

# Perioperative Management of Chronic Heart Failure

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Heart failure (HF) is one of the few cardiac conditions that is increasing. Despite a better understanding of how hormones and other signaling systems underlie the pathophysiology, and despite improved outcomes from pharmacologic therapy, many HF patients receive no effective treatment. Patients with HF commonly require medical diagnosis and management in operating rooms and critical care units; thus anesthesiologists are obliged to remain up-to-date both with advances in outpatient (chronic) medical management and with inpatient treatments for acute exacerbations of HF. Accordingly, we reviewed angiotensin-converting enzyme inhibitors, angiotensin receptor blockers,  $\beta$ -adrenergic receptor blockers, and aldosterone antagonists because these drugs prolong life and are included in current clinical practice guidelines for treating patients with chronic HF. We also reviewed the implications of chronic HF for patients undergoing surgery and anesthesia and discuss how best to provide intensive treatment for acute exacerbations of symptoms, such as might be caused by excessive intravascular volume, inappropriate drug "holidays," or worsening of the underlying cardiac disease.

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**C**hronic heart failure (HF), a clinical syndrome in which abnormalities of ventricular function and neurohormonal regulation lead to pulmonary venous congestion, exercise intolerance, and decreased life expectancy, remains the one major cardiovascular (CV) disorder that has increased both in incidence and prevalence in recent years (1). Chronic HF affects nearly five million persons in the United States, where roughly 550,000 new cases are diagnosed annually. Currently, 1% of those 50–59 yr of age and 10% of those older than 80 yr have HF (2). Thus HF is primarily a disease of the elderly, and its prevalence will likely increase two- to threefold over the next decade as the median age of world populations increases (3). The increasingly prolonged survival of patients with various CV disorders that culminate in left ventricular dysfunction (e.g., acute mortality after myocardial infarction has declined) adds to the HF epidemic. Treatment of HF costs the United States an estimated \$38 billion annually (4), and it contributes to

approximately 250,000 deaths per year (5). Given the rapid evolution of standard therapy and the frequency with which chronic HF patients present to the operating room and intensive care unit, anesthesiologists are obliged to know contemporary "best practices" to make appropriate diagnostic and treatment choices and appropriate judgments about the need for cardiac consultations.

We review the medical management of chronic HF, focusing on the results of large-scale, randomized clinical trials and on consensus guidelines published by the American College of Cardiology (ACC), the American Heart Association (AHA), the Heart Failure Society of America, and the European Society of Cardiology (6–8). These trials and guidelines emphasize chronic HF associated with left ventricular systolic dysfunction; nevertheless, we will also discuss HF with preserved systolic function (or diastolic HF). We also review the management of acutely decompensated HF. Finally, this review does not focus on the acute HF that appears for the first time during or after cardiac surgery, as the mechanisms and treatments of this condition are quite different from chronic HF.

## HF CLASSIFICATION

The updated ACC/AHA guidelines for evaluating and managing HF include a new, four-stage classification system emphasizing the progression of the disease (Fig. 1). The new guidelines include patients with "preclinical" stages of HF with the hope of slowing (and perhaps reversing) progression of disease. The staging system is meant to complement, not replace, the widely used New York Heart Association (NYHA) classification, which is organized according

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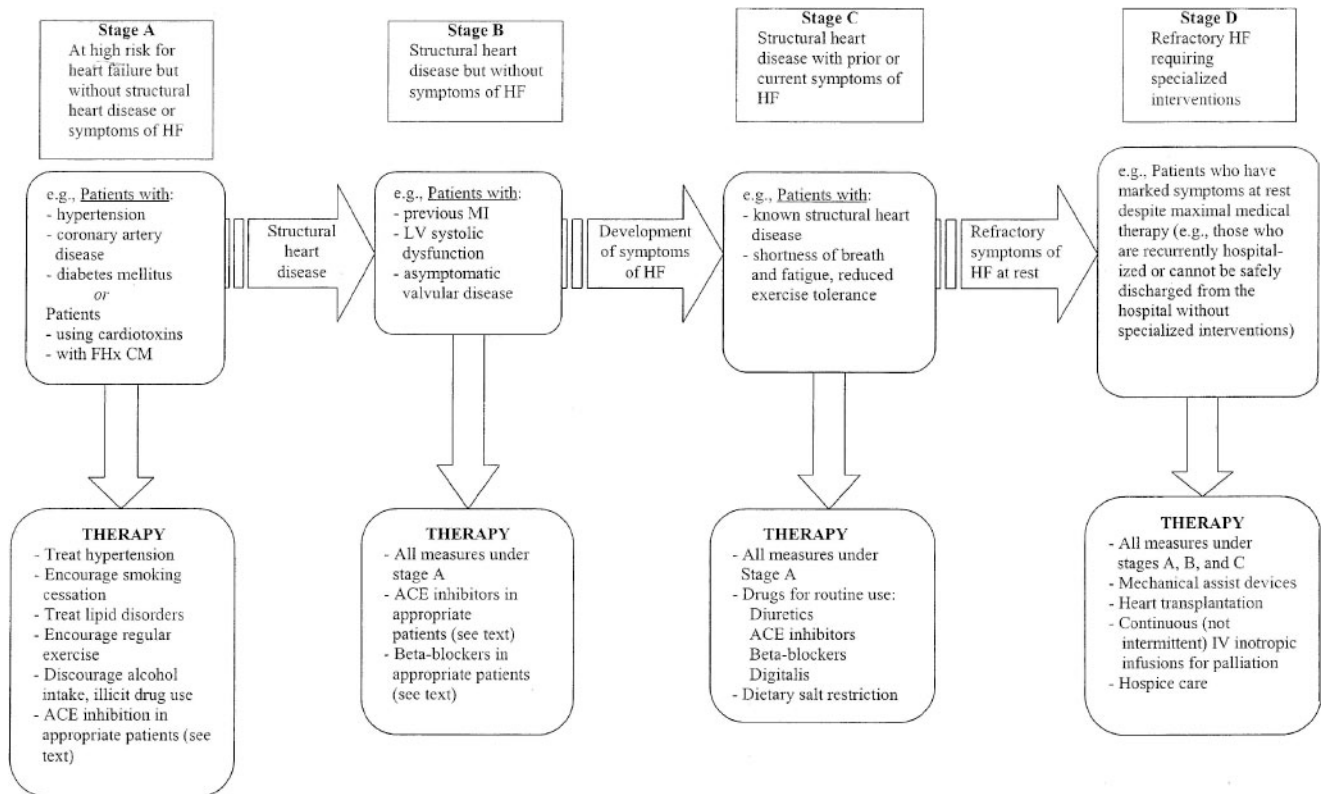
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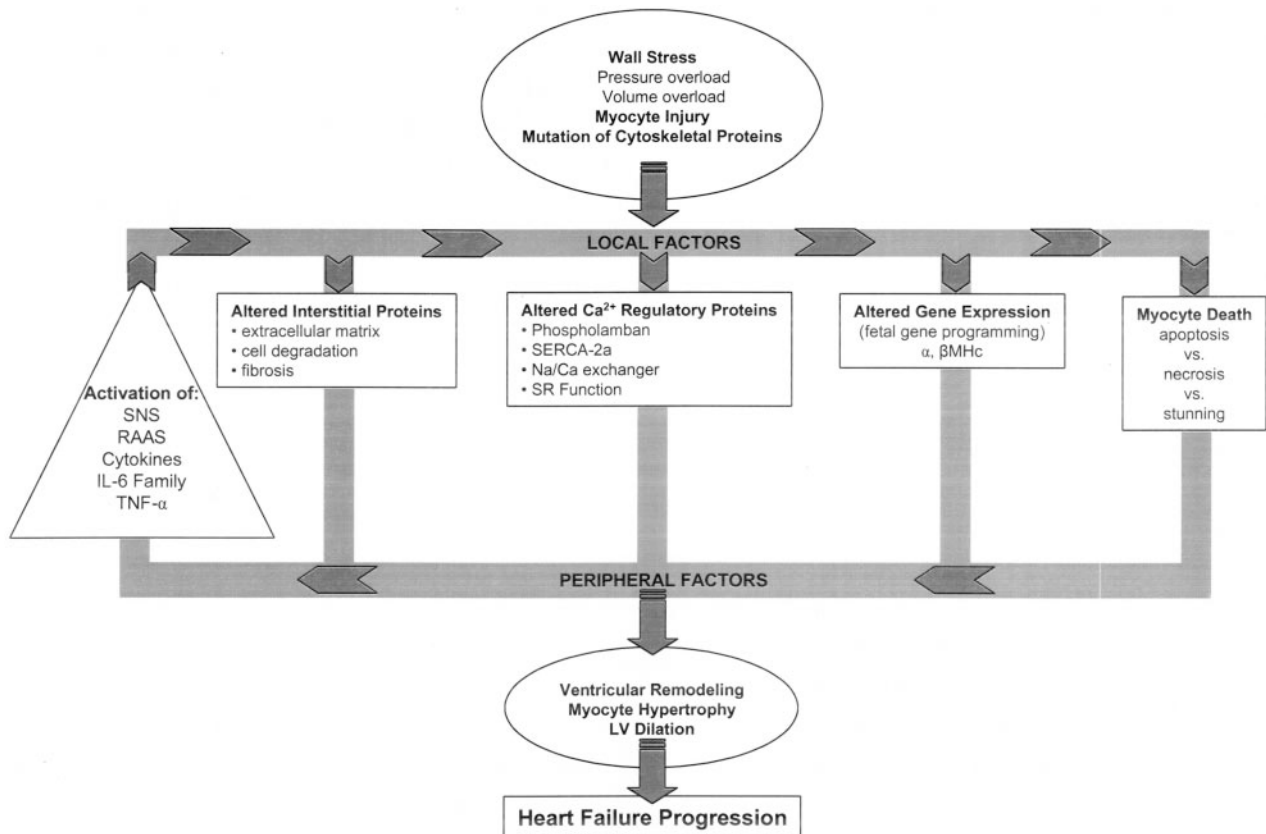
**Figure 1.** Reprinted with permission from Hunt SA et al. ACC/AHA Guidelines for the Evaluation and Management of Chronic Heart Failure in the Adult: An Executive Summary. *J Heart Lung Transplant* 2003;21:189–203.

to severity of symptoms. The latter remains useful because severity of symptoms has a robust correlation with survival and quality of life (9). The ACC/AHA classification system recognizes the progressive course of HF and identifies those at risk, reinforcing the importance of neurohormonal antagonism in an attempt to arrest disease progression.

HF may result from coronary artery disease, hypertension, valvular heart disease, or any of a long list of cardiomyopathies, in which progression of the underlying disease produces symptomatic or asymptomatic left ventricular dysfunction (specifically, left ventricular systolic dysfunction for the purposes of this discussion). The neurohormonal responses to impaired cardiac performance (sympathetic stimulation, salt and water retention, and vasoconstriction) are initially adaptive but over time become maladaptive, resulting in pulmonary congestion and excessive afterload. The end result is a vicious cycle of increased and inefficient cardiac energy expenditure and worsened pump function and tissue perfusion. The renal and peripheral circulatory consequences to the neurohormonal responses in HF provided the theoretical basis for treatment with diuretics, vasodilators, and positive inotropes (10,11).

Our understanding of treatment for patients with chronic HF changed in the 1990s when clinical trials showed that angiotensin-converting enzyme (ACE) inhibitors (12,13) and angiotensin receptor blockers (ARB) (14,15), but not most other vasodilators (16), prolonged

survival. Similarly, certain  $\beta$ -adrenergic blockers, despite negative inotropic effects, were found to improve morbidity and mortality in adequately powered, randomized, clinical trials (17–19). More recently, small doses of aldosterone antagonists added to conventional therapy for HF have reduced mortality in patients with severe HF (20,21). These accumulated outcome results support evidence from basic investigations showing that angiotensin II is a growth factor as well as a vasoconstrictor and that antagonizing this mediator accomplishes more than mere hemodynamic improvement (22). Growth factor actions of angiotensin II have been confirmed in models of inflammation, cancer, metabolic syndrome, and atherosclerosis. In a recent clinical study, increased angiotensin II receptor density was associated with increased tumor angiogenesis and poorer survival in patients with ovarian cancer (23). Overall, these data have promoted a shift in focus from renal and circulatory processes toward cardiac remodeling as the underlying mechanism of progression in HF (24). Although it is not entirely clear how the hemodynamic and neurohormonal factors interact to cause maladaptive cardiac remodeling and progression to HF, there is evidence to suggest that increased energy expenditure, increased wall stress, altered calcium regulatory function of the sarcoplasmic reticulum, altered cardiac gene expression, increased oxidative stress, myocyte necrosis, and apoptosis are involved (25) (Fig. 2).



**Figure 2.** Pathophysiology of chronic heart failure. Remodeling stimuli, such as wall stress from either pressure overload or volume overload, contribute to neurohormonal activation, oxidative stress, and cytokine activation, which lead to a complex series of local effects including myocyte loss and alterations in the cardiac extracellular matrix, intracellular calcium regulation, and gene expression. In addition to the local events, systemic effects leading to LV dilation, myocyte hypertrophy, and LV remodeling contribute to the progression of heart failure. IL, interleukin; LV, left ventricle, TNF, tumor necrosis factor; SR sarcoplasmic reticulum; MHC, myosin heavy chain. Adapted with permission from Drexler H, Hasenfuss G. Physiology of the normal and failing heart. In: Crawford MH, DiMarco JP, Paulus WJ, eds. *Cardiology*, 2nd ed. Philadelphia: Mosby (Elsevier), 2004.

With these underlying pathophysiologic concepts in mind, we will review the major classes of drugs that are used to treat HF, emphasizing those drugs that improve survival in chronic HF. However, even though the descriptions of each drug class are independent, clinical management of real patients will often require regimens that include multiple drugs. This will become obvious in the descriptions of recent clinical trials where “conventional therapy” will include 3 classes of drugs with the presence or absence of the “newest” drug being the only variable under study.

## INHIBITORS OF THE RENIN-ANGIOTENSIN SYSTEM

### ACE Inhibitors

#### Mechanism(s) of Action

ACE inhibitors inhibit the protease that cleaves the decapeptide angiotensin-I to form the octapeptide angiotensin-II. Because ACE also metabolizes bradykinin, ACE inhibitors increase circulating and tissue concentrations of bradykinin, which is thought to underlie the side effects of these drugs, including cough and angioedema (Fig. 3). ACE inhibitors have several useful actions in chronic HF. They are potent

vasodilators because they decrease concentrations of angiotensin-II and norepinephrine and increase concentrations of bradykinin, nitric oxide (NO), and prostacyclin (26). They reduce the secretion of aldosterone and antidiuretic hormone, thereby reducing salt and water reabsorption by the kidney, and they promote binding of angiotensin-I to receptors on nerve terminals, reducing norepinephrine release from sympathetic nerves. Within tissue, ACE inhibitors limit the production of angiotensin-II, attenuating angiotensin-II-mediated ventricular and vascular remodeling.

#### Clinical Evidence

The abundant evidence supporting the benefits from use of ACE inhibitors in chronic HF patients is summarized in Table 1. Initially, ACE inhibitors were evaluated for treatment of symptomatic HF (these clinical trials went by the acronyms of SOLVD, V-HeFT, and CONSENSUS). Patients with NYHA Class II–IV HF treated with ACE inhibitors had 16% to 31% reduced risk of mortality. In later trials, ACE inhibitors also improved outcome for asymptomatic patients with left ventricular systolic dysfunction in the following categories: patients with ejection fractions (EF)



## The Renin-Angiotensin Aldosterone System

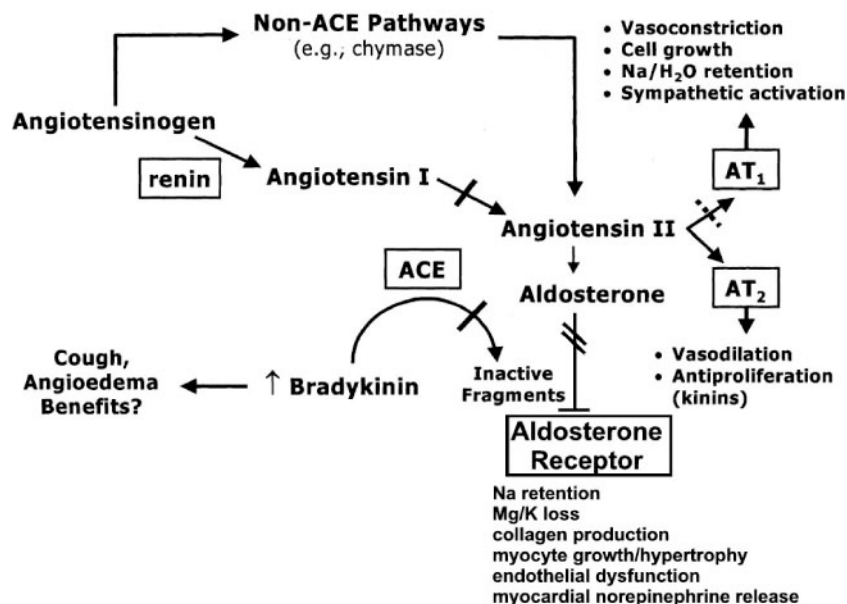


Figure 3. Schematic of the renin-angiotensin-aldosterone system and site of action of angiotensin-converting enzyme (ACE) inhibitors (one slash), angiotensin receptor blockers (dotted slash), and aldosterone receptor blockers (double slash). Adapted with permission from McMurray JJV, Pfeffer MA, Swedberg K, Dzau VJ. Which inhibitor of the renin-angiotensin system should be used in chronic heart failure and acute myocardial infarction? *Circulation* 2004;110:3281–8.

<35% resulting from cardiomyopathy (27), patients with EF <40% 2 wk after myocardial infarction (28), and patients presenting within the first 24 h of myocardial infarction regardless of EF (29). Results from the Heart Outcomes Prevention Evaluation (HOPE) study have further expanded the indications for ACE inhibitors to include prevention of new onset HF in asymptomatic, high-risk patients (30). In this trial of patients with either diabetes or peripheral vascular disease and an additional atherosclerotic risk factor (but without HF or systolic dysfunction), ramipril (10 mg/day) reduced the new occurrence of HF by 23% over a mean 4.5-yr treatment interval.

Together, these data expand the use of ACE inhibitors as first-line preventive therapy for a broad spectrum of patients, including those with left ventricular systolic dysfunction with or without symptoms (Class B–D) and those high-risk patients with vascular disease and/or diabetes, in addition to patients with the traditional risk factors for coronary artery disease (Class A). Interestingly, retrospective data from the SOLVD and V-HeFT (Vasodilator Heart Failure trials) suggest that renin-angiotensin-aldosterone system (RAAS) inhibition, particularly with ACE inhibitors, may not be as effective in the African-American HF patient as in Caucasians. In SOLVD, there was no ethnic difference in the efficacy of enalapril for reducing mortality and preventing the development of HF, but enalapril was more effective for Caucasians in reducing hospitalizations. Moreover, in V-HeFT-II, enalapril was more effective than the combination of isosorbide dinitrate and hydralazine for Caucasians in reducing mortality but not in African-Americans. Data from the A-HeFT (African American Heart Failure Trial) showed a survival benefit in African American HF patients treated with BiDil ( $n = 518$ ), a fixed-dose

combination of isosorbide dinitrate (60 up to 120 mg) and hydralazine (112.5 up to 225 mg) in 3 divided doses versus placebo ( $n = 532$ ), added to standard background RAS blockade (31).

Nevertheless, one should only cautiously initiate ACE inhibitor therapy in patients with low initial blood pressures (BP) (systolic blood pressures  $\leq 80$  mm Hg), marked renal dysfunction (serum creatinine levels  $>3.0$  mg/dL), serum potassium concentrations  $>5.5$  mEq/L, renal artery stenosis, or left ventricular outflow tract obstruction. ACE inhibitors are contraindicated in patients who are pregnant, have a history of porphyria, are in cardiogenic shock, or who have had a severe reaction (e.g., angioedema or anuric renal failure) to members of this drug class. As noted earlier (Fig. 1 and Table 1), ACE inhibitors are administered both to slow the progression of clinical HF through ACE inhibitor-mediated vasodilatory action and to inhibit the cellular mechanisms responsible for progression of HF.

### Perioperative Implications

Anesthetic drugs, surgical procedures, patient positioning on the operating table, and blood loss influence the RAAS and the sympathetic nervous system (SNS) (32). Controversy remains whether chronic ACE inhibitor therapy should be continued or withdrawn preoperatively. Patients treated with ACE-I are prone to hypotension with induction and maintenance of general anesthesia, most likely as a result of intravascular volume deficits and the inability of angiotensin-II to counterbalance the usual anesthetic effects on the SNS (including increased venous pooling of blood, reduced cardiac output, and reduced arterial BP) (33–35). Ryckwaert and Colson (34) report a 22% incidence of severe hypotension in patients who received ACE-I until the

**Table 1.** Selected Clinical Trials of Angiotensin-Converting Enzyme Inhibitors in Heart Failure (HF)

| Trial                           | Drug  | Population   | Outcome  |
|---------------------------------|---|--|--|
| Heart Failure<br>SOLVD (treat)* | Enalapril                                       | NYHA Class II–III (EF $\leq$ 35%), Stage C             | ♥ Lower incidence of death or hospitalization for HF in enalapril group vs. placebo (48% vs. 57%)<br>♥ At 2 yr, there was a decreased mortality with enalapril vs. hydralazine/ isosorbide dinitrate group (18% vs. 28.2%). Mortality benefit from reduction in sudden cardiac death.  |
| V-Heft II (153)                 | Enalapril vs. hydralazine/ isosorbide dinitrate | NYHA II–IV, EF <45%; Stage C                           | ♥ 31% decrease in mortality with enalapril vs. placebo<br>♥ 50% decrease in progressive HF death in enalapril vs. placebo  |
| CONSENSUS†                      | Enalapril                                       | NYHA IV, Stage D                                       |  |
| Asymptomatic LV Dysfunction     |   |  |  |
| SOLVD (prevent)‡                | Enalapril                                       | NYHA I, EF $\leq$ 35%, Stage B                         | ♥ At 37 months, combined end-point of death or HF was lower in enalapril group compared with placebo (30% vs. 39%). Fewer hospitalizations for enalapril group (21% vs. 25% for placebo).<br>♥ 22% reduction in mortality with or without HF<br>♥ 25% reduction in rate of nonfatal MI<br>♥ 7% reduction in mortality at 30 days vs. placebo |
| SAVE (28)                       | Captopril                                       | Post-MI, EF <40%, Stage B                              |  |
| GISSI-3                         | Lisinopril, captopril                           | Acute MI (with 36 h of symptoms), Stage B              |  |
| ISIS-4 (29)                     |   |  |  |
| Asymptomatic High-Risk          |   |  |  |
| HOPE (30)                       | Ramipril  | History of DM, PVD, and coronary risk factors, Stage A | ♥ Significant reduction in mortality, major vascular events, and development of HF. Incidence of HF 9% vs. 11.5% (placebo). Incidence of MI, stroke, or CV-related death 14% vs. 17.8% placebo.  |

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\*Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. The SOLVD Investigators. *N Engl J Med* 1991;325:293-302.

†Effects of enalapril on mortality in severe congestive heart failure. Results of the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS). *N Engl J Med* 1987;316:1429-35.

‡Effect of enalapril on mortality and the development of heart failure in asymptomatic patients with reduced left ventricular ejection fractions. The SOLVD Investigators. *N Engl J Med* 1992;327:685-91.

NYHA = New York Heart Association; EF = ejection fraction; MI = myocardial infarction; DM = diabetes mellitus; PVD = peripheral vascular disease; CV = cardiovascular.

day of surgery. Instability of BP and heart rate after induction of anesthesia was much the same in patients receiving chronic ACE inhibitor therapy regardless of whether there was left ventricular systolic dysfunction. There are multiple case reports about hypotension in patients treated with ACE inhibitors who are also receiving general, spinal, epidural, or combined general-epidural techniques (36), and it remains unclear whether any specific anesthetic technique is more or less likely than others to show adverse interactions in patients. Long-term ACE inhibitor treatment does not exaggerate the BP decrease associated with spinal anesthesia, perhaps because

vasopressin and norepinephrine concentrations remain sufficient to compensate for the inhibited RAAS (37). Although temporary withdrawal of ACE inhibitors may prevent or attenuate intraoperative hypotension and hypovolemia, the recovery of RAS control on BP may be at the expense of impaired regional circulation. Boldt et al. (38) showed, in 88 randomized cardiac surgical patients, that administration of IV enalapril after anesthetic induction until commencement of cardiopulmonary bypass (CPB) resulted in lower levels of cardiac enzyme release than clonidine, enoximone, or placebo. Perioperative ACE-I administration may also protect the

kidney. Aortocoronary bypass patients pretreated with captopril starting 2 days before surgery had better preserved renal plasma flow and glomerular filtration rate during CPB compared with placebo-treated patients (39). Moreover, patients undergoing aortic-abdominal surgery pretreated with a single dose of enalapril before anesthetic induction had a smaller reduction in cardiac output and glomerular filtration rate with aortic clamping and a significantly greater creatinine clearance on the first postoperative day compared with the placebo group (40). Whether the organ-protective benefits of ACE inhibitors justify their routine prophylactic administration to patients at risk requires further study.

There is overwhelming evidence of the benefit of RAS modulation in nonsurgical settings; however, the evidence supporting continuing these medications until the time of surgery is less complete and less convincing (41–43). Nevertheless, although we recognize the potential for hypotension on induction of anesthesia in patients chronically treated with an ACE inhibitor, on balance, we nevertheless suggest that anesthesiologists continue the medication. Such brief episodes of hypotension can usually be treated with modest doses of sympathomimetics (e.g., ephedrine) or  $\alpha$  adrenergic agonists (e.g., phenylephrine) and careful expansion of intravascular volume (39). In the rare event of hypotension refractory to these interventions either during noncardiac surgery or on weaning from CPB during cardiac surgery (44,45), the presumed ACE-I-induced decrease in catecholamine responsiveness can be managed with either small boluses (1–2 U) or an infusion of arginine vasopressin (4–6 U/h) (46). In the case of severe systemic hypotension (presumed secondary to reduced renin secretion) during spinal or epidural anesthesia,  $\beta$  adrenergic stimulation with epinephrine (0.5–1  $\mu\text{g}/\text{min}$ ) may also be considered (47). Certainly, the problem may often be prevented by incremental administration of induction drugs and/or by selecting drugs less likely to cause hypotension (e.g., ketamine or etomidate).

Because amiodarone can increase the incidence of hypotension when combined with ACE inhibitors in anesthetized patients (48) and because ACE inhibitors combined with aprotinin may lead to a greater propensity for renal insufficiency after CPB (49)—we recognize that this may be a primary aprotinin effect (50)—hypovolemia and hypotension may pose an increased risk to these patients. If one chooses to discontinue ACE inhibitors preoperatively (e.g., for an asymptomatic HF patient without hypertension), there is no risk of rebound or other circulatory complications (51). The long-term benefits of ACE inhibitor therapy (e.g., on ventricular remodeling) will likely not be harmed by brief drug holidays. However, in cardiac surgery, Pigott et al. (52) found no reduction in the incidence of hypotension on induction of anesthesia or in the need for vasoconstrictors after CPB when ACE inhibitors were omitted before surgery.

## ARBs

### Mechanism of Action

Plasma concentrations of angiotensin-II and aldosterone may increase during chronic ACE inhibitor therapy because of accumulation of substrate (angiotensin I) or because of increased production through non-ACE dependent pathways such as chymase. Moreover, non-ACE-generated angiotensin-II within the myocardium contributes to left ventricular remodeling and HF progression through AT1 receptor effects. Selective AT1-blockers prevent angiotensin-II from directly causing vasoconstriction, sodium retention, and release of norepinephrine (Fig. 3). They also delay or prevent left ventricular hypertrophy and interstitial fibrosis (53). Angiotensin type-2 receptors (AT-2) and their actions, including NO release and vasodilation, remain unaffected by AT-1 receptor blockade (Fig. 3). The putative counter-regulatory role of AT-2 receptor signaling in the heart (anti-growth and anti-fibrotic effects) and other effects that inhibit cell proliferate or promote apoptosis are of questionable clinical importance in the overall regulation of the RAS in HF (27).

### Clinical Evidence

Outcome benefit from ARBs was first suggested in the ELITE I trial, which showed, as a secondary end-point, a significantly reduced risk of sudden death with losartan (4.8%) compared with captopril (8.7%) (54), despite there being no between-group differences in the primary end-points: renal dysfunction or hypotension. The follow-up ELITE II trial (Table 2) had greater statistical power than ELITE I, but failed to confirm that losartan was superior to captopril in reducing mortality in older patients with HF (55). Moreover, in subgroup analyses, the ELITE II trial patients receiving preexisting  $\beta$ -adrenergic blockers tended to have less favorable outcomes with losartan, as opposed to captopril. Two more trials, Valsartan in Heart Failure (Val-HeFT) and Candesartan in Heart Failure Assessment in Reduction of Mortality (CHARM), tested the hypothesis that ARBs plus conventional therapy (including  $\beta$ -adrenergic blockers, ACE inhibitors, and diuretics) for symptomatic HF would provide additional clinical benefit. The Val-HeFT study supports the use of valsartan in patients with chronic HF who are intolerant to ACE inhibitors. However, among those patients who received ACE inhibitors and  $\beta$ -adrenergic blockers (93% of their patient population) there was a trend toward an increased risk of death or hospitalization when valsartan was added to standard treatment (14). On the other hand, the CHARM-Added trial (56) showed safety with regard to use of candesartan in combination with ACE inhibitors and  $\beta$ -adrenergic blockers (15% relative risk reduction in CV-related mortality or hospitalization). In patients intolerant to ACE (Alternative group), the relative risk reduction in mortality or hospitalization was 23%. Patients with left ventricular EF >40% not receiving ACE inhibition (Preserved

**Table 2.** Angiotensin Receptor Blocker Trial in Heart Failure (HF)

| Trial         | Drug   | Population                                      | Outcome  |
|---------------|--|---|--|
| ELITE II (55) | Losartan 50 mg every day   | Age $\geq$ 60 yr<br>NYHA II–IV<br>EF $\leq$ 40% | <ul style="list-style-type: none"> <li>• Losartan was not better than captopril</li> <li>• No difference in mortality</li> <li>• Losartan was better tolerated</li> <li>• Losartan + beta blocker had worse outcome</li> </ul>   |
| Val-HeFT (14) | Valsartan 160 mg twice daily, or placebo plus open label ACE-I (93%)                   | NYHA II–IV<br>EF <40%                           | <ul style="list-style-type: none"> <li>• No difference in all-cause mortality</li> <li>• 13% significant difference in combined morbidity/mortality</li> <li>• HF hospital decrease 27%</li> <li>• Most benefit observed in ACE-I intolerant patients (7% of study group) with 45% reduction in combined primary end-points</li> </ul> |
| CHARM         | Candesartan 32 mg every day vs. placebo with or without open label ACE-I<br>Added (56) | NYHA II–IV<br>EF $\leq$ 40%                     | <ul style="list-style-type: none"> <li>• 15% relative risk reduction in all-cause mortality</li> <li>• Mild reduction in HF-related hospitalizations</li> <li>• 23% relative risk reduction in HF-related mortality or hospitalizations</li> <li>• Significant difference in all-cause mortality</li> </ul>                            |
|               | Preserved (58)   | EF >40%   |  |
|               | Alternative (57)   | EF $\leq$ 40%                                   |  |
|               | Overall (15)   | ACE-I intolerant                                |  |

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ACE = angiotensin-converting enzyme; NYHA = New York Heart Association; EF = ejection fraction.

group) showed no difference in CV mortality and only a small reduction in HF hospitalizations (57,58). In the CHARM-overall trial, candesartan use significantly reduced both CV-related death and hospitalizations (relative risk reduction for CV death was 16%) (15).

Taken together, these studies show that ARBs are suitable alternatives to ACE inhibitors for the treatment of patients with symptomatic HF when there are side effects to ACE inhibitors (e.g., persistent coughing, angioedema, hyperkalemia, or worsening renal dysfunction) or persistent hypertension despite ACE inhibitors and  $\beta$ -adrenergic blockers. The available evidence is not convincing that patients with HF benefit from the addition of ARBs to standard therapy with ACE-I and  $\beta$ -adrenergic blockers.

### Perioperative Implications

As is true with ACE inhibitors, patients chronically treated with ARBs appear more prone to hypotension with induction of anesthesia (51,59,60) and are, we presume, also more likely to require vasoconstrictors during and after separation from CPB (44) than patients receiving other antihypertensive drugs and, perhaps, even compared with patients receiving ACE inhibitors (61). Moreover, patients receiving ARBs are less responsive to conventional vasopressors such as ephedrine and phenylephrine (59), in part because of an attenuated adrenergic responsiveness (62). Omission of the ARB on the day of surgery will not likely

improve CV stability because these drugs have a prolonged duration of action (63,64); however, after a drug-free interval of at least 24 h, patients will have significantly fewer episodes of hypotension than those who continue to receive their ARB therapy (65). Vasopressin and vasopressin analogs will treat intraoperative hypotension refractory to conventional drugs in ARB-treated, anesthetized patients (46,66–68). Hypotension during anesthetic induction may be accompanied by bradycardia, particularly when vagotonic drugs are used (e.g., sufentanil). Accordingly, we and others advocate administering a prophylactic dose of glycopyrrolate (0.2 mg) to elderly patients taking an ARB on a chronic basis (69).

### Aldosterone Receptor Antagonists

#### Mechanisms of Action

Aside from the “traditional” effects of mineralocorticoid receptor blockade (natriuresis, diuresis, and potassium retention) (70), beneficial nonrenal effects of aldosterone antagonism include decreased myocardial collagen formation (71), increased myocardial norepinephrine uptake, and decreased circulating norepinephrine levels (71), normalization of baroreceptor function, increased heart rate variability (72), reduced endothelial dysfunction, and increased basal vascular NO bioactivity (Fig. 3) (73).



Aldosterone receptor antagonists cause conservation of potassium, and hyperkalemia is a long-recognized complication (74–76).

### Clinical Evidence

Two large clinical trials have demonstrated improved outcomes with aldosterone receptor antagonists in chronic HF. The Randomized Aldactone Evaluation Study (RALES) (20), including more than 1600 symptomatic HF (e.g., Stage C, NYHA 3–4) patients, showed reduced mortality with spironolactone (26 mg/day) in combination with standard therapy (ACE inhibitor, loop diuretic, and in some cases digoxin and/or  $\beta$ -adrenergic blocker). Regardless of age, gender, or HF etiology, the treatment group experienced a 30% reduction in all-cause mortality and in CV mortality compared with standard therapy. Because  $\beta$ -adrenergic blockers were used inconsistently in the RALES study (10%–20%), the relative place of aldosterone antagonists in contemporary management of HF remained unclear. Moreover, in reports subsequent to the RALES study there was a marked increase in hospital admissions and deaths related to hyperkalemia associated with spironolactone (74). Some of the concerns were addressed in the Eplerenone Post-acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS). Eplerenone is a new aldosterone antagonist that lacks some of spironolactone's common side effects (most notably gynecomastia) (77). The study was conducted in more than 6600 patients with symptomatic HF 3 to 14 days post-myocardial infarction, and showed that eplerenone (25 to 50 mg/daily), in combination with ACE inhibitor, loop diuretic, and  $\beta$ -adrenergic blocker, significantly reduced all cause mortality, death from CV causes, and hospitalization for CV events (21). Large-scale randomized controlled trials in class A and B HF patients are lacking. Pilot data show that aldosterone inhibition improves endothelial function (73), exercise tolerance, and EF (78) and attenuates collagen formation. Laboratory studies have shown that even in the presence of ACE inhibitors and AT-1 receptor blockade, activation of aldosterone synthetase ("aldosterone escape") in the heart and vasculature leads to myocardial hypertrophy, myocardial and vascular collagen production, endothelial dysfunction, and increased sodium retention (79,80). Laboratory and clinical data suggest that aldosterone antagonists may provide organ protection (71,81). Thus, we suspect that the indications for aldosterone receptor blockers may be widened to include patients with asymptomatic systolic left ventricular dysfunction.

### Perioperative Implications

Although we doubt that doses of aldosterone receptor antagonists used for HF treatment contribute to anesthetic-induced hypotension, there is no doubt that

these drugs may cause life-threatening hyperkalemia. The risk of hyperkalemia is increased when aldosterone antagonists are administered in combination with other RAS blockers, preexisting renal insufficiency, diabetes, or anemia (74–76). Thus, intraoperative measurement of serum potassium would seem prudent when these conditions are present, particularly in the event of red cell transfusion.

### Beta-Adrenergic Receptor Antagonists

#### Mechanism of Action

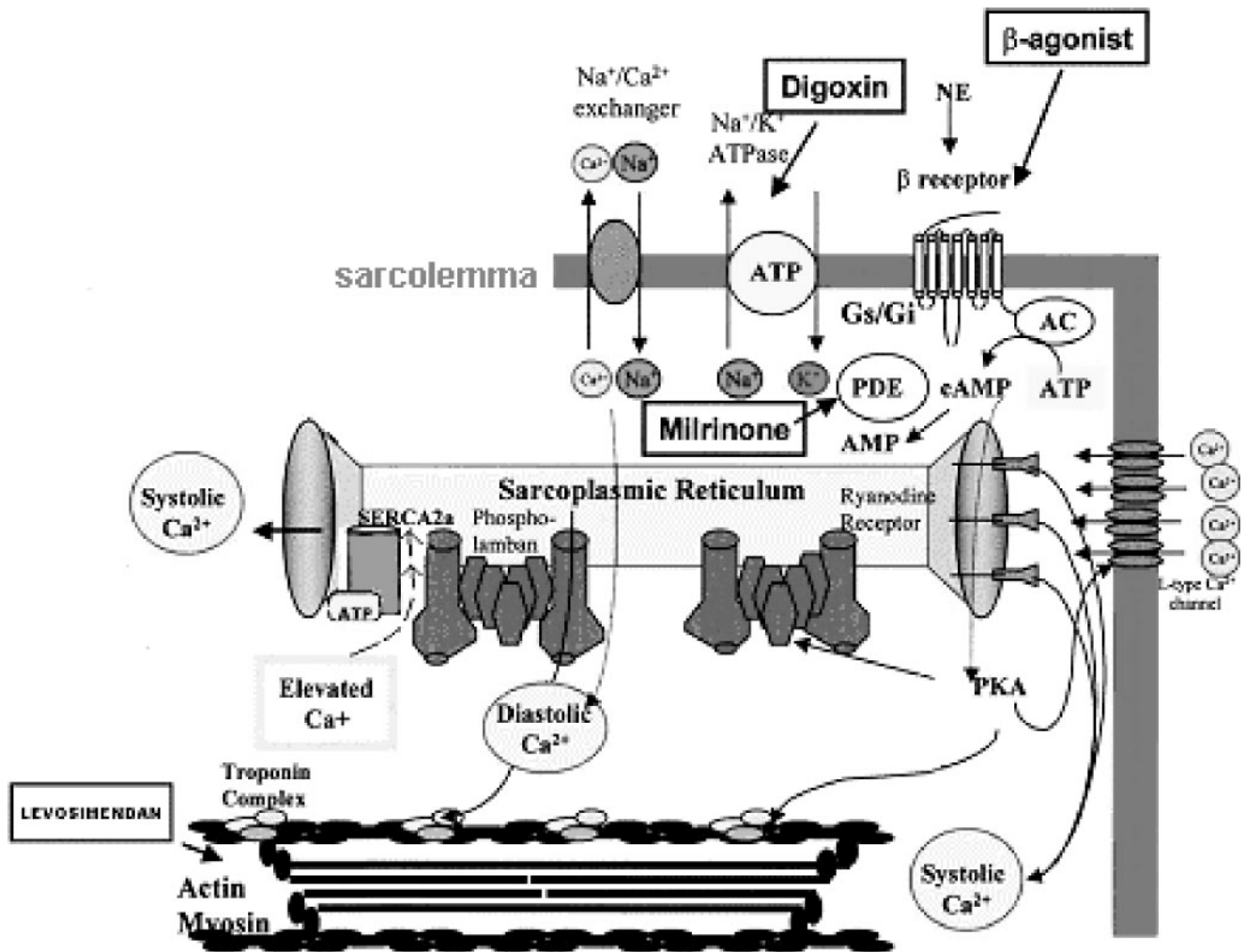
In chronic HF, the beneficial effects of  $\beta$ -adrenergic receptor blockade include improved systolic function and myocardial energetics and reversal of pathologic remodeling. A shift in substrate utilization from free fatty acids to glucose (a more efficient fuel during myocardial ischemia) may partly explain the improved energetics and mechanics (82).  $\beta$ -blockade also tends to offset the effects of neurohumoral activation, a central feature of both chronic HF and of major surgery with general anesthesia (83,84). Chronic neurohumoral activation leads to adverse cardiac remodeling. Heart rate, a major determinant of myocardial oxygen consumption, is reduced by  $\beta_1$ -receptor blockade.

Systolic dysfunction of individual myocytes is associated with up-regulation of gene expression for natriuretic peptides and fetal-like  $\beta$ -myosin heavy chain and increased expression of the cardiac sarcoplasmic-endoplasmic reticulum calcium uptake pump (SERCA2) and  $\alpha$ -myosin heavy chain (the more efficient, faster, adult isoform) (85).  $\beta$ -blockade reverses these changes in gene expression and concurrently improves left ventricular function (86).

$\beta$ -adrenergic blockade may also limit the disturbed excitation-contraction coupling and predisposition to ventricular arrhythmias associated with HF. In animal models of HF, the increases in L-type calcium currents and in cytosolic calcium concentrations that occur in response to  $\beta$ -adrenergic surges often result in ventricular arrhythmias and sudden death (87). These effects are likely the result of excess activation of intracellular  $\beta$ -adrenergic mediated pathways via cAMP and protein kinase A (PKA), ultimately leading to an "excessive phosphorylation" state.

As noted earlier, the SNS is chronically activated in the failing heart with reduced cardiac output. In this setting, excitation-contraction coupling becomes maladaptive because of "leaky"  $\text{Ca}^{2+}$  from the sarcoplasmic reticulum (SR) (Fig. 4). Protein kinase A (PKA)-hyperphosphorylated RYR2 channels cause a diastolic SR  $\text{Ca}^{2+}$  leak that, together with reduced SERCA2-mediated SR  $\text{Ca}^{2+}$  uptake (resulting from PKA-hyperphosphorylated phospholamban that inhibits SERCA2a), depletes SR  $\text{Ca}^{2+}$  and leads to contractile dysfunction of cardiac muscle (88). This depletion of SR  $\text{Ca}^{2+}$  stores may explain, in part, the reduced contractility and the predisposition to ventricular arrhythmias of





**Figure 4.** Effects of inotropic therapy on intracellular calcium handling in cardiac myocytes. Many sarcolemmal receptors affect calcium handling in cardiac myocytes. Agonists through G proteins increase adenylyl cyclase (AC) activity, which results in cAMP production. This results in activation of protein kinase A (PKA), which leads to phosphorylation of L-type calcium channels, phospholamban, and troponin I, ultimately leading to a greater release of calcium from the sarcoplasmic reticulum (SR) and faster relaxation. Digoxin inhibits  $\text{Na}^+/\text{K}^+$  ATPase pump, which increases intracellular  $\text{Na}^+$ . This results in increase in intracellular  $\text{Ca}^{2+}$  via  $\text{Na}^+/\text{Ca}^{2+}$  exchanger, which leads to enhanced  $\text{Ca}^{2+}$  loading of SR and increase in  $\text{Ca}^{2+}$  release. Phosphodiesterase inhibitors (PDEI) block breakdown of cAMP, which increases its intracellular level and activates PKA. Calcium sensitizers, e.g., levosimendan, increase sensitivity of myofilaments to  $\text{Ca}^{2+}$ , enhancing myofilament activation for any concentration of  $\text{Ca}^{2+}$ . PDE = phosphodiesterase; PKC = protein kinase C. Reprinted with permission from Stevenson LW. Clinical use of inotropic therapy for heart failure: looking backward or forward? Part I: Inotropic infusions during hospitalization. *Circulation* 2003;108:367–72. (Fig. 1, page 369).

cardiac muscle in HF (89). Interestingly, studies in animal models of HF show that chronic  $\beta$ -blockade may reverse the PKA hyperphosphorylated state and restore normal structure and function of the RYR2  $\text{Ca}^{2+}$  release channel (90). In studies after human cardiac transplantation,  $\beta$ -adrenergic blockade restored RYR2 function, phosphorylation, and levels of the binding proteins toward baseline, improving ventricular compliance and responses to  $\beta$ -adrenergic agonists (91). Besides normalizing the calcium leak, the benefit of  $\beta$ -adrenergic blockade in HF patients may also include a decrease in calcium-dependent apoptosis and a metabolic effect promoting improved work efficiency (92). In a dog model of HF,  $\beta$ -adrenergic blockade also reduced myocyte apoptosis (93). Thus, chronic  $\beta$ -adrenergic blockade reduces

the harmful effects of excessive SNS stimulation of the heart and reverses left ventricular remodeling.

### Clinical Evidence

For many years,  $\beta$ -adrenergic blockers were rarely given to patients with HF because of the perceived risk of decompensation from their negative inotropic effects. However, data from both human and animal studies have shown that  $\beta$ -adrenergic blockers improve energetics and ventricular function and reverse pathologic remodeling. Although these beneficial effects may take 3 mo or more to manifest, they have translated into improved outcomes (reduced deaths and hospitalizations) in patients with HF. This appears NOT to be a drug class effect, as not all  $\beta$ -adrenergic blockers improve outcomes in HF. The

**Table 3.** Large-Scale Placebo-Controlled Mortality Trials of Beta Blockade in Heart Failure (HF)

| Trial              | Drug             | HF Severity         | Patients (n) | Target Dose (mg) | Effect on all cause |                 |
|--------------------|------------------|---------------------|--------------|------------------|---------------------|-----------------|
|                    |                  |                     |              |                  | Mortality           | Hospitalization |
| US Carvedilol (94) | Carvedilol       | NYHA II–III         | 1094         | 6.25–50 bid      | ↓ 65%               | ↓ 27%           |
| CIBIS-II (18)      | Bisoprolol       | EF ≤35; NYHA III–IV | 2647         | 10 qd            | ↓ 34%               | ↓ 20%           |
| MERIT-HF*          | Metoprolol CR/XL | EF ≤40; NYHA II–IV  | 3991         | 200 qd           | ↓ 34%               | ↓ 18%           |
| BEST (95)          | Bucindolol       | EF ≤35; NYHA III–IV | 2708         | 50–100 bid       | NS                  | ↓ 8%            |
| COPERNICUS†        | Carvedilol       | EF ≤25; NYHA IV     | 2289         | 25 bid           | ↓ 35%               | ↓ 20%           |

Reprinted from Royster RL, Butterworth J, Groban L, Slaughter TF, Zvara DA. Cardiovascular pharmacology. In: Kaplan JA, ed., *Cardiac Anesthesia*, 5th ed. Philadelphia: WB Saunders (Elsevier), 2006:213–80.

\*Effects of controlled-release metoprolol on total mortality, hospitalization, and well-being in patients with heart failure: the Metoprolol CR/XL Randomized Intervention Trial in congestive heart failure (MERIT-HF). MERIT-HF Study Group. *JAMA* 2000;283:1295–302.

†Effect of carvedilol on the morbidity of patients with severe chronic heart failure; results of the carvedilol prospective randomized cumulative survival (COPERNICUS) study. *Circulation* 2002;106:2194–9.

NYHA = New York Heart Association; EF = ejection fraction.

available randomized trials show that metoprolol CR/XL, bisoprolol, and carvedilol (in conjunction with ACE inhibitors) reduce morbidity (hospitalizations) in symptomatic, Stage C and D (not in cardiogenic shock) HF patients (NYHA II–IV class) (Table 3) (18,19,94,95). Although  $\beta$ -adrenergic blocker therapy is recommended for asymptomatic HF patients (Stage A and B), there is no evidence from randomized trials to support this apparently widespread practice (96). In clinical trials,  $\beta$ -adrenergic blockers are initiated in small doses and increased progressively as tolerated by the patient. The goal in clinical management is to administer the doses shown to be effective for prolonging life in clinical trials, not to decrease heart rate by an arbitrary increment or to an arbitrary target value.

$\beta$ -adrenergic blockers are classified as being first-, second-, or third-generation based on specific pharmacologic properties. First-generation drugs, such as propranolol and timolol, block both  $\beta_1$  and  $\beta_2$  adrenoceptors, are considered nonselective, have no ancillary properties, and are not recommended for HF patients. Second-generation drugs, such as metoprolol, bisoprolol, and atenolol, are relatively specific for the  $\beta_1$  adrenoceptor subtype but lack additional mechanisms of CV activity. Third-generation drugs, such as bucindolol, carvedilol, and labetalol, block both  $\beta_1$  and  $\beta_2$  adrenoceptors and have vasodilatory and other ancillary properties. Specifically, labetalol and carvedilol produce vasodilation by  $\alpha_1$  adrenoceptor antagonism, whereas bucindolol produces mild vasodilation through a cyclic guanosine monophosphate (cGMP)-mediated mechanism. Carvedilol increases insulin sensitivity (97) and has antioxidant effects (98) and an affinity for  $\beta_3$  adrenoceptors (99,100).  $\beta_3$  adrenoceptors are up-regulated in HF, and their activation is thought to decrease contractility through a NO and cGMP-mediated pathway (101–104). Although it is not clear whether these ancillary properties of the third-generation  $\beta$ -adrenergic blocker, carvedilol, translate into better outcomes as compared with second generation drugs, findings from the Carvedilol or Metoprolol European Trial (COMET)

suggest that carvedilol may be more effective than other  $\beta$ -adrenergic blockers. COMET compared carvedilol (25 mg twice daily) to metoprolol tartrate (50 mg twice daily) in symptomatic patients with EF ≤35% and demonstrated that carvedilol reduced the risk of death relative to metoprolol (all-cause mortality risk reduction: 17%;  $P = 0.0017$  and CV death risk reduction: 20%;  $P = 0.00004$ ) (105). The superiority of carvedilol over metoprolol could reflect the importance of carvedilol’s ancillary effects, pharmacodynamic (e.g., half-life) differences or other, as yet unknown, differences (106). The COMET study did NOT use the long-acting metoprolol CR-XL but instead used “conventional” metoprolol. The BEST trial showed that not all  $\beta$ -adrenergic blockers improve outcome in HF. Bucindolol showed no benefit compared to placebo (95). Whether the selective  $\beta_1$ -specific drugs bisoprolol and metoprolol CR/XL exert similar clinical benefits to carvedilol remains unclear. Nonetheless, based on the results of the COMET study, carvedilol is preferred to conventional metoprolol, but not metoprolol CR/XL, for HF treatment.

Most guidelines now include long-term  $\beta$ -adrenergic blockade for Stage B–D HF patients, except for patients with continuing decompensation (e.g., requiring IV inotropes or vasodilators), to limit disease progression and reduce mortality (Fig. 1, Table 4). Despite concerns about inhibition of hypoglycemic symptoms,  $\beta$ -adrenergic blockers are advocated for diabetics with HF. There is strong evidence that the benefits from triple therapy including  $\beta$ -adrenergic blockers, ACE-I, and aldosterone antagonists are additive (Fig. 5) (107).

### Perioperative Implications

Although there is a lack of large clinical trials of RAAS modulation in the perioperative period, such is not the case for  $\beta$ -adrenergic blockers. Randomized clinical trials show that these drugs should be given to prevent ischemic events and arrhythmias in high-risk cardiac patients with ischemia, arrhythmias, or hypertension or a history of these conditions and to patients with ischemia in perioperative testing submitted for noncardiac surgery (particularly vascular surgery)

**Table 4. Diastolic Heart Failure Management**

| Goal  | Management Strategy   | Drugs/Recommended Doses   |
|---|---|---|
| Reduce the congestive state                                       | Salt restriction  | <2 g of sodium/day  |
|   | Diuretics (avoid reductions in CO)                                    | Furosemide, 10–120 mg<br>Hydrochlorothiazide, 12.5–25 mg  |
|   | ACE inhibitors  | Enalapril, 2.5–40 mg<br>Lisinopril, 10–40 mg  |
| Target underlying cause   | Angiotensin II-receptor blockers                                      | Candesartan, 4–32 mg<br>Losartan, 25–100 mg   |
|   | Control hypertension  | Antihypertensive drugs (<130/80)  |
| Restore sinus rhythm  | Cardioversion of atrial fibrillation                                  |   |
| Prevent tachycardia   | AV-sequential pacing  |   |
| Prevent/treat ischemia  | Beta-adrenergic blockers, calcium channel blockers                    |   |
|   | Morphine, nitrates, oxygen, aspirin angioplasty or revascularization? | Atenolol, 12.5–100 mg;<br>Metoprolol 25–100 mg;<br>Diltiazem, 120–540 mg  |
| Treat aortic stenosis   | Aortic valve replacement  |   |
| Target underlying mechanisms                                      | (theoretical)   |   |
| Promote regression of hypertrophy and prevent myocardial fibrosis | Renin-angiotensin axis blockade                                       | Enalapril, 2.5–40 mg  |
|   |   | Lisinopril, 10–40 mg<br>Captopril, 25–150 mg<br>Candesartan, 4–32 mg<br>Losartan, 50–100 mg<br>Spironolactone, 25–75 mg<br>Eplerenone, 25–50 mg |

Reprinted from Royster RL, Butterworth J, Groban L, Slaughter TF, Zvara DA. Cardiovascular pharmacology. In: Kaplan JA, ed., *Cardiac Anesthesia*, 5th ed. Philadelphia: WB Saunders (Elsevier), In Press.

CO = cardiac output; ACE = angiotensin-converting enzyme; AV = atrial-ventricular.

(108). Also,  $\beta$ -adrenergic blockers are indicated for the treatment of perioperative hypertension, ischemia, and arrhythmias identified preoperatively and previously untreated (108). Perioperative  $\beta$ -adrenergic blocker therapy in high-risk patients is underused (109). Nevertheless, whether  $\beta$ -adrenergic blockers should be newly initiated before surgery solely for management of HF remains highly speculative. Withdrawal of  $\beta$ -adrenergic blocker therapy from patients who have received it chronically may be particularly dangerous (108). Recent data also suggest that while initiating  $\beta$ -adrenergic blocker therapy may be highly advantageous for some surgical patient populations, it may be considerably less advantageous (perhaps even deleterious) for other patient populations (110).

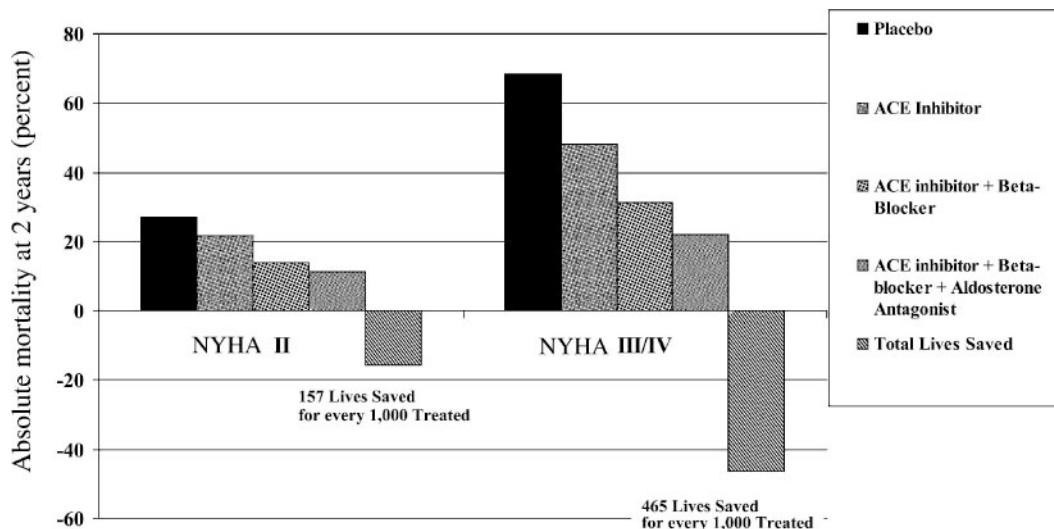
**Adjunctive Drugs**

In addition to ACE inhibitors and  $\beta$ -adrenergic blockers, diuretics and digoxin are often prescribed for patients with left ventricular systolic dysfunction and symptomatic HF. Diuretics provide rapid symptomatic relief of HF in the acute setting, and they maximize the benefits from ACE-I and  $\beta$ -adrenergic blockers, which are dependent on minimization of

excessive intravascular volume (16). Moreover, older hypertensive patients who use diuretics in combination with  $\beta$ -adrenergic blockers have lower mean pulse pressures as compared with those patients receiving  $\beta$ -adrenergic blockers alone (111). Widened pulse pressure is an independent predictor of adverse CV outcomes in older persons (112). Diuretics continue to have a role in the outpatient management of HF in conjunction with ACE-I,  $\beta$ -adrenergic blockers, and (in some cases) aldosterone antagonists even though no randomized controlled trials have demonstrated a survival benefit from diuretics in HF. Importantly, hospitalization or death from worsening HF were significantly more frequent in HF patients receiving non-potassium-sparing diuretics than those not receiving diuretics (relative risk = 1.31, 95% confidence interval, 1.09–1.57) in a large *post hoc* review of data from SOLVD (Studies of Left Ventricular Dysfunction) patients (113).

Digoxin continues to be useful for patients with HF and left ventricular systolic dysfunction who remain symptomatic despite receiving ACE inhibitor,  $\beta$ -adrenergic blocker, and diuretic. Digoxin is the only positive inotropic drug that does not increase





**Figure 5.** Lives saved over 2 yr. Effect of triple therapy with an angiotensin-converting enzyme (ACE) inhibitor,  $\beta$ -adrenergic blocker, and aldosterone antagonist. Based on SOLVD, MERIT, and EPHEUS (for NYHA II) and CONSENSUS < COPERNICUS, and RALES (for NYHA III/IV). Reprinted with permission from Cleland JG, Coletta AP, Nikitin N, Louis A, Clark A. Update of clinical trials from the American College of Cardiology 2003. EPHEUS, SPORTIF-III, ASCOT, COMPANION, UK-PACE and T-wave alternans. *Eur J Heart Fail* 2003;5:391–8.

mortality in chronic HF (Fig. 4). The Digitalis Investigators Group (DIG) trial (114), enrolling more than 6500 patients with an average follow-up of 37 mo, showed that digoxin reduced the incidence of HF exacerbations but had no effect on survival. Patients with mildly symptomatic chronic HF, who were randomized to digoxin withdrawal (PROVED and RADIANCE trials), had an increased likelihood of an acute exacerbation compared with those who continued to receive digoxin (115,116). On the other hand, doubling the dose of digoxin from 0.125 to 0.25 mg daily provided no significant benefit in terms of exercise tolerance or ventricular function, suggesting that doses of digoxin should be kept small (117).

### Perioperative Implications

Chronic treatment with diuretics can lead to hypovolemia and an imbalance of electrolytes, particularly hypokalemia. These side effects are most common in the elderly (118). Chronic diuretic therapy can lead to hypotension and arrhythmias (119) during anesthesia. However, chronic use of diuretics for the management of HF has not been associated with perioperative CV death (within 30 days of surgery) in emergency and urgent surgical patients (120). In contrast, complications of digoxin therapy can be life-threatening and often difficult to diagnose and treat, given digoxin's narrow therapeutic index. Aggravating conditions that predispose to digoxin toxicity include hypomagnesemia, hypercalcemia, and hypokalemia, all of which may occur during the perioperative period. Treatment of digoxin toxicity, which often manifests as nausea, arrhythmias, and visual symptoms consists of correcting any underlying electrolyte imbalances, administering antiarrhythmic drugs (most commonly phenytoin), and in refractory cases, commercially prepared antibodies to digoxin (e.g., digoxin-specific

Fab (Digibind; Glaxo-SmithKline, Research Triangle Park, NC), a mixture of antidigoxin Fab fragments prepared from sheep sera). Despite continuing concerns about digoxin toxicity, perioperative discontinuation of digoxin therapy remains controversial. After adjustment for the confounding effect of HF, Sear et al. (120) report that digoxin therapy was associated with an increased cardiac risk in urgent and emergent surgical patients. Given that rate and rhythm control and positive inotropy can be achieved with other drugs with shorter half-lives and less toxicity, we tend to discontinue digoxin in elderly surgical patients where age-related alterations in drug distribution and excretion may make toxicity increasingly likely (121).

### PHARMACOLOGIC TREATMENT OF DIASTOLIC HF

Abnormal diastolic ventricular function is present in nearly all patients with symptomatic HF (122). As many as one in three patients presenting with clinical signs of chronic HF have a normal or near-normal EF ( $\geq 40\%$ ). Although the prognosis of patients with isolated diastolic HF is better than for those with systolic HF (5%–8% versus 10%–15% annual mortality), the complication rate is the same (123). The 1-yr readmission rate for patients with isolated diastolic HF approaches 50% (124).

Large randomized trials have led to the treatment guidelines for systolic HF; however, there are few completed randomized, double-blind, placebo-controlled, multicenter trials performed in patients with diastolic HF. The CHARM-Preserved Trial (58) data of 3023 patients indicate that treatment with the ARB candesartan reduces hospitalization rates but does not alter mortality in patients with diastolic HF. Findings from the I-PRESERVE (Irbesartan in HF with preserved

**Table 5.** Management of Decompensated Heart Failure

| Class                                    | Drugs                      | Infusions   | Side Effects  |
|--|----------------------------|---|---|
| Diuretics                                | Furosemide                 | 5–20 mg/h   | Hyponatremia, hypokalemia, hypomagnesemia; predisposes patients to toxicity of cardiac glycosides   |
| Vasodilators                             | Bumetanide                 | 2–5 mg slow infusion  | Hypotension, nausea, headaches, tachycardia, tolerance  |
|  | Nitroglycerin              | 10–200 $\mu\text{g}/\text{min}$   |   |
| Inotropes                                | Nitroprusside              | 0.1–5 $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$  | Hypotension, nausea, headaches, thiocyanate poisoning<br>Tolerance (beta receptor down-regulation) hypotension, supraventricular and ventricular tachyarrhythmias |
|  | Dobutamine                 | 2.5–15 $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ load, 50 $\mu\text{g}/\text{kg}$ (eliminate load if systolic blood pressure <100 mm Hg) 0.375–0.75 $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ |   |
|  | Milrinone<br>Levosimendan* | 12 $\mu\text{g}/\text{kg}$ over 10 min (load); 0.1 $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$   |   |
| Vasodilator/<br>Diuretic/<br>Natriuretic | Nesiritide                 | 2 $\mu\text{g}/\text{kg}$ load; 0.01 $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$<br>0.005–0.03 $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ (preferred in perioperative setting)                   | Hypotension, nausea   |

\*Used for treatment of acute, decompensated heart failure in Europe.

systolic function) (125) trial of more than 4000 subjects will likely provide conclusive data regarding the primary end-point of death and the role of ARB blockade in the management of diastolic HF. Data from the Seniors trial (126) of nebivolol in 2128 HF patients, of whom 752 had diastolic HF (EF defined as >35%), suggest that  $\beta$ -adrenergic blockade is equally beneficial in patients with diastolic as with systolic HF. Preliminary findings from continuing studies suggest that aldosterone antagonists may also improve exercise tolerance and quality of life in patients with diastolic HF (127,128). However, until validation from adequately powered, randomized controlled trials becomes available, the contemporary treatment of chronic diastolic HF remains empiric (Table 4).

### MANAGEMENT OF ACUTE EXACERBATIONS OF CHRONIC HF

Patients with chronic HF may experience episodes of acutely decompensated HF, heralded by the classic symptoms of dyspnea or fatigue. These patients will require all the standard medications as outlined in previous sections (except for perhaps holding ACE-I when systolic BP <80 mm Hg), and may also require infusions of vasodilators or positive inotropic drugs (129) (Table 5).

IV vasodilators have long been used to treat the symptoms of low cardiac output in patients with decompensated chronic HF. In general, vasodilators reduce ventricular filling pressures and systemic vascular resistance while increasing stroke volume and cardiac output. Nitroglycerin is commonly used for

this purpose and has been studied in numerous clinical trials (129). In addition, recombinant brain natriuretic peptide (BNP) has received regulatory approval as a drug (nesiritide), indicated for patients with acute HF and dyspnea. Nesiritide binds to A- and B-type natriuretic peptide receptors on endothelial and vascular smooth muscle cells. It produces venous and arterial dilation, with subsequent reductions in preload and afterload, through increasing cGMP. Nesiritide does not increase heart rate, and has no effect on cardiac inotropy. Nesiritide exerts diuretic and natriuretic effects and causes coronary vasodilation. It has a rapid onset of action with a distribution half-life of 2 min and a terminal elimination half-life of 18 min. Onset of the drug's effects is later than would be predicted based on its pharmacokinetic parameters. For example, with an initial loading dose and maintenance infusion, only 60% of the reduction in pulmonary wedge pressure that will be measured at 3 h is achieved 15 min after the bolus dose (130). Clinical effects have also been observed to persist longer than would be anticipated (based on drug levels) after the drug is discontinued.

Nesiritide is metabolized by three mechanisms: endocytotic internalization by its surface receptor, hydrolysis by neutral endopeptidase, and renal excretion (minor role) (131). When initiated in the perioperative setting (e.g., post-CPB), a starting infusion dose of 0.005  $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ , without a bolus, is recommended to avoid hypotension in patients with increased filling pressures and low systemic vascular resistance (<800  $\text{dyne} \cdot \text{s} \cdot \text{cm}^{-5}$ ) who might also be receiving ACE-I and  $\beta$ -adrenergic blockers. Studies

have shown that nesiritide reduces symptoms of acute decompensated HF similarly to nitroglycerin, including a reduction of pulmonary artery pressure, without development of acute tolerance (132). In early studies, patients receiving nesiritide experienced fewer adverse events than those receiving nitroglycerin (133). Compared with dobutamine, nesiritide was associated with fewer instances of ventricular tachycardia or cardiac arrest (134). In the ADHERE registry (135) of more than 65,000 episodes of acute decompensated HF, treatment with either nesiritide or a vasodilator was associated with a 0.59 odds ratio for mortality compared with either milrinone or dobutamine. Recent data, however, suggest that not only may nesiritide not offer a compelling safety advantage, it may also be associated with an increased incidence of adverse side effects, including renal failure and mortality, when administered to patients with acutely decompensated chronic HF (136,137). These publications prompted the Food and Drug Administration to convene an expert panel, which made several recommendations, including that nesiritide be used only for hospitalized patients with acute decompensated HF and that the drug not be used to enhance diuresis or to “protect” the kidneys (138).

Clinical trials showed that chronic treatment with positive inotropes such as inamrinone and milrinone led to increased mortality (139–141). Nevertheless, positive inotropic drugs, principally dobutamine or milrinone, have long been used to treat decompensated HF (Fig. 4). There is a lack of data supporting their discretionary administration (142), e.g., on a monthly schedule to patients awaiting cardiac transplantation to avoid the need for ventricular assist devices. Levosimendan, a new cAMP-independent positive inotrope, may prove to have no negative outcome effects when used to treat acute decompensation of chronic HF (143). Levosimendan acts by increasing myocyte sensitivity to calcium via stabilizing the calcium-bound conformation of troponin C (Fig. 5). Levosimendan also opens  $K_{ATP}$  channels in vascular smooth muscle inducing vasodilation and in cardiac muscle, where these channels may protect against ischemia (144). When compared with dobutamine, levosimendan reduced 1-mo mortality (and reduced mortality compared with placebo at 14 days (145). Calcium sensitivity is increased during systole without causing calcium overload during diastole. This results in enhanced inotropic performance and preserved diastolic performance.

When drug treatment proves unsuccessful, HF patients may require invasive therapy, including ventricular assist devices, resynchronization with biventricular pacing, coronary bypass with or without surgical remodeling, or even cardiac orthotopic transplantation (146). These important modalities are beyond the scope of this review.

## Current Clinical Practice

### Diagnosis

For most patients, the diagnosis of HF will have been made long before they arrive for surgery or intensive care. Current guidelines provide a helpful framework by which primary care physicians and cardiologists can make the appropriate diagnoses and follow the disease process over time (6). On the other hand, how does a perioperative physician determine quickly, conveniently, and inexpensively whether a dyspneic patient's symptoms are the result of new or worsening HF, lung disease, or a combination of the two? Clearly the issue can be settled using the medical history and physical examination, electrocardiogram, echocardiogram, chest radiograph, and consultation with either a pulmonary medicine specialist or cardiologist. On the other hand, measurements of BNP in blood are widely used to help triage patients presenting with acute dyspnea (147). Taken together with physical examination and history, if the BNP is  $<100$  pg/mL, then HF is highly unlikely; negative predictive value, 90%, and if the BNP level is  $>500$  pg/mL, then HF is highly likely, positive predictive value is 90%. For BNP levels of 100–500 pg/mL, one must consider whether the baseline is increased as a result of advanced age, underlying stable left ventricular dysfunction, right ventricular failure secondary to pulmonary hypertension or acute pulmonary embolism (148,149).

### Treatment

Current guidelines begin pharmacotherapy of HF with primary prevention of left ventricular dysfunction (6,7) (Fig. 1). Because hypertension and coronary artery disease are leading primary causes of left ventricular dysfunction, adequate control of both hypertension (according to the Joint National Committee-7 guidelines) (150) and hypercholesterolemia has been endorsed after encouraging results in prevention trials (151). ACE inhibitors, and possibly  $\beta$ -adrenergic blockers, should be initiated in diabetic, hypertensive, and hypercholesterolemia patients (AHA/ACC, Stage A HF) who are at increased risk for CV events, despite normal contractile function, to reduce the onset of new HF (HOPE trial) (30). In patients with asymptomatic left ventricular dysfunction ( $EF \leq 40\%$ ) (Stage B), treatment with ACE inhibitors and  $\beta$ -adrenergic blockers can blunt the disease progression. In the symptomatic HF patient (Stage C), diuretics are titrated to relieve symptoms of pulmonary congestion and peripheral edema and to restore a normal state of intravascular volume (152). ACE inhibitors and  $\beta$ -adrenergic blockers are recommended to blunt disease progression. Although digoxin has no effect on patient survival, it may be considered in Stage C if the patient remains symptomatic despite adequate doses of ACE inhibitors and diuretics. An alternative for patients (particularly African-American patients) with systolic dysfunction



and contraindications, intolerance, or unresponsiveness to ACE inhibitors or ARBs is isosorbide dinitrate three times a day in combination with hydralazine three times a day (153) or BiDil (fixed dose combination of isosorbide dinitrate and hydralazine hydrochloride (A-HeFT trial) (31). The use of an NO donor (isosorbide) in HF heralds the new suggestion that "NO balance" may be important in the pathophysiology of HF (154).

In general, the primary treatment objectives for Stages A–C HF are: 1) improved quality of life, 2) reduced morbidity, and 3) reduced mortality. At this time, the most important way to improve long-term outcome is through inhibiting disease progression by counteracting neurohormonal effects. Pharmacologic therapy in patients with severe, decompensated HF (Stage D) is based on hemodynamic status. Symptomatic treatment with diuretics, vasodilators, and, in palliative circumstances, IV inotropic infusions is added to "standard" treatment. Finally, some of these patients may require device therapies or surgical procedures, such as cardiac transplants.

What is an anesthesiologist to do when faced with a patient with Stage D or decompensated Stage C HF who requires emergency surgery? If tracheal intubation and positive pressure ventilation are needed to manage pulmonary edema, then there is little reason to select a regional anesthesia technique. When feasible (this will be rare because these patients often cannot lie flat on the operating table), regional nerve block techniques, rather than general anesthesia or neuroaxial block techniques, may avoid intraoperative crystalloid infusions. There is no evidence basis by which to select either an induction or a maintenance anesthetic drug in these patients. We have successfully used most IV induction drugs in these patients (including thiopental, propofol, ketamine, etomidate, midazolam, and diazepam) and have seen no obvious reason to recommend any one of them over the others. Similarly, while many authors advocate maintaining anesthesia in these very sick patients using benzodiazepines and opioids, our usual practice is to maintain anesthesia with inhaled anesthetics. We find intraoperative fluid and medical management considerably more challenging than anesthetic choice in these patients. Accordingly, when HF patients must undergo major surgery, we suggest invasive arterial BP monitoring and transesophageal echocardiography (TEE) to help guide intraoperative decision-making. TEE is especially useful in diagnosing whether hypotensive episodes are the result of inadequate circulating blood volume, worsening ventricular function, or arterial vasodilation (155–157). Pulmonary artery catheters have long been used in these patients for this purpose; if TEE is not available, pulmonary artery catheters may be a useful, if controversial, alternative (158).

Large volumes of blood, colloid, or crystalloid should be used to treat hypotension in HF patients only when there is a reasonable suspicion that true

hypovolemia is present. This advice may be even more important for patients receiving spinal or epidural anesthesia (in the latter case there seems to be an even greater tendency to use IV fluid/colloid/blood rather than vasoactive drugs to treat hypotension). Patients receiving loop diuretics on an outpatient basis may prove refractory to the usual IV doses of furosemide and continuous infusions of furosemide (20 mg/h) or nesiritide ( $0.005\text{--}0.01 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ ) may be needed. Finally, transfusion for perioperative anemia in a hemodynamically stable patient with a history of HF (e.g., stage C) must be approached with greater caution than usual. It is easy to produce intravascular volume overload in these patients (159).

When we consider our aging patient population in which prolonged survival with hypertension and/or coronary artery disease is expected and the better HF treatment strategies now available to them, we conclude that anesthesiologists will encounter an increasing number of patients with either a predisposition to HF (stages A and B) or a history of HF (stages C and D). Thus, knowledge of the evolving pharmacologic strategies for the management of chronic HF is essential both for patient care and for our continued credibility as perioperative physicians.

## APPENDIX

**Abbreviations for Trials and Registries:** ADHERE: Acute Decompensated Heart Failure National Registry, A-HeFT: African-American Heart Failure Trial, ATLAS: Assessment of treatment with lisinopril and survival, BEST:  $\beta$ -Blocker evaluation of survival study, CHARM: Candesartan in heart failure assessment in reduction of mortality, CIBIS: Cardiac insufficiency bisoprolol study, COMET: Carvedilol or metoprolol European trial, CONSENSUS: Cooperative North Scandinavian Enalapril Survival Study, COPERNICUS: Carvedilol prospective randomized cumulative survival, DIG: Digitalis Investigation Group, ELITE: Evaluation of losartan in the elderly, EPHEUS: Eplerenone post-MI heart failure efficacy and survival study, GISSI: Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico Investigators, HOPE: Heart outcomes prevention evaluation, I-PRESERVE: Irbesartan in heart failure with preserved systolic function, ISIS: International study of infarct survival, MERIT-HF: Metoprolol CR/XL randomized intervention trial in congestive heart failure, PROVED: Prospective randomized study of ventricular function and efficacy of digoxin, RALES: Randomized aldactone evaluation study, RADIANCE: Randomized assessment of digoxin or inhibitors of the angiotensin-converting enzyme, SAVE: Survival and ventricular enlargement, SOLVD: Study of left ventricular dysfunction, US CARVEDILOL: United States carvedilol, V-Heft: Veteran's Administration Heart Failure Trial, Val-HeFT: Valsartan in heart failure trial.

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