Novel Perioperative Pharmacologic Therapy Of Heart Failure

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Objectives:
1) To review the pharmacologic management of outpatients with chronic heart failure and hospitalized patients with acute decompensated heart failure
2) To review novel pharmacologic management of heart failure patients during the perioperative period

Heart failure (HF) is a pathophysiological condition with an inability of the heart to fill or eject blood sufficient to meet metabolic demands. The etiology of HF appears evenly distributed between systolic and diastolic dysfunction and currently is the only cardiac condition with an increasing mortality rate. As the elderly population grows, so will the frequency of HF patients presenting to the hospital and operating room. An insult to the heart (ischemia, hypertension, virus, pregnancy, hemochromatosis, idiopathic) causes left ventricular (LV) dysfunction and a reduction in cardiac output with secondary neurohormonal activation (sympathetic nervous system; renin-angiotensin-aldosterone system or RAAS; vasopressin; endothelin; cytokines) and alterations in renal tubular sodium and water retention. This vicious cycle markedly alters left ventricular (LV) loading conditions and becomes a progressive disorder with LV remodeling, fibrosis, dilation, and failure.

Pharmacologic Management of Patients With Chronic Heart Failure

The goal of chronic HF management is symptomatic treatment of the adverse biological consequences from sustained neurohormonal activation. American Heart Association guidelines emphasize the development and progression of HF and subdivide patients into four categories with Stage A (high risk for HF development without structural heart disease or symptoms), Stage B (structural heart disease without HF symptoms), Stage C (structural heart disease with HF symptoms), and Stage D (refractory HF symptoms). Multimodal drug therapy using angiotensin converting enzyme inhibitors (ACEI), beta adrenergic blockers, angiotensin receptor blockers (ARB), aldosterone antagonists (AA), digoxin, and diuretics is aimed at neurohormonal suppression, reducing LV remodeling, and improving patient functional and exercise capacity (1). Medical management of HF can effectively reverse remodeling as shown by reductions in LV mass by 10% using ACEI, 8% with diuretics, 6% with beta blockers, and 13% with ARB. Each drug has an additive effect to improve mortality. The reduction in heart rate from beta blockage correlates significantly with improved LV ejection fraction and survival (2).

The anesthesiologist needs to be aware of the current guidelines because patients undergoing operation are frequently not prescribed appropriate medications or the correct dosages (3,4). A recent study indicates that only 60% of eligible HF patients receive ACEI, 34% beta blockers, 20% both, and 12% AA. In another study of HF patients followed 60-90 days after hospitalization, less than 18% and 8% of patients were being managed with recommended target doses of the beta blockers carvedilol and metoprolol, respectively. This alarming lapse in treatment can cause significant morbidity if LV remodeling is not prevented. Therapies which have not proven effective in managing HF patients are excessive beta blockage, endothelin antagonists, endopeptidase inhibition, cytokine inhibition, and metalloproteinase enzyme inhibitors (5).
Managing Patients With Acute Decompensated Heart Failure

Unlike the large number of prospective, randomized clinical trials which have clearly defined the optimal therapy of chronic HF patients, managing patients with acute decompensated heart failure (ADHF) is largely based on anecdotal reports and not evidence-based studies. Nearly 90% of the recommendations for ADHF management in the 2006 practice guidelines from the Heart Failure Society of America are evidence C level. Furthermore, many of the studies fail to differentiate factors which can influence outcome such as patient age, systolic blood pressure on arrival, diastolic HF with preserved ventricular function in contrast to systolic HF, and ischemic etiology in contrast to non-ischemic causes of HF. Hospital mortality increases by 34% for each 10-year increase in age (6). The combination of systolic pressure below 100 mmHg and serum creatinine > 2mg/dL increases mortality by 6-fold. Interestingly, hospital mortality is lower for patients managed chronically with ACEI and beta blockers but not for statins, digoxin, or diuretics.

![Figure 1. Treatment algorithm for acute decompensated heart failure proposed by the European Society of Cardiology. (SBP = systolic blood pressure on admission)](image)

The treatment algorithm proposed by the European Society of Cardiology is helpful by directing management according volume status, cardiac output, and blood pressure on admission (7). Approximately 90% patients are normo- or hypertensive and the remainder hypotensive which indicates a greater overall problem with vascular tone than underlying contractility. Loop diuretics are used primarily to manage ADHF symptoms of fluid overload although there are no large scale, controlled trials showing improved mortality or reduced hospitalizations with diuretics. Continuous, low-dose diuretic infusion is better than intermittent, high-dose boluses. Non-potassium sparing diuretics increase the risk of arrhythmias and death. Since diuretics can worsen renal dysfunction, ultrafiltration may be an effective alternative to acutely remove excess fluid. New insight in the cardiorenal syndrome with progressive heart and renal failure underscores the underlying causative role of elevated renal vein pressure (8).

Vasodilators and Diuretics for ADHF Management

Traditional vasodilator therapy has been confined to nitrates (venodilation) and nitroprusside (balanced arterial/venodilation). Nitrate use is complicated by development of acute tolerance within hours and nitroprusside infusion is problematic with cyanide and thiocyanate toxicity. The role of acutely adding
ACEI in the setting of ADHF is not well established. Unlike vasopressors, the use of vasodilators to manage ADHF does not by itself increase patient mortality.

1) Nesiritide
B-type natriuretic peptide is an endogenous hormone synthesized by the heart in response to increased wall stress and causes vasodilation, natriuresis, and suppression of the RAAS and sympathetic nervous system. Nesiritide is a recombinant form of human B-type natriuretic protein and was approved for treating ADHF patients in 2001 by the FDA but not in Europe. Nesiritide is a balanced arterial and venous dilator with 18-minute half-life and promotes natriuresis and diuresis while suppressing sympathetic outflow (9). In a large prospective clinical trial of 489 patients from 55 hospitals, nesiritide 2mcg/kg bolus followed by 0.01-0.03mcg/kg/min infusion improved patient symptoms and reduced LV filling pressures superior to nitroglycerin although the 30-day readmission rate and 6-month mortality remained unchanged (10). Subsequent meta-analysis of these data show a potential risk of inducing renal dysfunction and a trend towards increased 30-day mortality (7.6% vs 4%). Further study is underway to clarify these issues.

2) Vasopressin Antagonists
Vasopressin levels are elevated in ADHF and act on V1a receptors in the vascular wall to mediate vasoconstriction and on V2 receptors in the kidneys to promote water reabsorption causing hyponatremia (11). Tolvaptan is an oral, selective V2 antagonist that causes diuresis and natriuresis without detrimental effects on heart rate, blood pressure, or renal function. Although body weight and hyponatremia are reduced, tolvaptan had no effect on worsening HF 60 days after discharge or survival when compared with placebo. Vasopressin antagonists have the potential to promote free water excretion without compromising renal function but further study is needed.

3) Adenosine Antagonists
A-1 receptors are located in the afferent arteriole and proximal tubule and contribute to afferent vasoconstriction and tubuloglomerular feedback which modulate glomerular filtration (11). A-1 antagonism can induce diuresis, natriuresis, and improve creatinine clearance without adversely affecting underlying cardiac or renal function (12). Initial clinical trials show improved symptoms of dyspnea and reduced readmission for HF. There is theoretical concern that A-1 antagonism may worsen myocardial hypertrophy and lower the seizure threshold.

**Inotropes for ADHF Management**

Low systolic blood pressure on admission with ADHF is an extremely poor prognostic indicator and in-hospital mortality increases by 20% for each 10 mmHg decrement in blood pressure below 160 mmHg (6). Whereas chronic beta blocker therapy has reduced mortality from ADHF, the use of beta adrenergic agonists has not proved beneficial in the long run. Digoxin is the only FDA-approved inotrope for long-term use in ADHF patients even though mortality remains unchanged with digoxin use.

The major determinants of myocardial oxygen consumption (MVO2) are the inotropic state of the myocardium, wall stress, and heart rate (13). Under conditions of myocardial ischemia, an inotrope that increases the force of contraction could also increase MVO2 and infarct size. The traditional view for adding an inotrope to a patient with HF was that the reduction in ventricular cavity size and wall stress from improved ejection would exceed any increment in MVO2 from enhanced contractility so that the extent of ischemic injury would remain unchanged or even decrease (13). However, clinical studies of inotropes, specifically beta adrenergic agonists and phosphodiesterase inhibitors (PDEI), in ADHF patients while acutely improving NYHA score by nearly 2/3 point caused greater morbidity with atrial and ventricular arrhythmias and overall mortality. Using the University Health System Consortium
database, the in-hospital mortality for ADHF patients managed with dobutamine or milrinone was 3.5 and 3.9 times, respectively, higher than nesiritide (14). Inotropes which increase intracellular calcium (Ca\textsuperscript{++}) concentration without a reduction in wall stress actually increase MVO\textsubscript{2} (15). These findings have sparked clinical interest in developing other means of improving myocardial contractility without increasing Ca\textsuperscript{++} such as calcium sensitizers.

1) Levosimendan
Levosimendan improves contractility by enhancing Ca\textsuperscript{++} sensitivity of the myofibril specifically at the troponin C site to stabilize the Ca\textsuperscript{++}-induced conformation which facilitates and prolongs the number of actin-myosin crossbridge formation (16). Unlike other inotropes which act upstream, levosimendan does not increase sarcolemmal Ca\textsuperscript{++} influx, Ca\textsuperscript{++}i concentrations, or MVO\textsubscript{2}. In addition, levosimendan opens K\textsubscript{ATP} channels in peripheral and coronary arteries which may have a benefit in myocardial preconditioning. At high concentrations, levosimendan can act as a PDEI. Although the parent molecule has a serum half-life of one hour, an acetylated metabolite (OR-1896) is a potent calcium sensitizer and remains active for 80-90 hours. Consequently a 24 hour infusion of levosimendan will remain clinically active for 7-9 days.

Levosimendan is administered as a 3-36 mcg/kg bolus followed by continuous infusion of 0.05-0.6 mcg/kg/min for 24 hours. Steady state concentrations are reached in two hours; continuous infusion without loading achieves steady state in four hours. Neither acidosis nor the severity of HF affects levosimendan pharmacokinetics. No tolerance or rebound has been found with the clinical use of levosimendan. The drug has been approved in 140 countries for ADHF treatment but not by the FDA in this country. Prospective clinical trials with levosimendan in ADHF patients show greater and longer-lasting hemodynamic improvement than dobutamine by increasing ejection fraction and cardiac output, decreasing LV filling pressures, and improving glomerular filtration rate. Reduced hospital length of stay, symptomatic improvement, and reduction in cytokine expression and serum B-type natriuretic protein levels have been found with levosimendan. However, the incidence of hypotension and atrial and ventricular arrhythmias was greater than placebo and 6-month HF mortality remained unchanged with levosimendan when compared with dobutamine.

In ADHF patients refractory to dobutamine, the addition of levosimendan may cause significant further improvement in cardiac output (17). Similar results have been reported following cardiac surgery with low cardiac output. With the recent association of increased mortality using dobutamine to wean from cardiopulmonary bypass (18), levosimendan may offer an attractive alternative. In patients with cardiogenic shock following myocardial infarction, levosimendan produced similar benefits as intra-aortic balloon counterpulsation. One particular advantage of levosimendan is its use in ADHF patients who are chronically managed with beta blockers. Unlike dobutamine where beta blockade attenuates systolic and diastolic improvement, levosimendan maintains these beneficial effects despite carvedilol or metoprolol treatment. In particular, carvedilol inhibits the hemodynamic benefits of dobutamine but less so with PDEI or levosimendan.

2) Istaroxime
Istaroxime is a novel drug that inhibits sarcolemmal Na/K ATPase enzyme (similar to digoxin) as well as stimulation of the sarcoplasmic reticular ATPase activity to enhance diastolic Ca\textsuperscript{++}i sequestration (11). Accordingly, the drug exerts positive inotropic and lusitropic properties without proarrhythmic side effects. Administered at infusion rates of 0.5, 1.0, or 1.5 mcg/kg/min, istaroxime causes significant improvements in LV systolic and diastolic function, reduces filling pressures and heart rate, and increases cardiac output and systolic blood pressure in ADHF patients. In experimental animals, the addition of beta adrenergic blockers has no effect on the efficacy of istaroxime.
3) Stem Cell Transplantation
Various stem cells have been introduced into damaged regions by intracoronary or intramyocardial routes using bone-marrow cells, mesenchymal stem cells, skeletal myocytes, or adipose cells. Meta-analysis of 10 studies of 698 patients show modest but significant improvements in LV ejection fraction (3.7%) and reductions in infarct size (-5.6%) and end-systolic volume (-7.4 ml) (19). Cardiomyocyte transdifferentiation has been observed experimentally but incorporation of stem cells in the contractile myocardium replacing scar tissue has not been found. Benefits of stem cells may be secondary to paracrine function and angiogenesis. Phase 1 and 2 patient studies injecting stem cells directly into areas of impaired contractility are currently underway at five medical centers. Several phase 1 gene therapy trials have been initiated using intracoronary or intramyocardial injections of adenoviruses that specifically target myocardial sarcoplasmic reticulum ATPase enzyme to improve Ca$^{++}$ uptake and release.

Practical Recommendations in the Perioperative Management of Heart Failure Patients
The perioperative anesthetic management of ADHF patients can be challenging and several practical recommendations can be made. Since patients with systolic HF are frequently managed with escalating dosages of diuretics, preoperative hypovolemia should be treated appropriately. Patients with dilated cardiomyopathy maintain preload-recruitable function although limited by reduced myocardial compliance and elevated LV filling pressures (20). To accurately assess fluid volume status, dynamic indices such as systolic pressure variability may be useful as long as it is realized that an increase in magnitude of the delta up component could reflect afterload sensitivity from underlying heart failure (21). With the associated increase in blood volume, central venous access may allow prompt delivery and careful titration of vasoactive medications. Appropriate inotropic drug infusions should be readied preoperatively and started before induction of anesthesia to maintain blood pressure stability. Calcium sensitizers may prove more beneficial than traditional inotropic drugs (22). Postoperative pain should be carefully managed and patients should be observed for fluid shifts and worsening failure.

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