Perioperative Myocardial Failure

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Perioperative heart failure most commonly occurs in the form of one of two syndromes: acute exacerbations of chronic heart failure (CHF) or the perioperative low output syndrome that sometimes follows cardiac surgery. These syndromes have distinctly different underlying pathophysiologies, natural histories, and treatments, and much confusion results when physicians overlook these differences.

Chronic Heart Failure

Nearly 5 million Americans have been diagnosed with CHF, and an additional 550,000 cases will be newly diagnosed annually. The prevalence of CHF is projected to increase twofold to threefold over the next decade, as the median age of the United States population increases (1). CHF can be the end result of any of a long list of cardiac diagnoses, all of which include impaired left ventricular function. The neurohormonal responses to left ventricular dysfunction have been implicated as stimuli for maladaptive cardiac growth, and most of the hormones and receptors of the renin-angiotensin system (RAS) are expressed in the myocardium (2).

Therapeutic Advances in CHF

In the past 20 years large, randomized clinical trials showed that angiotensin-converting enzyme (ACE) inhibitors (3,4) and angiotensin receptor blockers (5,6), but not most other vasodilators (7), prolong survival in patients with CHF. ACE inhibitors reduced mortality of patients with symptomatic CHF as much as 31% and improved outcome for asymptomatic patients with left ventricular systolic dysfunction resulting from cardiomyopathy (2) or after myocardial infarction (8,9). Thus, ACE inhibitors should be given to all patients with CHF. Angiotensin receptor blockers may be used as alternatives for the treatment of patients with symptomatic CHF if there are intolerable side effects to ACE inhibitors. Two large trials have demonstrated reduced mortality with aldosterone receptor antagonists in CHF in patients with severe symptomatic heart failure and in patients with left ventricular dysfunction after myocardial infarction alone (10,11). Recent studies have reported marked increases in hospital admissions and deaths related to hyperkalemia with widespread use of spironolactone (12).

The heart in CHF is resistant to β-adrenergic receptor (βAR) agonists (13,14). Intracellular cyclic adenosine monophosphate (cAMP) concentrations decrease because of βAR down-regulation and impaired coupling between βARs and adenylyl cyclase from increased intracellular concentrations of $G_{i\alpha}$ and βAR kinase. Unlike the case for β_1 and β_2 ARs, β_3 ARs are up-regulated in heart failure (15–17). β_3 AR activation decreases contractility as a result of activation of a nitric oxide pathway and increased intracellular cGMP (18).

In CHF, long-term βAR blockade improves systolic function and myocardial energetics and reverses pathologic remodeling. βAR blockers reverse the up-regulation of gene expression of natriuretic peptides, fetal-like α-myosin heavy chain, SERCA2, and α-myosin heavy chain, and reduce myocyte apoptosis (19,20). Metoprolol CR/XL, bisoprolol, and carvedilol (in conjunction with ACE inhibitors) reduce morbidity (hospitalizations) in symptomatic, Stage C and D CHF patients (New York Heart Association II–IV class) (21–24).

Current evidence suggests that βAR blockers should be given to CHF patients with reduced ejection fraction who are stabilized on ACE inhibitors and diuretics unless there is a contraindication (25,26). Although βAR blocker therapy is recommended for asymptomatic patients with impaired left ventricular function, there is no supporting evidence from randomized trials (25).

In addition to agents that improve outcomes, diuretics and digoxin are often prescribed for patients with symptomatic CHF. Digoxin is the only positive inotropic drug approved for the management of chronic heart failure. Digoxin reduces the incidence of heart failure exacerbations but has no effect on survival (27). Patients with mildly symptomatic CHF who were randomized to digoxin withdrawal had an increased likelihood of treatment failure compared with those who continued to receive digoxin (28,29). Accordingly, digoxin is recommended for symptomatic CHF unless contraindicated.

Unsuccessful Therapies

Endothelin-1 produces vasoconstriction, remodeling of the myocardium, and neurohormonal activation, and it has proarrhythmic and negative inotropic effects. Plasma concentrations of endothelin-1 are increased in patients with CHF (30). However, clinical trials of multiple endothelin receptor antagonists (including bosentan, enrasentan, and darusentan) and of the cytokine antagonist etanercept failed to demonstrate efficacy (31–34). Two large-scale, randomized, controlled trials comparing the total mortality with omapatrilat (a neutral endopeptidase inhibitor) versus ACE inhibition showed no significant advantage with endopeptidase inhibition (35,36). Other agents in early stages of clinical investigation include vasopressin antagonists, positive inotropes, antiarrhythmics, and growth hormone.

Nonpharmacologic Therapies

Cardiac resynchronization therapy with a pacemaker-defibrillator decreased the likelihood of death from arrhythmias and the frequency of hospitalization compared with conventional therapy (37). Stem cell therapy has shown promise in the treatment for ischemic heart disease in small clinical studies (38,39). Finally, novel implantable pulse generators, defibrillators, and "destination" assist devices remain in development.

Management of Acute Exacerbations of CHF

Patients may require intensive management of exacerbations of CHF associated with myocardial ischemia or infarction, worsening valvular function, infections, failure to maintain an established drug and dietary regimen, or as a consequence of fluid resuscitation for trauma or major surgery (40,41). Such patients may undergo invasive monitoring of systemic and pulmonary arterial pressures, particularly in the perioperative period, but the safety of this practice has been questioned (42,43).

Positive inotropic drugs, principally dobutamine or milrinone, diuretics, and IV vasodilators, have long been used to treat decompensated heart failure (41). Some patients with severe CHF require infusion of positive inotropes, implantation of ventricular assist devices, or both while awaiting cardiac transplantation. A recent placebo-controlled study showed that CHF patients receiving milrinone were significantly more likely to require intervention for hypotension or to have new atrial arrhythmias (44). A new class of positive inotropes, the calcium sensitizers, has recently been introduced (45,46). Experience remains limited with these agents.

Brain natriuretic peptide (BNP), secreted in cardiac ventricles (47), functions as a natriuretic, diuretic, and direct vasodilator. With increasing severity of CHF, the concentrations of BNP in blood also increase (47). Measurements of BNP in blood are used to evaluate new onset of dyspnea (to discriminate between lung disease and heart failure). Recombinant BNP has been released as a drug (nesiritide), indicated for patients with exacerbations of acute heart failure. Nesiritide reduces symptoms of acute decompensated heart failure similarly to nitroglycerine, without development of acute tolerance, as is common with nitroglycerine (48), and may prove useful in surgical patients.

Low Cardiac Output Syndrome

The low cardiac output syndrome (LCOS) is generally a self-limited condition, and much less is known about its pathophysiology than about CHF. It occurs in association with heart surgery, most often after ischemia and reperfusion. These patients have a characteristic combination of left ventricular dysfunction, inadequate oxygen delivery to tissues, hemodilution, and mild hypocalcemia and hypomagnesemia. The underlying myocardial pathophysiology may include "stunning" (hypocontractile myocardium in response to ischemia and reperfusion) and myocardial ischemia (49). Cardiac βAR down-regulation has been reported after cardiopulmonary bypass (CPB) but has no known relationship to LCOS (50,51).

Diastolic dysfunction, although present in many patients after CPB, is not a prominent manifestation of LCOS. Increasing age, female sex, decreased left ventricular ejection fraction, 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 (52–54). 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. In most of these patients, ventricular function recovers to baseline values over the succeeding 18–24 h (55).

Treatment of LCOS

LCOS is usually treated with positive inotropic drugs to increase the contractility of normal, ischemic, hibernating, and "stunned" myocardium in the hope of increasing cardiac output and diastolic blood pressure to levels capable of maintaining adequate oxygen delivery to the myocardium. Positive inotropic drugs can be conveniently divided on the basis of their mechanism of action into cAMP-independent and cAMP-dependent agents (Table 1). The cAMP-dependent agents are the more useful for LCOS.

Table 1. Positive Inotropic Drugs

cAMP-independent
Cardiac glycosides (digoxin)
Calcium salts
Thyroid hormone (liothyronine, T_3)
Calcium sensitizers
Levosimendan
Pimobendan
cAMP-dependent
β-adrenergic agonists
Epinephrine
Norepinephrine
Dobutamine
Isoproterenol
Dopaminergic agonists
Dopamine
Dopexamine
Phosphodiesterase inhibitors
Inamrinone
Milrinone
Enoximone
Olprinone

cAMP-Independent Agents

Calcium Salts

Contractility of isolated cardiac, skeletal, or vascular muscle improves with increasing extracellular [Ca^{2+}], particularly when [Ca^{2+}] increases above the normal range. Despite long use, bolus doses of calcium salts have no consistent effects on cardiac output in patients emerging from CPB (56,57). In patients recovering from coronary artery bypass grafting (CABG), calcium inhibited responses to epinephrine and dobutamine but not to inamrinone (58,59). Calcium inhibition of βAR agonists likely results from direct inhibition of adenylyl cyclase (60,61). Calcium salts are ineffective at treating LCOS, other than increasing blood pressure.

Thyroid Hormone

Hypothyroidism causes profound cardiovascular depression that can be reversed rapidly by IV liothyronine (T_3) (62). T_3 increases myocardial contractile function as potently as isoproterenol, even with overwhelming βAR blockade, without increasing cAMP (63). Both children and adults exhibit low circulating T_3 concentrations and inappropriately low thyrotropin concentrations after cardiac surgery (64). Nevertheless, the routine administration of T_3 to cardiac surgery patients is neither effective nor recommended (65,66).

Calcium-Sensitizing Drugs

Levosimendan and pimobendan stabilize the calcium-bound conformation of troponin C, increasing systolic inotropy without increasing energy demand or impairing diastolic relaxation. They have not been associated with an increase in arrhythmogenicity. The calcium sensitizers open K_{ATP} channels in vascular smooth muscle and cardiac myocytes inducing vasodilation and cardioprotection (in theory), respectively. Although several studies have described the successful use of levosimendan after coronary bypass surgery, there is no consensus as to how and when calcium sensitizers should be used relative to other better established agents (67,68).

cAMP-Dependent Positive Inotropes

Beta-adrenergic Receptor (βARs) Agonists

Catecholamines bind βARs and activate a membrane-bound guanine nucleotide binding protein. This activates adenylyl cyclase, generating cAMP. Increased cAMP increases calcium influx and increases calcium sensitivity of calcium-regulatory proteins and decreases the sensitivity of the contractile myofilaments to calcium, promoting relaxation.

Epinephrine binds and activates β_1, β_2, and αARs dose-dependently. Norepinephrine binds α_1, α_2, and β_1 ARs much more readily than β_2 ARs. 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 (56). 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 (69). Norepinephrine has also been used as a powerful vasoconstrictor to counteract the "vasoplegic syndrome" which sometimes occurs after CPB (70). Vasoplegia can also be treated with vasopressin.

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 (71). Conventional wisdom 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 (71,72).

Dopaminergic Agonists

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 and may also produce nausea and vomiting. Dopamine activates dopamine (DA_1 and DA_2) receptors, βARs, and αARs dose dependently. Traditional teaching is that dopamine activates specific receptors at defined infusion rates. However,

the relationship between dopamine doses and concentrations is highly variable (73). Low doses of dopamine may increase renal blood flow and modulate corticomedullary distribution of renal blood flow more than they increase cardiac output (74,75). Dopamine is often infused during periods of renal stress, such as during cardiovascular surgery, sepsis, and norepinephrine infusion, but has never been shown to prevent renal failure (75). Dopamine increases splanchnic oxygen consumption in cardiac surgery patients (76). Dopexamine lacks any direct αAR agonist activity but binds β_2AR and DA_1 receptors. Dopexamine and dopamine increase jejunal mucosal perfusion more than dobutamine (77). After CPB, dopexamine and dobutamine were equally effective at increasing cardiac index; however, tachycardia was more common with dopexamine (71).

Phosphodiesterase Inhibitors

The phosphodiesterase inhibitors inamrinone, milrinone, enoximone, and olprinone block 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.

During separation from CPB, inamrinone was more effective and produced fewer complications than dobutamine (78). Inamrinone was as effective as epinephrine, and the combination proved superior to either drug alone (79,80). After CABG, inamrinone increased stroke volume and cardiac index and decreased systemic and pulmonary vascular resistances dose dependently but increased intrapulmonary shunt and decreased Pao_2 (81).

Milrinone has inotropic and vasodilator properties similar to those of inamrinone but is 15–30 times more potent (82,83). A 50 μg/kg milrinone loading dose is preferable to either 25 or 75 μg/kg in patients emerging from CPB (84). 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 single 50 μg/kg milrinone dose will suffice to facilitate separation from CPB (85). In a randomized comparison of inamrinone with milrinone in adult surgical patients, no significant hemodynamic differences were detected (86).

In a study of patients with poor left ventricular function, preemptive inamrinone reduced the subsequent need for "rescue" drug support (79). Patients receiving preemptive infusions of either inamrinone or milrinone required significantly less dopamine, and demonstrated lower postoperative concentrations of lactate, lactate dehydrogenase, creatine kinase, C-reactive protein, and glucose, than did those receiving placebo (87). A controlled clinical trial recently showed that prophylactic milrinone improved outcomes after cardiac surgery in children (88).

Enoximone has been widely used in Europe. Olprinone has been used in Japan (89). These agents' hemodynamic effects resemble those of inamrinone and milrinone. When infused at doses similarly effective at increasing cardiac index, olprinone produced greater increases in hepatosplanchnic blood flow than inamrinone or milrinone (90). Olprinone has vascular capacitance effects opposite to those of dobutamine with capacitance decreasing after dobutamine and increasing after olprinone (91).

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. There is antagonism between calcium and βAR agonists and between dobutamine and epinephrine (58–61,92). Combinations of phosphodiesterase inhibitors and βAR agonists appear more effective than agents of either class alone (79,80).

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 and pressure without increasing myocardial oxygen consumption. Unfortunately, the 30-day mortality of patients undergoing balloon implantation for LCOS is 34% (93). Patients with severe persisting ventricular dysfunction or cardiomyopathy may require right or left ventricular assist devices (or both). These devices are usually only implanted in patients who can be expected to have recovery of ventricular function or who may be potential candidates for orthotopic heart transplantation. Trials are underway of assist devices as "destination therapy."

Summary

Perioperative heart failure, in the forms of acute exacerbations of CHF and LCOS, continues to occur, despite improvements in medical management, myocardial preservation, and surgical techniques. This may be the result of patients undergoing heart surgery despite extremes of age and debilitating comorbidities and of the increasing survival of patients with CHF. Fortunately, effective treatments are available, and most patients will recover from an episode of perioperative heart failure.

References

1. Eriksson H. Heart failure: a growing public health problem. J Intern Med 1995;237:135–41.
2. Dell' Italia LJ, Sabri K. Activation of the renin-angiotensin system in human cardiac hypertrophy and heart failure. In: Mann DL, ed. Heart Failure. Philadelphia: WB Saunders, 2004:129–43.
3. Garg R, Yusuf S. Overview of randomized trials of angiotensin-converting enzyme inhibitors on mortality and morbidity in patients with heart failure. Collaborative Group on ACE Inhibitor Trials. JAMA 1995;273:1450–6.
4. Flather MD, Yusuf S, Kober L, et al. Long-term ACE-inhibitor therapy in patients with heart failure or left-ventricular dysfunction: a systematic overview of data from individual patients. ACE-Inhibitor Myocardial Infarction Collaborative Group. Lancet 2000;355:1575–81.
5. Cohn JN, Tognoni G, Valsartan Heart Failure Trial Investigators. A randomized trial of the angiotensin-receptor blocker valsartan in chronic heart failure. N Engl J Med 2001;345: 1667–75.
6. Pfeffer MA, Swedberg K, Granger CB, et al. Effects of candesartan on mortality and morbidity in patients with chronic heart failure: the CHARM-Overall programme. Lancet 2003;362: 759–66.
7. Consensus recommendations for the management of chronic heart failure on behalf of the membership of the advisory council to improve outcomes nationwide in heart failure. Am J Cardiol 1999;83:1A–38A.
8. Pfeffer MA, Braunwald E, Moye LA, et al. Effect of captopril on mortality and morbidity in patients with left ventricular dysfunction after myocardial infarction: results of the survival and ventricular enlargement trial. The SAVE Investigators. N Engl J Med 1992;327:669–77.
9. ISIS-4 (Fourth International Study of Infarct Survival) Collaborative Group. ISIS-4: a randomised factorial trial assessing early oral captopril, oral mononitrate, and intravenous magnesium sulphate in 58,050 patients with suspected acute myocardial infarction. Lancet 1995;345:669–85.
10. Pitt B, Zannad F, Remme WJ, et al. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. Randomized Aldactone Evaluation Study Investigators. N Engl J Med 1999;341:709–17.
11. Pitt B, Remme W, Zannad F, et al. Eplerenone, a selective aldosterone blocker, in patients with left ventricular dysfunction after myocardial infarction. N Engl J Med 2003;348:1309–21.
12. Juurlink DN, Mamdani MM, Lee DS, et al. Rates of hyperkalemia after publication of the randomized aldactone evaluation study. N Engl J Med 2004;351:543–51.
13. Bristow MR, Ginsburg R, Minobe W, et al. Decreased catecholamine sensitivity and beta-adrenergic-receptor density in failing human hearts. N Engl J Med 1982;307:205–11.
14. Ungerer M, Bohm M, Elce JS, et al. Altered expression of beta-adrenergic receptor kinase and beta 1-adrenergic receptors in the failing human heart. Circulation 1993;87:454–63.
15. Cheng HJ, Zhang ZS, Onishi K, et al. Upregulation of functional beta(3)-adrenergic receptor in the failing canine myocardium. Circ Res 2001;89:599–606.
16. Morimoto A, Hasegawa H, Cheng HJ, et al. Endogenous beta3-adrenoreceptor activation contributes to left ventricular and cardiomyocyte dysfunction in heart failure. Am J Physiol Heart Circ Physiol 2004;286:H2425–33.
17. Moniotte S, Kobzik L, Feron O, et al. Upregulation of beta(3)-adrenoceptors and altered contractile response to inotropic amines in human failing myocardium. Circulation 2001;103: 1649–55.
18. Gauthier C, Leblais V, Kobzik L, et al. The negative inotropic effect of beta3-adrenoceptor stimulation is mediated by activation of a nitric oxide synthase pathway in human ventricle. J Clin Invest 1998;102:1377–84.
19. Weber KT. Fibrosis and hypertensive heart disease. Curr Opin Cardiol 2000;15:264–72.
20. Sabbah HN, Sharov VG, Gupta RC, et al. Chronic therapy with metoprolol attenuates cardiomyocyte apoptosis in dogs with heart failure. J Am Coll Cardiol 2000;36:1698–705.
21. Packer M, Coats AJ, Fowler MB, et al. Effect of carvedilol on survival in severe chronic heart failure. N Engl J Med 2001;344: 1651–8.
22. The Cardiac Insufficiency Bisoprolol Study II (CIBIS-II): a randomised trial. Lancet 1999;353:9–13.
23. Effect of metoprolol CR/XL in chronic heart failure: Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure (MERIT-HF) Lancet 1999;353:2001–7.
24. Packer M, Bristow MR, Cohn JN, et al. The effect of carvedilol on morbidity and mortality in patients with chronic heart failure. United States Carvedilol Heart Failure Study Group. N Engl J Med 1996;334:1349–55.
25. Hunt SA, Baker DW, Chin MH, et al. ACC/AHA guidelines for the evaluation and management of chronic heart failure in the adult: executive summary. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to revise the 1995 Guidelines for the Evaluation and Management of Heart Failure). J Am Coll Cardiol 2001;38:2101–13.
26. Remme WJ, Swedberg K, Task Force for the Diagnosis and Treatment of Chronic Heart Failure, European Society of Cardiology. Guidelines for the diagnosis and treatment of chronic heart failure. Eur Heart J 2001;22:1527–60.
27. The Digitalis Investigation Group. The effect of digoxin on mortality and morbidity in patients with heart failure. N Engl J Med 1997;336:525–33.
28. Adams KF Jr., Gheorghiade M, Uretsky BF, et al. Patients with mild heart failure worsen during withdrawal from digoxin therapy. J Am Coll Cardiol 1997;30:42–8.
29. Rahimtoola SH. Digitalis therapy for patients in clinical heart failure. Circulation 2004;109:2942–6.
30. Ergul A, Grubbs AL, Zhang Y, Spinale FG. Selective upregulation of endothelin converting enzyme-1a in the human failing heart. J Card Fail 2000;6:314–20.
31. Teerlink JR. Recent heart failure trials of neurohormonal modulation (OVERTURE and ENABLE): approaching the asymptote of efficacy? J Card Fail 2002;8:124–7.
32. Kalra PR, Moon JC, Coats AJ. Do results of the ENABLE (Endothelin Antagonist Bosentan for Lowering Cardiac Events in Heart Failure) study spell the end for non-selective endothelin antagonism in heart failure? Int J Cardiol 2002;85:195–7.
33. Neunteufl T, Berger R, Pacher R. Endothelin receptor antagonists in cardiology clinical trials. Expert Opin Investig Drugs 2002;11:431–43.
34. Mann DL, McMurray JJ, Packer M, et al. Targeted anticytokine therapy in patients with chronic heart failure: results of the Randomized Etanercept Worldwide Evaluation (RENEWAL). Circulation 2004;109:1594–602.
35. Packer M, Califf RM, Konstam MA, et al. Comparison of omapatrilat and enalapril in patients with chronic heart failure: the Omapatrilat Versus Enalapril Randomized Trial of Utility in Reducing Events (OVERTURE). Circulation 2002;106:920–6.
36. Worthley MI, Corti R, Worthley SG. Vasopeptidase inhibitors: will they have a role in clinical practice? Br J Clin Pharmacol 2004;57:27–36.
37. Bristow MR, Saxon LA, Boehmer J, et al. Cardiac-resynchronization therapy with or without an implantable defibrillator in advanced chronic heart failure. N Engl J Med 2004;350:2140–50.
38. Mathur A, Martin JF. Stem cells and repair of the heart. Lancet 2004;364:183–92.
39. Wollert KC, Meyer GP, Lotz J, et al. Intracoronary autologous bone-marrow cell transfer after myocardial infarction: the BOOST randomised controlled clinical trial. Lancet 2004;364: 141–8.
40. McMurray JJ: Heart failure in 10 years time: focus on pharmacological treatment. Heart 2002;88(Suppl 2):ii40–6.

41. DiDomenico RJ, Park HY, Southworth MR, et al. Guidelines for acute decompensated heart failure treatment. Ann Pharmacother 2004;38:649–60.
42. Ivanov R, Allen J, Calvin JE. The incidence of major morbidity in critically ill patients managed with pulmonary artery catheters: a meta-analysis. Crit Care Med 2000;28:615–9.
43. Robin ED. Death by pulmonary artery flow-directed catheter: time for a moratorium? Chest 1987;92:727–31.
44. Cuffe MS, Califf RM, Adams KF Jr, et al. Short-term intravenous milrinone for acute exacerbation of chronic heart failure: a randomized controlled trial. JAMA 2002;287:1541–7.
45. Follath F, Cleland JG, Just H, et al. Efficacy and safety of intravenous levosimendan compared with dobutamine in severe low-output heart failure (the LIDO study): a randomised double-blind trial. Lancet 2002;360:196–202.
46. Kivikko M, Lehtonen L, Colucci WS. Sustained hemodynamic effects of intravenous levosimendan. Circulation 2003;107:81–6.
47. de Denus S, Pharand C, Williamson DR. Brain natriuretic peptide in the management of heart failure: the versatile neurohormone. Chest 2004;125:652–68.
48. Elkayam U, Akhter MW, Singh H, et al. Comparison of effects on left ventricular filling pressure of intravenous nesiritide and high-dose nitroglycerin in patients with decompensated heart failure. Am J Cardiol 2004;93:237–40.
49. Bolli R. Myocardial "stunning" in man. Circulation 1992;86: 1671–91.
50. Schwinn DA, Leone BJ, Spahn DR, et al. Desensitization of myocardial beta-adrenergic receptors during cardiopulmonary bypass. Evidence for early uncoupling and late downregulation. Circulation 1991;84:2559–67.
51. Booth JV, Landolfo KP, Chesnut LC, et al. Acute depression of myocardial beta-adrenergic receptor signaling during cardiopulmonary bypass: impairment of the adenylyl cyclase moiety. Duke Heart Center Perioperative Desensitization Group. Anesthesiology 1998;89:602–11.
52. Royster RL, Butterworth JF 4th, Prough DS, et al. Preoperative and intraoperative predictors of inotropic support and long-term outcome in patients having coronary artery bypass grafting. Anesth Analg 1991;72:729–36.
53. Butterworth JF 4th, Legault C, Royster RL, Hammon JW Jr. Factors that predict the use of positive inotropic drug support after cardiac valve surgery. Anesth Analg 1998;86:461–7.
54. McKinlay KH, Schinderle DB, Swaminathan M, et al. Predictors of inotrope use during separation from cardiopulmonary bypass. J Cardiothorac Vasc Anesth 2004;18:404–8.
55. Breisblatt WM, Stein KL, Wolfe CJ, et al. Acute myocardial dysfunction and recovery: a common occurrence after coronary bypass surgery. J Am Coll Cardiol 1990;15:1261–9.
56. Royster RL, Butterworth JF 4th, Prielipp RC, et al. A randomized, blinded, placebo-controlled evaluation of calcium chloride and epinephrine for inotropic support after emergence from cardiopulmonary bypass. Anesth Analg 1992;74:3–13.
57. Johnston WE, Robertie PG, Butterworth JF 4th, et al. Is calcium or ephedrine superior to placebo for emergence from cardiopulmonary bypass? J Cardiothorac Vasc Anesth 1992;6:528–34.
58. Zaloga GP, Strickland RA, Butterworth JF 4th, et al. Calcium attenuates epinephrine's beta-adrenergic effects in postoperative heart surgery patients. Circulation 1990;81:196–200.
59. Butterworth JF 4th, Zaloga GP, Prielipp RC, et al. Calcium inhibits the cardiac stimulating properties of dobutamine but not of amrinone. Chest 1992;101:174–80.
60. Prielipp RC, Hill T, Washburn D, Zaloga GP. Circulating calcium modulates adrenaline induced cyclic adenosine monophosphate production. Cardiovasc Res 1989;23:838–41.
61. Abernethy WB, Butterworth JF 4th, Prielipp RC, et al. Calcium entry attenuates adenylyl cyclase activity: a possible mechanism for calcium-induced catecholamine resistance. Chest 1995;107: 1420–5.
62. Klemperer JD. Thyroid hormone and cardiac surgery. Thyroid 2002;12:517–21.
63. Ririe DG, Butterworth JF 4th, Royster RL, et al. Triiodothyronine increases contractility independent of beta-adrenergic receptors or stimulation of cyclic-3',5'-adenosine monophosphate. Anesthesiology 1995;82:1004–12.
64. Ririe DG, Butterworth JF, Hines M, et al. Effects of cardiopulmonary bypass and deep hypothermic circulatory arrest on the thyroid axis during and after repair of congenital heart defects: preservation by deep hypothermia? Anesth Analg 1998;87: 543–8.
65. Klemperer JD, Klein I, Gomez M, et al. Thyroid hormone treatment after coronary-artery bypass surgery. N Engl J Med 1995; 333:1522–7.
66. Bennett-Guerrero E, Jimenez JL, White WD, et al. Cardiovascular effects of intravenous triiodothyronine in patients undergoing coronary artery bypass graft surgery: a randomized, double-blind, placebo-controlled trial. Duke T3 Study Group. JAMA 1996;275:687–92.
67. Lilleberg J, Nieminen MS, Akkila J, et al. Effects of a new calcium sensitizer, levosimendan, on haemodynamics, coronary blood flow and myocardial substrate utilization early after coronary artery bypass grafting. Eur Heart J 1998;19:660–8.
68. Nijhawan N, Nicolosi AC, Montgomery MW, et al. Levosimendan enhances cardiac performance after cardiopulmonary bypass: a prospective, randomized placebo-controlled trial. J Cardiovasc Pharmacol 1999;34:219–28.
69. Fullerton DA, St Cyr JA, Albert JD, Grover FL. Hemodynamic advantage of left atrial epinephrine administration after cardiac operations. Ann Thorac Surg 1993;56:1263–6.
70. Kristof AS, Magder S. Low systemic vascular resistance state in patients undergoing cardiopulmonary bypass. Crit Care Med 1999;27:1121–7.
71. MacGregor DA, Butterworth JF 4th, Zaloga CP, et al. Hemodynamic and renal effects of dopexamine and dobutamine in patients with reduced cardiac output following coronary artery bypass grafting. Chest 1994;106:835–41.
72. Butterworth JF 4th, Prielipp RC, Royster RL, et al. Dobutamine increases heart rate more than epinephrine in patients recovering from aortocoronary bypass surgery. J Cardiothorac Vasc Anesth 1992;6:535–41.
73. MacGregor DA, Smith TE, Prielipp RC, et al. Pharmacokinetics of dopamine in healthy male subjects. Anesthesiology 2000;92: 338–46.
74. Frishman WH, Hotchkiss H. Selective and nonselective dopamine receptor agonists: an innovative approach to cardiovascular disease treatment. Am Heart J 1996;132:861–70.
75. Richer M, Robert S, Lebel M. Renal hemodynamics during norepinephrine and low-dose dopamine infusions in man. Crit Care Med 1996;24:1150–6.
76. Jakob SM, Ruokonen E, Takala J. Effects of dopamine on systemic and regional blood flow and metabolism in septic and cardiac surgery patients. Shock 2002;18:8–13.
77. Thoren A, Elam M, Ricksten SE. Differential effects of dopamine, dopexamine, and dobutamine on jejunal mucosal perfusion early after cardiac surgery. Crit Care Med 2000;28:2338–43.
78. Dupuis JY, Bondy R, Cattran C, et al. Amrinone and dobutamine as primary treatment of low cardiac output syndrome following coronary artery surgery: a comparison of their effects on hemodynamics and outcome. J Cardiothorac Vasc Anesth 1992;6:542–53.
79. Butterworth JF 4th, Royster RL, Prielipp RC, et al. Amrinone in cardiac surgical patients with left-ventricular dysfunction: a prospective, randomized placebo-controlled trial. Chest 1993; 104:1660–7.
80. Royster RL, Butterworth JF 4th, Prielipp RC, et al. Combined inotropic effects of amrinone and epinephrine after cardiopulmonary bypass in humans. Anesth Analg 1993;77:662–72.
81. Prielipp RC, Butterworth JF 4th, Zaloga GP, et al. Effects of amrinone on cardiac index, venous oxygen saturation and venous admixture in patients recovering from cardiac surgery. Chest 1991;99:820–5.
82. Levy JH, Bailey JM, Deeb GM. Intravenous milrinone in cardiac surgery. Ann Thorac Surg 2002;73:325–30.

83. Bailey JM, Levy JH, Kikura M, et al. Pharmacokinetics of intravenous milrinone in patients undergoing cardiac surgery. Anesthesiology 1994;81:616–22.
84. Butterworth JF 4th, Hines RL, Royster RL, James RL. A pharmacokinetic and pharmacodynamic evaluation of milrinone in adults undergoing cardiac surgery. Anesth Analg 1995;81: 783–92.
85. Lobato EB, Florete O Jr, Bingham HL. A single dose of milrinone facilitates separation from cardiopulmonary bypass in patients with pre-existing left ventricular dysfunction. Br J Anaesth 1998; 81:782–4.
86. Rathmell JP, Prielipp RC, Butterworth JF, et al. A multicenter, randomized, blind comparison of amrinone with milrinone after elective cardiac surgery. Anesth Analg 1998;86:683–90.
87. Kikura M, Sato S. The efficacy of preemptive milrinone or amrinone therapy in patients undergoing coronary artery bypass grafting. Anesth Analg 2002;94:22–30.
88. Hoffman TM, Wernovsky G, Atz AM, et al. Prophylactic intravenous use of milrinone after cardiac operation in pediatrics. Prophylactic intravenous use of milrinone after cardiac operation in pediatrics (PRIMACORP) study. Am Heart J 2002;143: 15–21.
89. Orime Y, Shiono M, Hata H, et al. Post-operative effects of olprinone after coronary artery bypass grafting. Ann Thorac Cardiovasc Surg 1998;4:340–6.
90. Iribe G, Yamada H, Matsunaga A, Yoshimura N. Effects of the phosphodiesterase III inhibitors olprinone, milrinone, and amrinone on hepatosplanchnic oxygen metabolism. Crit Care Med 2000;28:743–8.
91. Tanoue Y, Morita S, Nagano I, et al. Effect of phosphodiesterase III inhibitor on contractility, afterload, and vascular capacitance during right heart bypass preparation. Jpn J Thorac Cardiovasc Surg 2001;49:607–13.
92. Prielipp RC, MacGregor DA, Royster RL, et al. Dobutamine antagonizes epinephrine's biochemical and cardiotonic effects: results of an *in vitro* model using human lymphocytes and a clinical study in patients recovering from cardiac surgery. Anesthesiology 1998;89:49–57.
93. Hausmann H, Potapov EV, Koster A, et al. Prognosis after the implantation of an intra-aortic balloon pump in cardiac surgery calculated with a new score. Circulation 2002;106(Suppl 1): I203–6.