Perioperative Myocardial Failure

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Objectives

- Describe the pathophysiology, treatment, and outcomes of congestive heart failure in patients presenting for surgery.
- Describe the risk factors, physiology, natural history, treatment, and outcomes of postcardiopulmonary bypass ventricular dysfunction.
- Compare and contrast these two syndromes.

Introduction

Ventricular dysfunction sometimes occurs perioperatively, most often in association with cardiopulmonary bypass (CPB). This perioperative myocardial failure can often be predicted by using the medical history and selected intraoperative indicators. There are a number of effective drug treatments and, in resistant patients, mechanical assist devices can be lifesaving.

Characteristics of Patients with Perioperative Heart Failure

Chronic Heart Failure

Several million Americans have been diagnosed with chronic heart failure (CHF), and an additional 400,000 cases will be newly diagnosed each year. CHF can be the end result of any one of many conditions. In adult patients, the most common etiologies are ischemic heart disease and hypertension; in children, the most common are viral infections and congenital heart disease. In CHF, intracellular cyclic AMP (cAMP) concentrations are decreased from β-adrenergic receptor (βAR) down-regulation and impaired coupling between βARs and adenylyl cyclase. Impaired coupling results from increased intracellular concentrations of $G_{i\alpha}$ and βAR kinase. Patients with CHF respond well to preload reduction with salt restriction and diuretics; preload and afterload reduction with vasodilators (angiotensin converting enzyme inhibitors, hydralazine, or nitrates); and digoxin. Mortality is increased when positive inotropes (other than digoxin) are administered chronically, even though symptoms may decrease and quality of life improve (1). Some patients with severe CHF require infusion of positive inotropes, implantation of ventricular assist devices, or both while awaiting cardiac transplantation. There is accumulating evidence that the prognosis in CHF can be improved through "myocardial protection," either indirectly through unloading the heart (diuretics and vasodilatation) or directly, through preventing the adverse effects of neuroendocrine activation (βAR blockers and angiotensin converting enzyme inhibitors).

Low Cardiac Output Syndrome

Low cardiac output syndrome (LCOS) patients emerging from CPB demonstrate a peculiar combination of inadequate oxygen delivery to tissues, hemodilution, mild hypocalcemia and hypomagnesemia, kaliuresis, tissue thermal gradients, and variable levels of systemic vascular resistance (2). The underlying pathophysiology may include myocardial "stunning," or hypocontractile myocardium in response to ischemia and reperfusion (3). βAR down-regulation has been reported after CPB (4,5). These patients receive positive inotropic drug therapy to increase the contractility of normal and "stunned" myocardium, increase cardiac output, and maintain diastolic blood pressure at levels capable of maintaining adequate oxygen delivery to the myocardium. The LCOS often includes hypotension and, unlike CHF, responds poorly to vasodilators alone. Diastolic dysfunction, although present in many patients after CPB, is not the more prominent manifestation of LCOS. Increasing age, female sex, decreased left-ventricular ejection fraction (measured before surgery), and increased duration of CPB are all associated with a greater likelihood that inotropic drug support will be administered after coronary surgery; increased age and reduced left-ventricular ejection fraction are associated with the use of positive inotropic drugs after cardiac valve surgery (6,7).

Even patients who do not experience LCOS demonstrate declines in ventricular function after CPB, reaching a nadir some hours after arriving in the intensive

care unit. Ventricular function recovers to baseline values over the succeeding 18–24 h (8).

In a critically ill general surgical population, increased levels of oxygen delivery and consumption have been associated with improved outcome (9). Recently, Pölönen et al. (10) used a similar goal-oriented therapy to maintain venous oxygen saturation >70% and arterial blood lactate ≤2 mmol/L after heart surgery, using dobutamine infusions as necessary, and noted a shorter hospital length of stay and reduced mortality in the treatment group.

Positive Inotropic Agents

Positive inotropic drugs can be conveniently divided on the basis of their mechanism of action into cAMP-independent and cAMP-dependent agents (see Table 1).

cAMP-Independent Agents

Digoxin. Digoxin inhibits Na^+ and K^+-ATPase, increasing intracellular [Na^+] and, indirectly, intracellular [Ca^{2+}]. Intracellular calcium ions may bind to troponin-C, increasing cardiac inotropy. In patients with chronic CHF, digoxin increases left-ventricular shortening and ejection fraction (11). Digoxin is not effective for acute management of LCOS.

Calcium Salts. Contractility of isolated cardiac or skeletal muscle improves with increasing extracellular [Ca^{2+}], particularly when [Ca^{2+}] rises above the normal range. Calcium for muscle contraction derives mostly from the sarcoplasmic reticulum, not from extracellular sources. The administration of calcium consistently increases systemic vascular resistance (12,13). Calcium interacts with vasoactive drugs. In patients recovering from coronary artery bypass grafting (CABG), calcium inhibited responses to epinephrine and dobutamine, but not to amrinone (14,15). Calcium inhibition of βAR agonists likely results from direct inhibition of adenylyl cyclase (16,17). Bolus dosing of calcium has no consistent effect on cardiac output in patients emerging from CPB (12,13).

Thyroid Hormone. Hypothyroidism causes profound cardiovascular depression. The IV administration of liothyronine (T_3) rapidly restores heart rate, stroke volume index, cardiac index, and peripheral vascular resistance to normal values. Patients recovering from CPB usually exhibit low circulating T_3 concentrations and inappropriately low thyrotropin concentrations (18). The routine administration of T_3 to cardiac surgery patients increases contractile function but may not produce an inotrope-sparing effect (19). How thyroid hormone increases myocardial contractility remains unclear: T_3 increases myocardial contractile function as potently as isoproterenol, even with overwhelming βAR blockade (20), without increasing cAMP.

Table 1. Positive Inotropic Drugs

cAMP-Independent
Cardiac glycosides (digoxin)
Calcium salts
Thyroid hormone (liothyronine, T_3)
Calcium sensitizers (levosimendan)
cAMP-Dependent
β-adrenergic agonists
Epinephrine
Norepinephrine
Dobutamine
Isoproterenol
Dopaminergic agonists
Dopamine
Dopexamine
Phosphodiesterase inhibitors
Amrinone
Milrinone
Enoximone
Olprinone

Calcium-Sensitizing Drugs. Levosimendan stabilizes the calcium-bound conformation of troponin C, and its effects are highly dependent on the intracellular [Ca]. It increases systolic inotropy without impairing diastolic relaxation. Levosimendan also opens K_{ATP} channels in cardiac myocytes and vascular smooth muscle. In experimental animals, levosimendan-induced activation of K_{ATP} channels reduces myocardial infarct size (21). Levosimendan may be particularly useful for inotropic support in patients prone to arrhythmias (22).

cAMP-Dependent Agents

βAR Agonists. Catecholamines bind to βARs and activate a membrane-bound guanine nucleotide binding protein. This activates adenylyl cyclase, generating cAMP (23). Increased cAMP increases calcium influx and increases calcium sensitivity of calcium-regulatory proteins. βAR agonists decrease the sensitivity of the contractile myofilaments to calcium, promoting relaxation. This effect is opposite to that of phosphodiesterase (PDE) inhibitors and βAR agonists (24).

Epinephrine binds and activates β_1, β_2, and βARs dose dependently. Norepinephrine binds α_1, α_2, and β_1 receptors much more readily than β_2 receptors. Compared with norepinephrine, for a comparable increase in mean arterial pressure, epinephrine produces a significantly greater cardiac output. Epinephrine is often used as a first-line positive inotrope after CPB (12,14). The administration of epinephrine into the left (rather than right) atrium offers higher concentrations of epinephrine for action on the heart and peripheral vasculature, while reducing the likelihood of pulmonary hypertension. Norepinephrine has also been used as a relatively selective β_1AR agonist, particularly when combined with phentolamine to counteract its potent α_1AR and α_2AR agonist activity, and

as a powerful vasoconstrictor to counteract the "vasoplegic syndrome" that sometimes follows CPB (25).

Dobutamine binds β_1 and β_2 receptors, producing dose-dependent increases in heart rate and cardiac output and dose-dependent reductions in filling pressures (26). βAR-mediated reduction of venous capacitance, which increases the effective circulating blood volume, also contributes to the increased cardiac output. Conventional wisdom, on the basis of studies in patients with CHF and βAR down-regulation, often recommends dobutamine as a unique drug that can increase cardiac output without increasing heart rate; this notion is false. Dobutamine increases heart rate more than epinephrine after CABG (26,27). Dobutamine has been widely used to increase oxygen delivery to tissues in patients with critical illness in the hope that this measure will improve outcome (9,28–30).

Isoproterenol is a potent βAR agonist, devoid of αAR agonist activity. Isoproterenol's current applications include treatment of bradycardia (especially after orthotopic cardiac transplantation), pulmonary hypertension and right-ventricular failure, and heart failure after pediatric cardiac surgery.

Dopaminergic Agonists. Dopamine activates dopamine (DA_1 and DA_2), βARs, and αARs dose-dependently. Dopexamine lacks any direct αAR agonist activity but expresses β_2AR and DA_1 receptor agonist activity. Dopexamine also inhibits presynaptic reuptake of norepinephrine. Activation of DA_1 receptors produces vasodilation in renal, mesenteric, coronary, and cerebral arteries. Activation of DA_2 receptors inhibits release of norepinephrine and prolactin. Dopamine A_2 receptor agonists may also produce nausea and vomiting (31). Dopamine activates DA_2 receptors in the dosage range from 0.2 to 0.4 $\mu g \cdot kg^{-1} \cdot min^{-1}$; slightly higher dosages (0.5–3.0 $\mu g \cdot kg^{-1} \cdot min^{-1}$) recruit DA_1 receptors. Still higher dosages (5–10 $\mu g \cdot kg^{-1} \cdot min^{-1}$) activate βARs and αARs and have been widely used for inotropic support after heart surgery. Low doses of dopamine may increase renal blood flow and modulate corticomedullary distribution of renal blood flow (32) more than they increase cardiac output (33). Dopamine is often infused during periods of renal stress, such as during aortic surgery, sepsis, resuscitation, CPB, and norepinephrine infusion (33). However, the efficacy of dopamine in this setting is unknown, and the relationship between dopamine dose and concentrations is highly variable (34). Dopexamine and dopamine produce a more pronounced increase in jejunal mucosal perfusion than dobutamine (35). After CPB, dopexamine and dobutamine were equally effective at increasing cardiac index; however, tachycardia was more common with dopexamine (26).

PDE Inhibitors. PDE inhibitors slow the metabolism of cAMP to 5′-AMP, increasing intracellular cAMP concentrations. They also increase the calcium sensitivity of contractile proteins, increase calcium influx, and antagonize adenosine.

Amrinone proved more effective with fewer complications than dobutamine during separation from CPB (36). In patients with poor left-ventricular function, amrinone was as effective as epinephrine (37). Amrinone and epinephrine proved superior to either drug alone (37,38). After CABG, amrinone increased stroke volume and cardiac index and decreased systemic and pulmonary vascular resistances dose dependently. Amrinone increased intrapulmonary shunt and decreased Pao_2 (39).

Milrinone has inotropic and vasodilator properties similar to those of amrinone, but it is 15–20 times more potent (40,41). A 50 μg/kg milrinone loading dose is preferable to either 25 or 75 μg/kg in patients emerging from CPB (42). A loading dose of 50 μg/kg plus 0.5 $\mu g \cdot kg^{-1} \cdot min^{-1}$ infusion maintains effective plasma concentrations >100 ng/mL. In some cases, a simple 50 μg/kg milrinone dose will suffice to facilitate separation from CPB (43). In a randomized comparison of amrinone with milrinone in adult surgical patients, both drugs significantly increased cardiac index and decreased systemic and pulmonary vascular resistances (44).

Enoximone and olprinone are other PDE inhibitors that have been tested in surgical patients. Enoximone has been widely used in Europe. Olprinone is undergoing development in Japan (45). Both agents' hemodynamic effects resemble those of amrinone and milrinone.

Drug Synergism/Antagonism

Clinicians often combine two (or more) drugs, hoping to maximize their positive attributes while limiting their adverse effects. Two drugs may interact in an additive, synergistic, or antagonistic fashion. We found antagonism between calcium and βAR agonists and between dobutamine and epinephrine (14–17,46). We and others have found a combination of PDE inhibitors and βAR agonists to be more effective than either agent alone (37,38).

Mechanical Assist Devices

Patients with coronary artery disease and LCOS may benefit from intraaortic balloon counter pulsation, which has the advantage of increasing diastolic coronary blood flow without increasing myocardial oxygen consumption. Patients with severe ventricular dysfunction or cardiomyopathy may require right- or left-ventricular assist devices, or both. Use of these devices is appropriate only for patients who can be expected to have recovery of ventricular function or

who are potential candidates for orthotopic heart transplantation.

Complications of Positive Inotropes

Catecholamines may produce local tissue ischemia from subcutaneous infiltration, increase oxygen consumption, enhance lipolysis and gluconeogenesis, alter electrolyte concentrations, activate coagulation, override microvascular control mechanisms, alter distribution of cardiac output, increase myocardial work, and increase the risk of cardiac arrhythmias. The PDE-inhibitors and β-agonists increase pulmonary shunt after CABG surgery (39). Catecholamine support was associated with critical illness polyneuropathy after heart surgery (47).

Summary

Perioperative heart failure, in the form of acute exacerbation of CHF and in the form of LCOS, continues to occur, despite improvements in medical management, myocardial preservation, and surgical techniques. This may be the result of patients now undergoing heart surgery as a routine despite extremes of age and debilitating comorbidities. Fortunately, effective drug treatments are available, and most patients will make a full recovery despite an episode of perioperative heart failure.

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