14, 678 patients showed that withholding these medications on the day of surgery was associated with reductions (~ 18%) in death, stroke, and myocardial injury on day 30 after non-cardiac surgery (74). However, only 3-5% of patients in the cohort had HFrEF. Another study, which investigated patients on ACEIs who were being admitted for coronary artery bypass grafting (CABG), showed that continuing the drug throughout the perioperative period (preop through 30 days postop) reduced composite outcome, reduced cardiovascular events, and improved in-hospital outcomes at 30 days after surgery (75). In addition, adding an ACEI de novo postoperatively had similar positive outcomes. Patients who withdrew from ACEIs had worse outcomes than those who continued ACEIs preoperatively. It is worth mentioning that approximately 13% of study patients had HF. These two studies suggest that withholding ACEIs / ARBs is beneficial during non-cardiac surgeries but harmful during cardiac surgeries. However, given the small percentage of HF patients involved in these studies, it remains debatable whether to hold or continue ACEIs / ARBs preoperatively in HFrEF patients. Proponents of halting the medicine argue that the severe hypotension is sometimes very difficult to manage. Opponents argue that: i) clinical evidence of intraoperative hypotension caused solely by ACEIs or ARBs is not convincing; ii) even if moderate hypotension occurs, it is usually transient and responsive to treatment, and more importantly, not associated with increased adverse outcome (76, 77); and iii) continuing the medication might have some yet-to-be-proved benefits (e.g., cardioprotection, attenuated sympathetic responses, and improved renal function) (78). Given all of these arguments, we support the continuation of these drugs until the day of surgery, holding them during the intraoperative period, and restarting them as soon as possible after surgery when the patient's hemodynamics have stabilized. It is clear that studies are needed to investigate whether preoperative withholding of ACEIs/ARBs is beneficial to these patients.

Intraoperative Management

General considerations

The failing heart not only exhibits severely depressed contractility, but also behaves differently from a normal heart in other ways. Failing myocardium is arrhythmogenic, ischemic, and energy-deprived. These traits render the myocardium much less tolerant to disturbances in hemodynamics, imposing genuine challenges during the intraoperative period. The main goal of intraoperative management is to protect the failing heart by optimizing oxygen supply and decreasing oxygen demand (i.e., maintaining cardiac output and coronary perfusion), by maximizing the cardioprotective effect of inhalational agents, especially during cardiac procedures (79), minimizing the potential negative effect of anesthetics (80), and meticulously executing intraoperative fluid management. The aggressiveness with which these techniques and therapies are used to achieve this goal should be tailored to each individual patient

Table 3. Perioperative Anesthesia Management of HFrEF Patients.

Phase of Care	Managment
Preoperative	
Assessment of risk stratification	Evaluation focus: functional capabilities, other organ involvements, cardiopulmonary exercise test, plasm levels of natriuretic peptides, delay elective surgery if exacerbations exist.
Medical optimization	All patients should be on RAAS inhibitors and β-blockers. Continue them until the day of surgery, hold during OR, and restart as soon as possible after the procedure if patient's condition permits.
Intraoperative	
General goals	Optimize myocardial O2 supply/demand balance, maximize myocardial protection, minimize myocardial injury, optimal goal-directed fluid managemnet, consider invasive monitors (arterial line, CVP, PA, TEE) in the patient at advanced stages.
Specific issues	
Choice of anesthesia	Type of anesthesia should be tailored to patient's procedure, medical conditon, and desire.
Unstable patients and use of positive inotropic agents	Start positive inotropic agents in decompensated patients. Epinephrine is preferred, other agents (levosimendan, milrinone, and norepinephrine) can be considered.
Fluid management and blood transfusion	Maintain normovolumia (use vasopressors if necessary to avoid volume overload). Blood transfusion is generally not recommended in stable patients. However, keeping hemoglobin > 8-9 g/dl is recommended.
Postoperative	Consider continuous monitoring for 23 hours for most patients. Avoid postoperative volume overload and pulmonary edema.

HFrEF, heart failure with reduced ejection fraction; RAAS, renin-angiotensin-aldosterone system; OR, operation room; CVP, central venous pressure; PA, pulmonary artery; TEE, Transesophageal echocardiography.

and related procedure. If the associated risks (patients, anesthesia, and surgery) are high, intra-arterial, central venous cannulae, and transesophageal echocardiography should be placed for close hemodynamic monitoring.

Specific considerations

Choice of anesthesia techniques. There is no conclusive literature support for which type of anesthesia (general anesthesia or regional or neuraxial blocks) is better than the other for HFrEF patients. In a retrospective, propensity-matched cohort study of 3362 patients from the American College of Surgeons National Safety Quality Improvement Program (ACS-NSQIP) national database who were undergoing below-knee amputations, 135 HF patients had regional or neuraxial blocks and 118 had general anesthesia. The study found no differences in 30-day mortality and other complications. However, those who had general anesthesia tended to have more blood transfusions (81). In the landmark GALA study (82), no differences in hospital outcomes were reported between 90 HF patients who received general anesthesia and 93 who received regional block for carotid endarterectomy. Thus, the type of anesthesia for HF patients should be tailored to the patient's procedure, medical condition, and desire. The expertise of the anesthesiologist (e.g., regional expert) can also be a factor.

Management of unstable patients and choice of positive inotropic agents. Anesthesiologists should always be prepared to manage acute decompensation. Positive inotropic agents are usually administered immediately for acute heart failure. However, the use of inotropic agents has several caveats. First, conventional inotropic agents such as dopamine, epinephrine, and milrinone increase contractility by increasing intracellular Ca2+. Because Ca2+ responsiveness is decreased in failing myocardium, these agents can have poor efficacy and efficiency while worsening Ca2+ overload. Second, levosimendan (Simdax), a myofilament Ca2+ sensitizer (see above), has been increasingly used in HFrEF patients during surgeries. However, recent large randomized trials have not shown clear benefits for HFrEF patients in the perioperative setting (83). Nevertheless, experts in the field still recommend its perioperative use, given that many small clinical trials have shown favorable results. Third, among the conventional inotropic agents,

epinephrine is the preferred drug because the predominance of β1 receptors are in the heart. In some institutions, anesthesiologists are reluctant to start using epinephrine for fear of raising blood lactate level and thus causing metabolic acidosis. This view has not been supported by current literature. A small clinical study (36 patients with CABG) found that epinephrine infusion increased blood lactate levels and caused metabolic acidosis, but was not associated with worse outcomes (84). Thus, epinephrine-induced lactic acidosis is benign (and may even be beneficial). Other important factors should also be considered with regard to postoperative lactic acidosis (85, 86). Fourth, milrinone increases Ca2 + by inhibiting phosphodiesterase degradation of cAMP, and to maximize its action, mechanisms to generate cAMP (e. g., β1 stimulation) are often required.

Fluid management and blood transfusion. Normovolemia is imperative and can be achieved by maintaining vascular tone and intravascular volume through the judicial use of pressors and fluid. Because blood transfusion can easily produce volume overload (87), transfusions should be avoided in stable (even if somewhat anemic) patients unless absolutely needed (i. e., major bleeding). In surgical patients with normal cardiac function, including those undergoing open heart surgeries, those who received a restrictive transfusion protocol (hemoglobin [Hb] maintained at 8-9 g/dL) had outcomes similar to those in the liberal transfusion group (Hb maintained above 10 g/dL) (88, 89). In a recent study of 5243 patients undergoing cardiac surgery (39% of whom had at least moderately reduced cardiac function), a restrictive strategy (Hb trigger <7.5 g/dL) was proven non-inferior to a liberal strategy (Hb trigger <9.5 g/dL) with respect to the composite outcome of death from any cause, myocardial infarction, stroke, or new-onset renal failure with dialysis (90). However, it should be noted that the final level of Hb in these patients was >8.5 g/dL.

Postoperative Care

Postoperative care depends on a patient's HF status and the risks of procedures. Most patients with HF should be monitored closely for a prolonged period of time (e. g., 23 hours' continuous monitoring) because postoperative heart failure may be difficult to diagnose. Continuing meticulous fluid management in the postoperative period is important to avoid hypervolemia and pulmonary edema. Patients with more advanced stages of HF (stages III and IV) or new exacerbations should be managed aggressively.

Perioperative Care for Patients with Cardiac Devices

LVAD

Patients with an LVAD can be safely anesthetized for various procedures. However, given the complex nature of the device and graveness of a patient's underlying disease, special considerations are necessary when caring for these patients during surgery (91). LVAD flow depends completely on preload and afterload. Thus, any decrease in preload (such as anesthesia-induced vasodilation, dehydration, body positioning, or bleeding) and increase in afterload (hypertension) will decrease pump flow. Pulmonary hypertension reduces right heart output, and thus pump flow, because of decreased blood return to the left heart.

Besides careful evaluation in terms of general wellbeing, preoperative preparation should include proper bridging from long-term anticoagulation to short-term intravenous heparin before surgery. During emergencies, fresh frozen plasma should be infused to reverse anticoagulation. For intermediate- and high-risk procedures, invasive blood pressure monitoring is needed, given the unpredictability of hemodynamic and volume changes. For low- and intermediate-risk procedures, the trend is to use noninvasive blood pressure monitoring (92). Patients who have general anesthesia usually need invasive blood pressure monitoring. Intraoperative management is focused on hemodynamic changes as reflected by pump flow, pulsatility index (PI), and blood pressure. For HeartMate II, it should be mentioned that the flow is calculated from the speed (i. e., rotations per minute) and power used by the pump. So, if the power is high, the flow is high if pump speed does not change. If the increased power is due to thrombus on the rotor, the flow can be erroneously high. In general, flow below 3.0 L/min is inaccurate. It is cautioned that the calculated flow is not the absolute flow through the device (about 20% lower (93)). PI (maximal

flow – minimal flow divided by averaged flow) reflects the relative contributions of native left ventricle and LVAD to cardiac output. Decreased PI means a decreased native left ventricular contribution to the pulsatile flow (usually caused by more emptied left ventricle). If it becomes more difficult to maintain pump flow and blood pressure with fluid and vasopressors, prompt administration of inotropic agents (e.g., epinephrine) is recommended to treat the likely occurrence of right heart dysfunction.

CRT and Implantable Cardioverter Defibrillator

An individualized, multidisciplinary approach should be used when administering anesthesia to HF patients with CRT plus implantable cardioverter defibrillator (ICD) (94). In general, these devices need to be reprogramed preoperatively and their anti-tachycardia function turned off. Intraoperatively, electromagnetic interference is always a potential concern, but its occurrence decreases markedly if the source is beyond 6 inches. Applying a magnet is still useful but less reliable because of the difficulties of keeping it in place and the potential to turn off the device completely or deliver inappropriate shocks when removed (95). After the procedure, these devices should be examined for damage and reprogrammed back to pre-procedure modes.

Anesthetic management for lead extractions in HF patients with CRT and ICDs is also challenging (96). These patients usually have substantial heart disease, from lethal arrhythmias to severe HF. A detailed preoperative evaluation includes not only a thorough history and physical exam (presence of HF symptoms, functional capacity, disease processes, etc.), but also understanding the reasons for lead extraction (malfunction, infection, perforation, etc.). Blood products should be immediately available if needed. Besides standard intraoperative care, attention should be given to obtaining large-bore intravenous access (preferably central access), invasive blood pressure monitoring, intraoperative transesophageal echocardiography, and cardiac surgery backup. Most of these patients require routine postoperative care and go home the next day. If major complications occur (such as tamponade, pulmonary embolism, hemothorax, severe bleeding), these patients will be transferred to the intensive care unit.

Summary

The pathophysiology of HFrEF involves activation of multiple signaling pathways that include neurohormones, neurotransmitters, cytokines, and growth factors. It affects membrane receptors that activate various protein kinases and mobilizes responses and reactions from cell nuclei to the cytoplasm. As a result, the processes of excitation-contraction coupling become altered and cardiac remodeling occurs. The heart becomes dilated and loses significant contractility. The failing myocardium is ischemic, arrhythmogenic, and energy-deprived. Treatments for patients with HFrEF include routine use of ACEIs/ARBs and β-blockers at early stages, and device therapies at advanced stages. Heart transplantation and ventricular assist devices are reserved for end-stage HFrEF. Perioperative care of HFrEF patients is challenging because perioperative morbidity and mortality are high. These patients need to be optimized before coming to the OR. Holding ACEIs/ARBs may be beneficial to patients undergoing non-cardiac surgeries. No specific myocardial protectant is available, but efforts should always be made to minimize myocardial damage. Types of anesthesia do not seem to affect the outcome of most patients. Positive inotropic agents should be used when needed, and blood transfusion should be limited to low Hb levels. When taking care of patients with cardiac devices, a clear understanding of the mechanics is helpful for monitoring and identifying problems. In addition to standard anesthesia care, management should be tailored to the specific needs of each device to avoid complications.

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