Reassessment of Dobutamine, Dopamine, and Milrinone in the Management of Acute Heart Failure Syndromes

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The appropriate role of intravenous inodilator therapy (inotropic agents with vasodilator properties) in the management of acute heart failure syndromes (AHFS) has long been a subject of controversy, mainly because of the lack of prospective, placebo-controlled trials and a lack of alternative therapies. The use of intravenous inodilator infusions, however, remains common, but highly variable. As new options emerge for the treatment of AHFS, the available information should be reviewed to determine which approaches are supported by evidence, which are used empirically without evidence, and which should be considered inappropriate. For these purposes, we reviewed data available from randomized controlled trials on short-term, intermittent, and long-term use of intravenous inodilator agents (dobutamine, dopamine, and milrinone) in AHFS. Randomized controlled trials failed to show benefits with current medications and suggested that acute, intermittent, or continuous use of inodilator infusions may increase morbidity and mortality in patients with AHFS. Their use should be restricted to patients who are hypotensive as a result of low cardiac output despite a high left ventricular filling pressure. **(Am J Cardiol 2005;96[suppl]:47G–58G)**

Acute heart failure syndromes (AHFS) resulting in hospitalization represent a major public health problem because of the high numbers of patients (1 million in the United States), postdischarge mortality and readmission rates (10% and 25% at 60 days, respectively), and significant associated costs ($27.9 billion per year).[1] Most patients with AHFS present to the emergency room with a relatively high blood pressure and systemic congestion without signs of systemic hypoperfusion (normal cardiac output). In addition, based on the Acute Decompensated Heart Failure National Registry (ADHERE), almost 50% of the patients admitted with AHFS had a relatively preserved systolic function (PSF).[2] These patients had a higher incidence of hypertension, left ventricular hypertrophy, and diabetes mellitus than patients admitted with AHFS and systolic dysfunction.[3]

How we manage AHFS is important because selection of therapeutic agents, which are used for only days or hours, may influence long-term mortality and morbidity. The initial therapy for patients with AHFS should improve symptoms and hemodynamics without causing myocardial injury that may adversely affect postdischarge morbidity and mortality.

Randomized controlled trials failed to show a benefit with the acute,[4] intermittent,[5] or continuous[6] use of inodilators in patients with heart failure (HF). Despite these negative results, dobutamine, dopamine, and milrinone are often given to improve cardiac performance and to relieve congestive symptoms of AHFS, even in patients with normal blood pressure and relatively preserved cardiac output.

Use of Inodilator Therapy in Acute Heart Failure Syndromes Registries

The ADHERE database was designed to study prospectively the outcomes, characteristics, and management of AHFS. In this registry, which currently comprises >150,000 patients, <3% presented with a systolic blood pressure of <90 mm Hg and approximately 50% presented with relative PSF.[3] Approximately 14% of the patients in ADHERE were treated with ≥1 acute infusions of inodilator agents (dobutamine 6%, dopamine 6%, and milrinone 3%) in the hospital.[7] Furthermore, among home discharges of patients with a prior history of HF during this period, 1% were discharged on chronic dobutamine, and 1% on chronic milrinone infusion therapy.[2]

Importantly, 15% of patients receiving inodilators had PSF.[8] The inodilator-treated patients with PSF had a higher mortality rate (19%) than all other inodilator-treated patients (14%).[8] Patients with PSF who were treated with inodilators also had a higher mortality rate than patients

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with PSF who were not treated with inodilators (19% vs 2%, respectively).[8] Among the inodilator-treated patients, those with PSF also had a longer hospital stay compared with all other inodilator-treated patients (mean, 12.9 vs 9.6 days).[8] Although these results may be confounded by unmeasured differences in the patients and treatment settings in which inodilator treatments were used, they do raise the possibility that these agents may be harmful, especially when used in patients who are not appropriate for this therapy.

Recently, in a retrospective observational analysis of ADHERE, Abraham and coworkers[9] compared in-hospital mortality in a subset of 65,180 patients, 15,230 of whom were receiving either intravenous vasodilator therapy (nitroglycerin or nesiritide) or inodilator therapy (dobutamine or milrinone). Short-term vasodilator therapy was associated with significantly lower in-hospital mortality than was positive inodilator therapy in patients hospitalized with AHFS. Unadjusted in-hospital mortality varied widely, ranging from 4.1% for the entire cohort to as much as 14% for patients who received inodilators.[9,10]

The Organized Program to Initiate Life-Saving Treatment in Hospitalized Patients with Heart Failure (OPTIMIZE-HF) study has been designed to improve medical care and education of hospitalized patients with HF.[11] Among the approximately 50,000 patients with HF enrolled to date, 4% received dobutamine, 4% received dopamine, and 1% received milrinone during hospitalization.[12]

In a recent OPTIMIZE-HF subanalysis investigating the relation between admission systolic blood pressure and outcomes in hospitalized patients with HF, inodilators were used in 5.5% of patients with and without hypertension (admission systolic blood pressure between 119 and 200 mm Hg), compared with 18.5% of those with relative hypotension (admission systolic blood pressure $<$119 mm Hg) (M. Gheorghiade et al, unpublished data, 2005).

In Myocardial Viability

HF often results in myocyte hypertrophy and/or myocyte apoptosis or necrosis. However, in HF, a significant number of patients with both ischemic and nonischemic cardiomyopathy and reduced systolic function have viable but noncontractile myocardium. This condition can occur for a variety of reasons, including excessive and continuous neurohormonal stimulation, hemodynamic abnormalities, and chronic ischemia. The decrease in cardiac contractility that occurs in HF has been hypothesized to be an important compensatory mechanism that decreases energy use by the failing myocardium and thereby improves long-term survival of cardiac myocytes.[13] It has been suggested that although augmentation of contractility by various drugs produces a temporary improvement in cardiac performance, it may do so at the expense of increasing myocardial energy consumption and accelerating myocardial cell death.[14]

Recent studies using positron emission tomography suggest that $>$50% of patients with chronic HF and coronary artery disease (CAD) have hibernating myocardium, an adaptive response to a sustained reduction in coronary vasodilator reserve in which the level of tissue perfusion is sufficient to maintain cellular viability but not sufficient for normal contractile function.[15,16] This precarious balance between perfusion and tissue viability, however, is not sustained indefinitely and will progress to myocardial necrosis unless the blood flow increases.[15,17–26] Areas of hibernating myocardium or contractile reserve may be adversely affected by inodilator agents. In fact, inodilators may cause worsening of ischemia by increasing myocardial oxygen demand through increased contractility and induction of tachycardia. Schulz et al[24] found that experimentally increasing the contractility of hibernating myocardium by using relatively low doses of an inodilator, such as dobutamine, for short periods can lead to myocardial necrosis.

Regardless of whether the myocytes are hibernating because of CAD or are alive but not contracting for other reasons, as is the case in idiopathic cardiomyopathy, stimulation of these cells with an inodilator may result in cell death through necrosis or apoptosis, thereby further reducing contractility, creating a vicious cycle. For this reason, patients treated with inodilators may improve clinically in the short term but may become more dependent on the use of inodilators. Thus, despite the apparent clinical improvement, there may be progression of HF in these patients.

Mechanisms of Action and Effects of Inodilators

The most commonly used inodilator agents work through a common pathway of increased intracellular cyclic adenosine monophosphate (cAMP) and calcium concentrations. These include β-adrenergic agonists, endogenous catecholamines, and phosphodiesterase inhibitors.

Dobutamine—β-adrenergic agonists: Dobutamine is a racemic mixture that stimulates β_1- and β_2-receptors. The negative enantiomer is also an agonist for β_1-receptors, whereas the positive enantiomer is a very weak partial agonist. Through its action on β_1-receptors, dobutamine activates a guanine nucleotide regulatory cascade (via G proteins). This leads to increased adenylate cyclase activity and increased conversion of adenosine triphosphate (ATP) to the intracellular second messenger cAMP. Intracellular cAMP causes release of calcium from the sarcoplasmic reticulum. The calcium is used by contractile proteins and results in increased stroke volume.[27] In the vasculature, the α-adrenergic agonist effect of the negative enantiomer appears to be counteracted by the partial agonism of the positive enantiomer and the vasodilatory action caused by β_2-receptor stimulation. This usually results in a modest decrease in systemic vascular resistances and venous filling pressures.[27]

The rate of infusion doses of dobutamine needed to increase cardiac output usually ranges from 2.5 to 15 μg/kg

per min. Onset of action is within 1 to 2 minutes, but it may take as long as 10 minutes to see the peak effect of a particular infusion rate. The plasma half-life of dobutamine is 2 minutes. In studies with infusion periods ≥24 to 72 hours, cardiac output was noted to return toward baseline values in some study subjects, raising the concern of pharmacologic tolerance with prolonged infusion.

The overall effect of dobutamine on blood pressure is variable, depending on the relative effects on the vascular tone and cardiac output achieved. Heart rate is often decreased because of reflex withdrawal of sympathetic tone in response to improved cardiovascular function. However, this is not always the case. The major side effects of dobutamine include tachycardia, especially in patients with atrial fibrillation, and atrial and ventricular arrhythmias. Patients taking a β-blocker may have an attenuated initial response to dobutamine until the β-blocker has been metabolized.

It has been hypothesized that the increased energy demands of the failing myocardium lead to a state of relative energy depletion through an initial compensatory phase of increased oxygen extraction.[28,29] This paradigm suggests that further inodilator stimulation would impose further energy demands and ultimately accelerate myocardial cell death. Several investigators have attempted to demonstrate this using a variety of methods to investigate myocardial oxygen consumption and a variety of in vitro and in vivo models. Studies in animal models with left ventricular dysfunction demonstrated that dobutamine infusion is associated with an increase in myocardial oxygen consumption with a shift in myocardial metabolism, evidenced by an increased preference for glycolytic substrates.[30,31] Studies in patients with ischemic or nonischemic dilated cardiomyopathy also suggested that dobutamine increases myocardial oxygen consumption and the work-metabolic index.[32,33]

Dopamine—endogenous catecholamines: Dopamine is an endogenous substance with dose-dependent effects. At doses of ≤2 μg/kg per min, based on estimated lean body weight, dopamine causes vasodilation by direct stimulation of dopamine postsynaptic type 1 and presynaptic type 2 receptors in the splanchnic and renal arterial beds.[27] Dopamine also has direct effects on renal tubular epithelial cells, resulting in increased natriuresis.

Intermediate infusion rates of 2 to 5 μg/kg per min cause direct stimulation of β-adrenergic receptors in the heart and induce norepinephrine release from vascular sympathetic neurons. This results in increased heart rate and cardiac output. Infusion rates of 5 to 15 μg/kg per min generally stimulate β- and α-adrenergic receptors, leading to an increased heart rate and peripheral vasoconstriction.

A major side effect of dopamine is tachycardia, which tends to be much more pronounced with dopamine than dobutamine.[27] Another concern when using dopamine is correct dosing. Dopamine dose is based on lean body weight, which can be difficult to estimate. A new or unexplained tachycardia or arrhythmia in a patient receiving "low-dose" dopamine should make a clinician suspect an inaccurate estimation of lean body weight resulting in an inappropriately high dopamine infusion rate.[27] The effects of dopamine on cardiac function and energy metabolism have been compared with those of bucladesine.[34] In this setting, dopamine enhanced anaerobic metabolism at both doses, with a concomitant decrease in systolic pressure and coronary flow.

Milrinone—phosphodiesterase inhibitors: Phosphodiesterase is the enzyme that breaks down intracellular cAMP to its inactive metabolite (5′AMP). Milrinone is a bipyridine derivative that selectively inhibits the phosphodiesterase III enzyme, leading to increased intracellular cAMP.[27] This results in increased intracellular calcium concentration and myocardial contractility as well as acceleration of myocardial relaxation. Increased cAMP peripherally produces vasodilation in both the arterial and venous circulation. The end result is decreased systemic and pulmonary vascular resistances, decreased left and right ventricular filling pressures, and increased cardiac output.

Treatment with milrinone may be initiated with a loading dose of 50 μg/kg per min followed by a continuous infusion of between 0.25 and 1.0 μg/kg per min or as an infusion without the loading dose. Most patients have improvement in hemodynamic function in 5 to 15 minutes after initiation of therapy. The elimination half-life is 30 to 60 minutes when tested in healthy individuals, but it is doubled in patients with severe HF.[27]

A major side effect of milrinone is hypotension, and milrinone is often administered without a loading dose in an attempt to minimize the decrease in blood pressure. Other side effects include increased atrial and ventricular ectopy (eg, nonsustained ventricular tachycardia). The metabolic cost of milrinone in patients with congestive HF is unclear, particularly when compared with other inodilator agents.[35]

White et al[36] determined the immediate effects of milrinone on exercise performance in 14 patients with New York Heart Association (NYHA) class III to IV congestive HF, in a randomized, double-blind, placebo-controlled study. Compared with placebo, intravenous milrinone caused a higher peak oxygen uptake and oxygen uptake at the anaerobic threshold with a concomitant decrease in blood lactate concentrations at matched submaximal exercise intensities.

Trials: Intravenous Inodilator Therapy

There are several different regimens of intravenous inodilator therapy that have been used to treat patients with congestive HF. These agents are used for short-term inpatient therapy to treat AHFS. In this setting, patients are usually infused over several hours to a few days in combination with diuretics. Acute treatment is discontinued when patients are clinically stable. However, some patients de-

Table 1
Mortality at 1 month and 6 months in the Calcium Sensitizer or Inotrope or None in Low-Output Heart Failure Study (CASINO)

End Point	Dobutamine (n = 100)	Placebo (n = 99)	Levosimendan (n = 100)
1-mo mortality	14.0%	8.1%	6.0%*
6-mo mortality	42.0%†	28.3%	18.0%‡

* $p = 0.04$ vs dobutamine.
† $p = 0.02$ vs placebo.
‡ $p = 0.0001$ vs dobutamine and 0.03 vs placebo.
Adapted from Program and abstracts of the European Society of Cardiology, Heart Failure Update 2004[40] and *Eur J Heart Fail.*[41]

compensate when intravenous inodilator infusions are stopped, and they cannot be weaned off or switched to an oral agent. In such cases, patients may need to be on continuous intravenous infusions. This is usually done on an outpatient basis. It has also been proposed to use intermittent inodilator treatment to prevent rehospitalization. This infusion schedule involves intermittent intravenous therapy, usually given as a 4- to 6-hour pulse infusion for several days per week or as a single 24- to 72-hour infusion once weekly.

Short-Term Use of Inodilator Treatment

Dopamine and dobutamine: There are no randomized, controlled trials studying the effects of short-term dopamine infusion. Liang and associates[37] studied the effects of continuous infusion of dobutamine for 72 hours in 15 patients with NYHA class III to IV HF with a follow-up period of 4 weeks. No deaths were observed in this 4-week period. Maximal exercise time and left ventricular ejection fraction (LVEF) increased significantly in the dobutamine group. NYHA functional class improved in 6 of 8 patients in the treatment group compared with 2 of 7 control patients.

Recent randomized trials have compared the effects of a short-term intravenous infusion of dobutamine with levosimendan, a new calcium sensitizer and ATP-dependent potassium channel opener (see also the article by Mebazaa and colleagues[38] in this supplement). The Levosimendan Infusion Versus Dobutamine (LIDO) study demonstrated the acute hemodynamic benefits of levosimendan (loading dose of 24 μg/kg followed by an infusion of 0.1 μg/kg per min for 24 hours) compared with dobutamine (started with a continuous infusion of 5 μg/kg per min) in patients with severe low-output HF.[39] In addition, levosimendan was associated with a significantly lower all-cause mortality and readmission rate at 180 days.

In the Calcium Sensitizer or Inotrope or None in Low-Output Heart Failure Study (CASINO), dobutamine was associated with lower 6-month survival compared with levosimendan or placebo in patients with decompensated low-output HF (Table 1).[40,41] Moreover, this trial demonstrated a survival benefit associated with levosimendan treatment compared with placebo. The CASINO trial suggests that short-term treatment with dobutamins is associated with increased postdischarge mortality.

The ongoing Survival of Patients with Acute Heart Failure in Need of Intravenous Inotropic Support (SURVIVE) trial will further analyze the effects of levosimendan compared with those of dobutamine on mortality during 180 days after the start of treatment.[42]

Milrinone: Milrinone was approved for short-term intravenous use in the late 1980s. Amrinone, the parent drug of milrinone, however, has had limited use because it has a 10% rate of thrombocytopenia caused by reversible bone marrow suppression. As mentioned before, oral milrinone as a continuous treatment has been shown to increase mortality.[43] Its intravenous use in the acute setting has been studied in a few randomized controlled trials. The largest of these trials is the Outcomes of Prospective Trial of Intravenous Milrinone for Exacerbations of Chronic Heart Failure (OPTIME-CHF).[4,44] Most of the controlled trials, including OPTIME-CHF, evaluated the effects of short-term use of milrinone (Table 2).[4,44–47]

The OPTIME-CHF investigators[44] randomized 949 patients (mean age, 65 years) admitted with an exacerbation of systolic HF with NYHA class III to IV HF and an LVEF <0.40 (mean LVEF, 0.23) to study the effect of short-term milrinone infusion (48 to 72 hours) on the primary outcome: cumulative days of hospitalization within 60 days of randomization (the period with the highest risk of rehospitalization[48]). They also studied the effects on secondary outcomes, including adverse events and mortality. Patients who were judged to need inodilator therapy were excluded from the study (eg, for shock or severe hypotension) as well as those who had myocardial ischemia in the last 3 months, atrial fibrillation with poor rate control (>110 beats per minute), or sustained ventricular tachycardia or ventricular fibrillation. The study concluded that there were no significant differences between the treatment and placebo groups for the number of days hospitalized within the 60-day period, the number of rehospitalizations, the length of initial stay, in-hospital mortality, or 60-day mortality (Table 3). Clinical status measured by an HF score was also similar

Table 2
Short-term (acute) infusions: milrinone versus placebo trials

Trial	Milrinone	Comparison	Patient Population	Number	Follow-up	Outcome
Anderson et al 1987[46], 1991[45]	50 μg/kg loading dose followed by infusion with 0.5 μg/kg/min × 1 hr	Placebo	NYHA class III–IV with CI <2.5 L/min/m^2 or PCWP >15 mm Hg	31	1 hr	Milrinone caused significant increases in CI (41%) and SV (32%) and decreases in PCWP (25%), SVR (24%), and MAP (5%) at 1 hr of infusion.
Seino et al, 1996[47]	50 μg/kg loading dose followed by continuous infusion with 0.5 μg/kg/min for 6 hr	Placebo	Patients with acute heart failure with PCWP >18 mm Hg	52	1 hr	37% decrease in PAOP, 39% decrease in RAP, 31% increase in CI, and 21% increase in SV at 15 min compared with decreased CI at 60 min and no other significant changes in placebo group. Subjective symptoms also improved compared with no improvement in placebo. 16% rate of ventricular arrhythmias in milrinone group.
Cuffe et al, 2002[44]	48–72-hr infusion with 0.5 μg/kg/min	Saline placebo	NYHA class III–IV; mean LVEF = 0.23	951	2 mo	No significant difference in number of days hospitalized, in-hospital mortality, 60-day mortality, or composite incidence of death or re-admissions.
Felker et al, 2003[4]	48–72-hr infusion with 0.5 μg/kg/min	Saline placebo	NYHA class III–IV; mean LVEF = 0.23	951	2 mo	Milrinone-treated patients with ischemic heart disease tended to have worse outcomes for the composite of death and rehospitalizations.

CI = cardiac index; LVEF = left ventricular ejection fraction; MAP = mean arterial pressure; NYHA = New York Heart Association; PAOP = pulmonary artery open pressure; PCWP = pulmonary capillary wedge pressure; RAP = right atrial pressure; SV = stroke volume; SVR = systemic vascular resistance.

Table 3
Results from the Outcomes of Prospective Trial of Intravenous Milrinone for Exacerbations of Chronic Heart Failure (OPTIME-CHF)[4]

Outcome	Placebo (n = 472)	Milrinone (n = 477)	p Value
Cardiovascular hospitalization within 60 days, mean days	12.5 ± 14	12.3 ± 14	0.71
Death within 60 days	8.9%	10.3%	0.41
Death or readmission within 60 days	35.3%	35.0%	0.92
Treatment failures during the infusion period	9.2%	20.6%	<0.001
New atrial fibrillation or flutter during index hospitalization	1.5%	4.6%	0.004
Sustained hypotension during index hospitalization*	3.2%	10.7%	<0.001

* Defined as a systolic blood pressure <80 mm Hg for >30 minutes, requiring intervention.
Adapted from *JAMA*.[44]

between the 2 groups, although patients treated with milrinone subjectively reported feeling better at 30 days compared with the placebo group. The 2 groups, however, differed in the treatment failures caused by adverse events within 48 hours. There were more incidents of sustained hypotension, atrial fibrillation, atrial flutter, ventricular tachycardia, and ventricular fibrillation in the treatment group. The results from this study do not support the use of short-term milrinone infusion in decompensated patients who do not present with hypotension resulting from a low cardiac output.

The OPTIME-CHF investigators retrospectively evaluated the outcomes of the study to assess the interaction between HF etiology (ischemic vs nonischemic) and short-term intravenous milrinone treatment in decompensated patients with HF.[4] A total of 485 patients had ischemic HF (defined as prior history of bypass grafting, percutaneous coronary intervention, or myocardial infarction [MI]) compared with 464 patients in the nonischemic group. In each group, approximately 50% of the patients were found to be randomized initially to milrinone. The study concluded that the response to milrinone was different in the ischemic and nonischemic groups. Patients with nonischemic HF benefited from short-term use of milrinone. The composite of death or rehospitalization at 60 days was significantly lower in the treatment group compared with placebo (28% vs 35%, p = 0.01), as well as the in-hospital mortality rate (2.6% for milrinone compared with 3.1% for placebo, p =

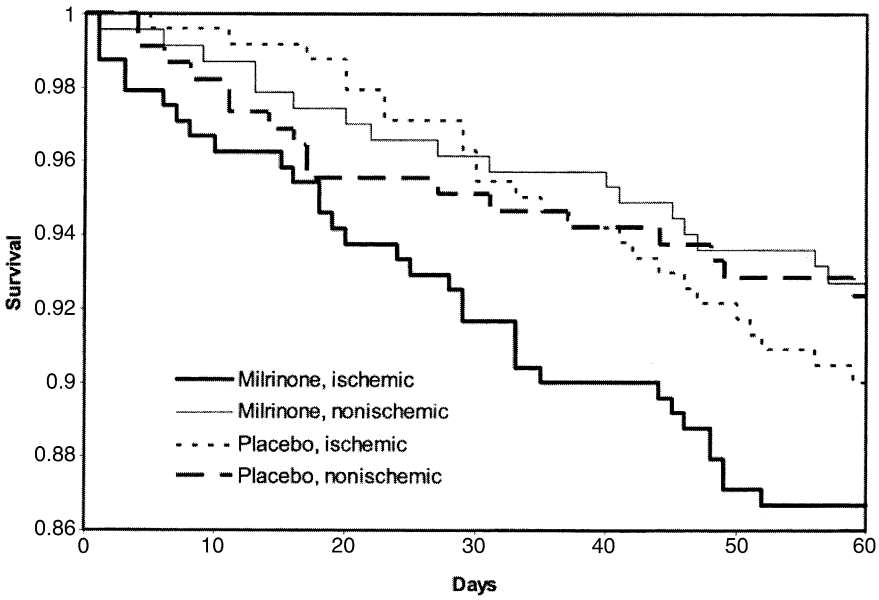

Figure 1. Kaplan-Meier survival curves for in-hospital survival to 60 days by heart failure etiology and treatment assignment in a post hoc analysis of the Outcomes of Prospective Trial of Intravenous Milrinone for Exacerbations of Chronic Heart Failure (OPTIME-CHF). (Adapted from *J Am Coll Cardiol*.[4])

0.04). Mortality at 60 days was similar between the treatment and placebo groups. The total number of hospital days tended to be lower in the milrinone-treated group compared with the placebo group (10.9 days vs 12.6 days, $p = 0.055$).

In contrast, the ischemic group was adversely affected by short-term intravenous milrinone treatment.[4] The milrinone treatment group trended toward prolonged hospitalizations and increased mortality. Days hospitalized at 60 days was 13.6 for treated patients versus 12.4 days for placebo patients ($p = 0.055$). The composite of death or rehospitalization at 60 days was significantly greater in the milrinone group (42% compared with 36% for placebo, $p = 0.01$). In-hospital mortality was also significantly higher in the treatment group (Figure 1), whereas 60-day mortality rates were similar.

Anderson,[45] Anderson and colleagues,[46] and Seino and associates[47] also studied the effects of short-term use of intravenous milrinone. However, they analyzed data only for the 1-hour period after infusion and did not analyze long-term mortality or worsening HF. They found that milrinone provided symptomatic relief compared with placebo. However, there was also a tendency toward increased ventricular arrhythmias associated with the use of milrinone in both studies. Transient occurrence of ventricular arrhythmias was observed in 16% and 12.2% of the milrinone-treated patients in the placebo-controlled, double-blind study by Seino and associates[47] and in the multicenter study by Anderson[45] and Anderson and colleagues.[46] So far, OPTIME-CHF investigators provided the largest randomized controlled trial and raised questions about the beneficial effects of short-term infusion of milrinone in decompensated patients with HF, especially in the presence of an ischemic etiology. However, it is important that the patients in OPTIME-CHF were not critically ill in that they did not require inodilator treatment as judged by their physicians. Nonetheless, data from the trial indicated that patients in this trial had severe HF, with event rates up to 35% within 60 days after discharge.[44] Regarding the reanalysis of the OPTIME-CHF study outcomes for ischemic versus nonischemic etiology of HF, it should be remembered that this is a retrospective study and can only be used to derive a hypothesis, not a conclusion.[4,44]

Numerous studies compared milrinone with dobutamine as an alternative to replace dobutamine in the acute setting. A list of the randomized, controlled trials comparing the 2 agents is shown in Table 4.[49–52] All of these trials studied short-term infusion of dobutamine and milrinone, whereas in the study by Aranda and coworkers,[53] the infusion was continued until patients received cardiac transplant. The follow-up periods were brief and mostly ended with completion of the infusion. Thus, no data were available comparing long-term effects on morbidity or mortality. It is difficult to reach a common conclusion from these trials because the patient population in each trial varied broadly: trials studied stable patients with HF,[49,50] patients post-MI,[51] patients after cardiac surgery,[52] and patients waiting for cardiac transplantation.[53] Overall, in these trials both milrinone and dobutamine seemed to be reasonable options to be used in the acute setting. Biddle and colleagues[49] found that supraventricular arrhythmias and sinus tachycardia occurred more frequently in the dobutamine group. In this study, nonsustained ventricular tachycardia occurred in 2 patients in each group and resolved spontaneously. Also, the milrinone group had 1 patient with ventricular tachycardia requiring cardioversion and 1 patient with ventricular fibrillation. Ventricular arrhythmias tended to occur in patients receiving larger boluses of milrinone. However, given the small number of patients studied in these trials, larger

Table 4
Short-term (acute) infusions: milrinone vs dobutamine trials

Trial	Milrinone	Dobutamine	Patient Population	N	Follow-up	Outcome
Biddle et al (1987)[49] Open label	50 or 75 μg/kg bolus then 0.5–1 μg/kg/min infusion × 48 hr	Incremental doses of 2.5–15 μg/kg/min × 48 hr	NYHA class III–IV (stable for ≥2 wk before study)	79	48 hr	No difference in hemodynamic effects between groups: SV increased, HR increased, SVR decreased, and PCWP decreased similarly in both groups.
Eichhorn et al (1987)[50]	50 μg/kg bolus then 0.5 μg/kg/min	2.5–15 μg/kg/min (dose adjusted to achieve equal increases in CO)	NYHA class III–IV	14	During hemodynamic and radionuclide recordings	24% increase in CI from baseline in both groups; increase in RV systolic performance. Significant RV afterload and PAESP reduction only in milrinone group.
Karlsberg et al (1996)[51] Open label	50 μg/kg bolus then 24-hr infusion of 0.25–0.75 μg/kg/min (titrated up similar to dobutamine)	24-hr infusion of 2.5–15 μg/kg/min (titrated up until >30% increase in CI or >25% decrease in MPCWP)	Within 12 hr to 5 days after acute MI	33	24 hr	Criteria for decrease in MPCWP were met by 94% of the milrinone-treated patients and 57% of the dobutamine-treated patients (p = 0.03). Maximal reduction in MPCWP was greater for the milrinone (53.2% vs 31%, p = 0.01). Both improved global EF.
Feneck et al (2001)[52] Open label	50 μg/kg bolus then 0.5 μg/kg/min infusion × 4 hr	10–20 μg/kg/min infusion × 4 hr	Patients with low CO after cardiac surgery	120	4 hr	Dobutamine group had greater increases in CI, MAP, and LV stroke work index. Milrinone group had greater decreases in MPCWP. Dobutamine group had higher incidences of hypertension and atrial fibrillation; milrinone group had higher incidence of sinus bradycardia.

CI = cardiac index; CO = cardiac output; EF = ejection fraction; HR = heart rate; LV = left ventricle; MAP = mean arterial pressure; MI = myocardial infarction; MPCWP = mean pulmonary capillary wedge pressure; NYHA = New York Heart Association; PAESP = pulmonary artery end-systolic pressure; PCWP = pulmonary capillary wedge pressure; RV = right ventricular; SV = stroke volume; SVR = systemic vascular resistance.

randomized controlled trials are needed to conclude which drug is better in which group of patients.

Concomitant use of milrinone and β-blockers: The increase in mortality associated with inodilator therapy has been attributed to a proarrhythmic effect and to direct myocyte toxicity with acceleration of disease progression.[54,55] This toxicity may be related to cAMP-mediated calcium overload.[56,57] β-Blockers have been shown to attenuate these changes at a molecular and cellular level.[58,59] For these and other reasons, these agents may be ideal in attenuating the undesirable side effects of inodilators.[60] Phosphodiesterase inhibitors, such as milrinone, would be expected to retain their positive inotropic and vasodilator effects in the presence of a β-blocker because their site of action is beyond the β-adrenergic receptor.[61] Several studies demonstrated that phosphodiesterase inhibitors, in contrast to dobutamine and dopamine, have continued positive inotropic effects in patients with advanced HF receiving chronic β-blocker therapy.[62,63] Thus, the addition of a β-blocker to a phosphodiesterase inhibitor would be expected to attenuate the negative inotropic side effects of the former and the long-term adverse effects of the latter.[64–66]

Intermittent Use of Inodilator Treatment

No randomized, controlled studies have been designed to study the effects of using intermittent infusions of dopamine. A randomized, controlled trial (the Randomized Outpatient Milrinone Evaluation [ROME] trial) studying the effects of intermittent outpatient infusions of milrinone has been terminated after enrollment of approximately 100 patients, and no data on the results are available yet.[67] All of the randomized, controlled trials retrieved in our search analyzed intermittent infusions of dobutamine (Table 5).[68–73]

Dobutamine: We identified 6 randomized, controlled trials that analyzed the effects of intermittent infusions of dobutamine.[68–73] A review of the outcomes supports a tendency for symptomatic improvement[68,69,71] and increased exercise tolerance[68–72] with dobutamine compared with placebo. The Dobutamina nell'Insufficienza Cardiaca Estrema (DICE) trial, however, found no improvement in functional status.[72] There was a nonsignificant trend toward decreased hospitalizations in the DICE trial,[72] whereas Elis and associates[73] found no difference in the number of hospitalizations between groups at 6 months. Other prospective trials did not provide data on the number of hospitalizations.

Mortality data were provided in 5 of the prospective studies.[68–70,72,73] Adamopoulos and coworkers[71] reported no deaths in either group. Mortality was increased in the treatment groups in the trial by Dies and colleagues,[69] which was stopped because of increased mortality in the dobutamine group. In the dobutamine group, death was more common among patients with >4 episodes of ventricular tachycardia per day at baseline, although dobutamine did not seem to increase the frequency of arrhythmias. The study by Elis and associates[73] and the DICE trial[72] did not find a significant difference in mortality between the dobutamine and placebo groups (3 of 19 in the placebo group vs 5 of 19 in the dobutamine group). However, in the DICE trial, 2 patients in the dobutamine group underwent cardiac transplantation and 1 patient discontinued the protocol because of severe ventricular arrhythmias. In this trial, dobutamine was not associated with an increased number of ventricular arrhythmias. No adverse effects on mortality were observed by Leier and coworkers[68] or Erlemeier and colleagues[70] (1 death in 10 patients in the placebo group vs 1 death in 10 in the dobutamine group). A meta-analysis by Thackray and colleagues[5] included 6 trials[37,69,70,72,73] and calculated an odds ratio of 1.5 (95% confidence interval, 0.51 to 3.92) for all-cause mortality in the dobutamine group compared with the control group. It is challenging to derive conclusions based on the results of these controlled trials for several reasons: (1) the small numbers of patients enrolled in each of these trials only allow detection of large differences between the treatment and control groups; (2) the infusion patterns of dobutamine varied widely between different trials (eg, the average rate of infusion by Dies and colleagues[69] was high [8.1 μg/kg per min], which may have played a role in the increased mortality associated with dobutamine); (3) patient populations studied in these trials were not always comparable (Liang and associates[37] excluded patients with ischemic heart disease, whereas Elis and associates,[73] Erlemeier and colleagues,[70] and the DICE trial[72] enrolled patients with CAD or ischemic HF); and (4) follow-up duration was varied between trials. However, until more conclusive trials are conducted analyzing the safety of using dobutamine in HF, this inodilator agent should be avoided whenever a safer option is available.

Continuous Inodilator Treatment

Many patients with advanced HF are hospitalized because of exacerbated of congestive symptoms. The use of optimal HF therapy does not suffice for symptomatic relief in some of these patients, and intravenous inodilator therapy is commonly used. Of patients who are started on intravenous inodilators for refractory HF symptoms, some cannot be successfully weaned off after being stabilized clinically and become dependent on inodilator therapy. In this setting, continuous inodilator infusions are used either as a bridge to cardiac transplantation or for palliative purposes. At this stage, patients have no other option, regardless of the effect of continuous inodilator infusions on survival. Thus, those who really need the continuous infusions would not be enrolled in placebo-controlled, randomized trials. Indeed, there are no data from randomized, controlled trials studying the effects of continuous administration of intravenous inodilator drugs prospectively compared with placebo effects. Reports in the literature indicate that the use of continuous inodilator treatment has a significant impact on quality of life and is associated with an increased mortality rate. In the past, several large-scale trials were designed to study the effects of long-term oral inodilator use in HF and showed increased mortality with these agents.[43,74–76] The Prospective Randomized Milrinone Survival Evaluation (PROMISE) analyzed 1,088 patients with severe chronic HF (NYHA class III or IV). Compared with placebo, milrinone increased hospitalizations, mortality from all causes by 28%, and cardiovascular mortality by 34%.[43] This increase in mortality was particularly evident in patients with very severe HF or class IV HF. This finding argues against the common belief that these agents are most useful for patients with the most advanced stage of HF.

Other agents that have been studied are pimobendan, a phosphodiesterase inhibitor with calcium-sensitizing properties[74]; ibopamine, an oral dopaminergic agonist with renal and peripheral vasodilatory effects[75]; and vesnarinone, a phosphodiesterase inhibitor with effects on sodium ion channels.[76] All 3 agents increased mortality when used in patients with advanced HF. Vesnarinone appeared to improve the quality of life at the expense of increasing the risk of death.[76]

In contrast to oral inodilator agents, no large-scale trials have been designed to study the effects of long-term intravenous inodilator therapy. There are no randomized controlled trials looking at the effects of continuous infusions of dopamine. For intravenous use of milrinone, Aranda et al[53] studied 36 patients awaiting cardiac transplantation who were randomized to receive either milrinone or dobutamine, and followed them until death, transplantation, or placement of mechanical cardiac support. No difference between the 2 groups was observed in right heart dynamics, death, or need for other inodilator/vasodilator treatment or for mechanical cardiac support.[53] Similar to other inodilator agents, there are no data from prospective, randomized controlled trials on chronic intravenous infusion of dobutamine. A retrospective analysis of the Flolan International Randomized Survival Trial (FIRST) is the only source of data looking at chronic infusion of this agent.[6] Caution must be exercised in interpreting the results of this post hoc analysis because a higher proportion of the dobutamine patients had NYHA class IV HF.

Dobutamine: In FIRST, 471 patients with NYHA class III to IV HF were enrolled initially to study the effects of conventional therapy with and without intravenous epoprostenol. The results of the study showed a trend toward increased mortality rate in the epoprostenol group.[77] The data from this trial were later analyzed to compare the

Table 5
Intermittent infusions: dobutamine versus placebo trials

Trial	Dobutamine	Control	Patient Population (NYHA class)	Number	Follow-up	Outcome
Leier et al (1982)[68]	IV infusion for 4 hr weekly × 24 wk	Matched control group	III–IV	26	24 wk	No significant change in CI or resting LVEF. Improved functional classification ($p < 0.05$); increased exercise tolerance ($p < 0.05$). 2 of 15 died in dobutamine group vs 1 of 11 in control group.
Dies et al (1986)[69]	IV infusion for 48 hr/wk × 24 wk	Placebo	III–IV, EF 0.20±0.11	60	8 wk	Increased treadmill times; improved symptom scores. Increased mortality in treatment group (44% vs 17% in placebo group).
Erlemeier et al (1992)[70]	8 × 24-hr infusions over a 4-wk period with at least 3 days in between	5% dextrose solution	IV	20	3 days after last infusion	Increased exercise duration on treadmill test; decreased body weight. 1 death in treatment group (1/10) and 1 death (1/10) in control group.
Adamopoulos et al (1995)[71]	IV infusion 4 days/wk × 3 wk to raise HR to 70%–80% maximum for 30 min/day	Usual activity only	Mostly III, EF 0.23 ± 0.03	20	6 wk after intervention	Increased exercise tolerance at 3 and 6 wk; increased chronotropic responsiveness to exercise; improved symptoms; increased β-receptor density. No clinically significant arrhythmias and no deaths reported.
Oliva et al (1999)[72]	Infusion for 48 hr/wk × 6 mo	Optimal standard treatment	III–IV, EF <0.30	38	8 wk for CI; 6 mo for other outcomes	Did not improve functional status; nonsignificant tendency toward decreased hospitalizations. Nonsignificant trend to improve exercise tolerance. No increase in ventricular arrhythmias. Did not significantly increase mortality.
Elis et al (1998)[73]	24-hr infusion every 2 wk × 6 wk then every 3 wk × 6 mo	Placebo	III–IV, EF 0.30 (ischemia-induced HF)	19	Until death or Dec. 1996 (survival analysis at 32 mo)	No difference in number of hospitalizations between groups at 6 mo. No significant difference between survival curves at 32 mo ($p = 0.7$)

CI = cardiac index; EF = ejection fraction; HF = heart failure; HR = heart rate; IV = intravenous; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association.

outcomes in 2 patient groups: patients who were receiving intravenous continuous dobutamine at the time of randomization for the initial study versus patients who were not receiving dobutamine at the time of randomization.[6] There were 391 patients in the no-dobutamine group and 80 patients in the dobutamine group. The median age, ratio of men to women, and etiology of HF were similar in the 2 groups. However, more patients in the dobutamine group had NYHA class IV HF. The median dose of dobutamine administered was 9 μg/kg per min (5 to 12 μg/kg per min) and the median duration of treatment was 14 days (7 to 52 days). This study concluded that the dobutamine group had a higher occurrence of first events and a higher mortality rate compared with the no-dobutamine group. Caution is warranted when interpreting these results, given the limitations of a retrospective study. It is not possible to identify what proportion of the increased mortality was attributable to dobutamine versus the baseline characteristics of the dobutamine group. However, the investigators concluded that even when the baseline differences were adjusted for, the treatment group had a 2-fold increase in mortality rate.[6] The results of this study apply only to continuous intravenous dobutamine treatment, not to short-term or intermittent intravenous treatment.

Indications for Inodilators in Current Guidelines

The current guidelines on chronic HF from the American College of Cardiology and the American Heart Association accept the use of continuous intravenous inodilator infusions for stage D patients (those with HF refractory to therapy) as a palliative treatment or as a bridge to cardiac transplantation, only after all alternative attempts to achieve stability have failed (class IIb recommendation: usefulness/efficacy is less well established by evidence/opinion).[78] These guidelines do not approve of using intermittent or continuous intravenous inodilator therapy in stage C patients (those with severe HF who appear to respond to other therapies; long-term intermittent infusions of a positive inodilator drug in these patients is considered a class III recommendation [conditions for which there is evidence and/or general agreement that a procedure/therapy is not useful/effective and in some cases may be harmful]), or in

stage D patients who can be successfully weaned from inodilator therapy (routine intermittent infusions in these patients are considered a class III recommendation). Conversely, the European Society of Cardiology guidelines suggest the use of inodilator agents in the presence of peripheral hypoperfusion (hypotension, decreased renal function) with or without congestion or pulmonary edema refractory to diuretics and vasodilators at optimal doses (class IIa recommendation: weight of evidence/opinion is in favor of usefulness/efficacy).[79]

Conclusion

Randomized, controlled studies conducted to date do not support the use of intravenous inodilator agents (dopamine, dobutamine, and milrinone) in the acute, intermittent, or chronic setting. Despite the belief that these agents improve symptoms acutely and facilitate diuresis, this is not substantiated by data from randomized trials. In contrast, the use of these inodilators may induce hypotension and arrhythmias and may cause myocardial injury. In addition, short-term use of these agents has also been associated with increased postdischarge mortality, particularly in patients with ischemic heart disease.

Data from recent registry studies indicate that these inodilator agents are being used in a significant number of patients with normal or high systolic blood pressure and PSF. Available clinical trial data do not support the use of dobutamine, dopamine, or milrinone in this population. The effects of inodilator therapy, when they are used specifically in patients with hypotension because of a low-output state, remain to be determined. Accordingly, we recommend that inodilator therapy with dopamine, dobutamine, or milrinone should only be used in patients who have low blood pressure because of low cardiac output in spite of a high LV diastolic pressure and who are not responding to other treatments.

1. American Heart Association. *Heart Disease and Stroke Statistics—2005 Update*. Dallas, TX: American Heart Association, 2005.
2. Adams KF Jr, Fonarow GC, Emerman CL, LeJemtel TH, Costanzo MR, Abraham WT, Berkowitz RL, Galvao M, Horton DP. Characteristics and outcomes of patients hospitalized for heart failure in the United States: rationale, design, and preliminary observations from the first 100,000 cases in the Acute Decompensated Heart Failure National Registry (ADHERE). *Am Heart J* 2005;149:209–216.
3. Fonarow GC. The Acute Decompensated Heart Failure National Registry (ADHERE): opportunities to improve care of patients hospitalized with acute decompensated heart failure. *Rev Cardiovasc Med* 2003;4(suppl 7):S21–S30.
4. Felker GM, Benza RL, Chandler AB, Leimberger JD, Cuffe MS, Califf RM, Gheorghiade M, O'Connor CM. Heart failure etiology and response to milrinone in decompensated heart failure: results from the OPTIME-CHF study. *J Am Coll Cardiol* 2003;41:997–1003.
5. Thackray S, Easthaugh J, Freemantle N, Cleland JG. The effectiveness and relative effectiveness of intravenous inotropic drugs acting through the adrenergic pathway in patients with heart failure: a meta-regression analysis. *Eur J Heart Fail* 2002;4:515–529.
6. O'Connor CM, Gattis WA, Uretsky BF, Adams KF Jr, McNulty SE, Grossman SH, McKenna WJ, Zannad F, Swedberg K, Gheorghiade M, Califf RM. Continuous intravenous dobutamine is associated with an increased risk of death in patients with advanced heart failure: insights from the Flolan International Randomized Survival Trial (FIRST). *Am Heart J* 1999;138:78–86.
7. Fonarow GC, Yancy CW, Heywood JT, for the ADHERE Scientific Advisory Committee, Study Group, and Investigators. Adherence to heart failure quality-of-care indicators in US hospitals: analysis of the ADHERE registry. *Arch Intern Med* 2005;165:1469–1477
8. Adams KF Jr, De Marco T, Berkowitz R, Chand S. Inotrope use and negative outcomes in treatment of acute heart failure in patients with preserved systolic function: data from the ADHERE database [abstract]. *Circulation* 2003;108:IV-695.
9. Abraham WT, Adams KF Jr, Fonarow GC, Costanzo MR, Berkowitz RL, Lejemtel TH, Cheng ML, Wynne J. In-hospital mortality in patients with acute decompensated heart failure requiring intravenous vasoactive medications: an analysis from the Acute Decompensated Heart Failure National Registry (ADHERE). *J Am Coll Cardiol* 2005;46:57–64.
10. Dec GW. Acute Decompensated Heart Failure: the shrinking role of inotropic therapy. *J Am Coll Cardiol* 2005;46:65–67.
11. Fonarow GC, Abraham WT, Albert NM, Gattis WA, Gheorghiade M, Greenberg B, O'Connor CM, Yancy CW, Young J. Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure (OPTIMIZE-HF): rationale and design. *Am Heart J* 2004;148:43–51.
12. Fonarow G, Abraham WT, Albert N, Gattis W, Gheorghiade M, Greenberg B, O'Connor CM, She L, Yancy CW, Young JB. Impact of evidence-based heart failure therapy use at hospital discharge on treatment rates during follow-up: a report from the Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure (OPTIMIZE-HF) [abstract]. *J Am Coll Cardiol* 2005;45(suppl):345A.
13. Katz AM. A new inotropic drug: its promise and a caution. *N Engl J Med* 1978;299:1409–1410.
14. Packer M, Medina N, Yushak M. Hemodynamic and clinical limitations of long-term inotropic therapy with amrinone in patients with severe chronic heart failure. *Circulation* 1984;70:1038–1047.
15. Auerbach MA, Schoder H, Hoh C, Gambhir SS, Yaghoubi S, Sayre JW, Silverman D, Phelps ME, Schelbert HR, Czernin J. Prevalence of myocardial viability as detected by positron emission tomography in patients with ischemic cardiomyopathy. *Circulation* 1999;99:2921–2926.
16. Cleland JG, Pennel D, Ray S, Murray G, MacFarlane P, Cowley A, Coats A, Lahiri A, for the CHRISTMAS Study Steering Committee and Investigators. The Carvedilol Hibernation Reversible Ischaemia trial; marker of success (CHRISTMAS). *Eur J Heart Fail* 1999;1:191–196.
17. Scarabelli T, Stephanou A, Rayment N, Pasini E, Comini L, Curello S, Ferrari R, Knight R, Latchman D. Apoptosis of endothelial cells precedes myocyte cell apoptosis in ischemia/reperfusion injury. *Circulation* 2001;104:253–256.
18. Wijns W, Vatner SF, Camici PG. Hibernating myocardium. *N Engl J Med* 1998;339:173–181.
19. Lim H, Fallavollita JA, Hard R, Kerr CW, Canty JM Jr. Profound apoptosis-mediated regional myocyte loss and compensatory hypertrophy in pigs with hibernating myocardium. *Circulation* 1999;100:2380–2386.
20. Shan K, Bick RJ, Poindexter BJ, Nagueh SF, Shimoni S, Verani MS, Keng F, Reardon MJ, Letsou GV, Howell JF, Zoghbi WA. Altered adrenergic receptor density in myocardial hibernation in humans: a possible mechanism of depressed myocardial function. *Circulation* 2000;102:2599–2606.
21. Kloner RA, Przyklenk K, Patel B. Altered myocardial states: the stunned and hibernating myocardium. *Am J Med* 1989;86:14–22.

22. Elsasser A, Schlepper M, Klovekorn WP, Cai WJ, Zimmermann R, Muller KD, Strasser R, Kostin S, Gagel C, Munkel B, Schaper W, Schaper J. Hibernating myocardium: an incomplete adaptation to ischemia. *Circulation* 1997;96:2920–2931.
23. Schulz R, Guth BD, Pieper K, Martin C, Heusch G. Recruitment of an inotropic reserve in moderately ischemic myocardium at the expense of metabolic recovery: a model of short-term hibernation. *Circ Res* 1992;70:1282–1295.
24. Schulz R, Rose J, Martin C, Brodde OE, Heusch G. Development of short-term myocardial hibernation: its limitation by the severity of ischemia and inotropic stimulation. *Circulation* 1993;88:684–695.
25. Buja LM, Entman ML. Modes of myocardial cell injury and cell death in ischemic heart disease. *Circulation* 1998;98:1355–1357.
26. Chaudhry FA, Tauke JT, Alessandrini RS, Vardi G, Parker MA, Bonow RO. Prognostic implications of myocardial contractile reserve in patients with coronary artery disease and left ventricular dysfunction. *J Am Coll Cardiol* 1999;34:730–738.
27. Hardman JG, Limbird LE, Gilman AG. *Goodman & Gilman's The Pharmacological Basis of Therapeutics*. Columbus, OH: The McGraw-Hill Companies, Inc, 2001:1825.
28. Katz AM. Cellular mechanisms in congestive heart failure. *Am J Cardiol* 1988;62(suppl):3A–8A.
29. Katz AM. Is the failing heart energy depleted? *Cardiol Clin* 1998;16: 633–644, viii.
30. Nikolaidis LA, Hentosz T, Doverspike A, Huerbin R, Stolarski C, Shen YT, Shannon RP. Catecholamine stimulation is associated with impaired myocardial O_2 utilization in heart failure. *Cardiovasc Res* 2002;53:392–404.
31. Nikolaidis LA, Trumble D, Hentosz T, Doverspike A, Huerbin R, Mathier MA, Shen YT, Shannon RP. Catecholamines restore myocardial contractility in dilated cardiomyopathy at the expense of increased coronary blood flow and myocardial oxygen consumption (MvO_2 cost of catecholamines in heart failure). *Eur J Heart Fail* 2004;6:409–419.
32. Nanbu T, Nakakoshi T, Yonezawa K, Kitabatake A. Myocardial high-energy phosphate metabolism in patients with stable chronic dilated cardiomyopathy under a dobutamine-induced prolonged mild workload. *Am Heart J* 1999;138:641–645.
33. Beanlands RS, Bach DS, Raylman R, Armstrong WF, Wilson V, Montieth M, Moore CK, Bates E, Schwaiger M. Acute effects of dobutamine on myocardial oxygen consumption and cardiac efficiency measured using carbon-11 acetate kinetics in patients with dilated cardiomyopathy. *J Am Coll Cardiol* 1993;22:1389–1398.
34. Hashimoto H, Kunitada S, Tamura K. Functional and metabolic effects of bucladesine (dibutyryl cyclic AMP) in the working rat heart preparation: comparison with dopamine. *Arch Int Pharmacodyn Ther* 1989;301:200–214.
35. Monrad ES, Baim DS, Smith HS, Lanoue AS. Milrinone, dobutamine, and nitroprusside: comparative effects on hemodynamics and myocardial energetics in patients with severe congestive heart failure. *Circulation* 1986;73:III168–III174.
36. White HD, Ribeiro JP, Hartley LH, Colucci WS. Immediate effects of milrinone on metabolic and sympathetic responses to exercise in severe congestive heart failure. *Am J Cardiol* 1985;56:93–98.
37. Liang CS, Sherman LG, Doherty JU, Wellington K, Lee VW, Hood WB, Jr. Sustained improvement of cardiac function in patients with congestive heart failure after short-term infusion of dobutamine. *Circulation* 1984;69:113–119.
38. Mebazaa A, Barraud D, Welschbillig S. Randomized clinical trials with levosimendan. *Am J Cardiol* 2005;96(suppl 6A):74G–79G.
39. Follath F, Cleland JG, Just H, Papp JG, Scholz H, Peuhkurinen K, Harjola VP, Mitrovic V, Abdalla M, Sandell EP, Lehtonen L. 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.
40. Zairis MN, Apostolatos C, Anastassiadis F, Kouris N, Grassos H, Sifaki M, Babalis D, Foussas S. Comparison of the effect of levosimendan, or dobutamine or placebo in chronic low output decompensated heart failure. CAlcium Sensitizer or Inotrope or NOne in low output heart failure (CASINO) study. In: Program and abstracts of the European Society of Cardiology, Heart Failure Update 2004; June 12–15, 2004; Wroclaw, Poland. Abstract 273.
41. Coletta AP, Cleland JG, Freemantle N, Clark AL. Clinical trials update from the European Society of Cardiology Heart Failure meeting: SHAPE, BRING-UP 2 VAS, COLA II, FOSIDIAL, BETACAR, CASINO, and meta-analysis of cardiac resynchronisation therapy. *Eur J Heart Fail* 2004;6:673–676.
42. Mebazaa A, Cohen-Solal A, Kleber FX, Nieminen M, Packer M, Pocock SJ, Poder P, Sarapohja T, Kivikko M. Study design of a mortality trial with intravenous levosimendan (the SURVIVE study) in patients with acutely decompensated heart failure [abstract]. *Crit Care* 2004;8(suppl 1):P87.
43. Packer M, Carver JR, Rodeheffer RJ, Ivanhoe RJ, DiBianco R, Zeldis SM, Hendrix GH, Bommer WJ, Elkayam U, Kukin ML, et al, for the PROMISE Study Research Group. Effect of oral milrinone on mortality in severe chronic heart failure. *N Engl J Med* 1991; 325:1468–1475.
44. Cuffe MS, Califf RM, Adams KF Jr, Benza R, Bourge R, Colucci WS, Massie BM, O'Connor CM, Pina I, Quigg R, Silver MA, Gheorghiade M. Short-term intravenous milrinone for acute exacerbation of chronic heart failure: a randomized controlled trial. *JAMA* 2002;287:1541–1547.
45. Anderson JL. Hemodynamic and clinical benefits with intravenous milrinone in severe chronic heart failure: results of a multicenter study in the United States. *Am Heart J* 1991;121:1956–1964.
46. Anderson JL, Baim DS, Fein SA, Goldstein RA, LeJemtel TH, Likoff MJ. Efficacy and safety of sustained (48 hour) intravenous infusions of milrinone in patients with severe congestive heart failure: a multicenter study. *J Am Coll Cardiol* 1987;9:711–722.
47. Seino Y, Momomura S, Takano T, Hayakawa H, Katoh K, for the Japan Intravenous Milrinone Investigators. Multicenter, double-blind study of intravenous milrinone for patients with acute heart failure in Japan. *Crit Care Med* 1996;24:1490–1497.
48. McDermott MM, Feinglass J, Lee PI, Mehta S, Schmitt B, Lefevre F, Gheorghiade M. Systolic function, readmission rates, and survival among consecutively hospitalized patients with congestive heart failure. *Am Heart J* 1997;134:728–736.
49. Biddle TL, Benotti JR, Creager MA, Faxon DP, Firth BG, Fitzpatrick PG, Konstam MA, Krebs C, Walton L, Kershner RP, et al. Comparison of intravenous milrinone and dobutamine for congestive heart failure secondary to either ischemic or dilated cardiomyopathy. *Am J Cardiol* 1987;59:1345–1350.
50. Eichhorn EJ, Konstam MA, Weiland DS, Roberts DJ, Martin TT, Stransky NB, Salem DN. Differential effects of milrinone and dobutamine on right ventricular preload, afterload, and systolic performance in congestive heart failure secondary to ischemic or idiopathic dilated cardiomyopathy. *Am J Cardiol* 1987;60:1329–1333.
51. Karlsberg RP, DeWood MA, DeMaria AN, Berk MR, Lasher KP, for the Milrinone–Dobutamine Study Group. Comparative efficacy of short-term intravenous infusions of milrinone and dobutamine in acute congestive heart failure following acute myocardial infarction. *Clin Cardiol* 1996;19:21–30.
52. Feneck RO, Sherry KM, Withington PS, Oduro-Dominah A. Comparison of the hemodynamic effects of milrinone with dobutamine in patients after cardiac surgery. *J Cardiothorac Vasc Anesth* 2001;15: 306–315.
53. Aranda JM Jr, Schofield RS, Pauly DF, Cleeton TS, Walker TC, Monroe VS Jr, Leach D, Lopez LM, Hill JA. Comparison of dobutamine versus milrinone therapy in hospitalized patients awaiting cardiac transplantation: a prospective, randomized trial. *Am Heart J* 2003;145:324–329.
54. Remme WJ. Inodilator therapy for heart failure: early, late, or not at all? *Circulation* 1993;87(suppl):IV97–IV107.
55. Oakley C. Genesis of arrhythmias in the failing heart and therapeutic implications. *Am J Cardiol* 1991;67(suppl):26C–28C.

56. Netticadan T, Temsah RM, Kawabata K, Dhalla NS. Sarcoplasmic reticulum Ca^{2+}/calmodulin-dependent protein kinase is altered in heart failure. *Circ Res* 2000;86:596–605.
57. Prestle J, Quinn FR, Smith GL. Ca^{2+}-handling proteins and heart failure: novel molecular targets? *Curr Med Chem* 2003;10:967–981.
58. Bristow MR. Beta-adrenergic receptor blockade in chronic heart failure. *Circulation* 2000;101:558–569.
59. Gheorghiade M, Colucci WS, Swedberg K. Beta-blockers in chronic heart failure. *Circulation* 2003;107:1570–1575.
60. Metra M, Nodari S, D'Aloia A, Muneretto C, Robertson AD, Bristow MR, Dei Cas L. Beta-blocker therapy influences the hemodynamic response to inotropic agents in patients with heart failure: a randomized comparison of dobutamine and enoximone before and after chronic treatment with metoprolol or carvedilol. *J Am Coll Cardiol* 2002;40:1248–1258.
61. Colucci WS, Wright RF, Braunwald E. New positive inotropic agents in the treatment of congestive heart failure: mechanisms of action and recent clinical developments. *N Engl J Med* 1986;314:290–299.
62. Lowes BD, Simon MA, Tsvetkova TO, Bristow MR. Inotropes in the beta-blocker era. *Clin Cardiol* 2000;23:III11–III16.
63. Lowes BD, Tsvetkova T, Eichhorn EJ, Gilbert EM, Bristow MR. Milrinone versus dobutamine in heart failure subjects treated chronically with carvedilol. *Int J Cardiol* 2001;81:141–149.
64. Shakar SF, Abraham WT, Gilbert EM, Robertson AD, Lowes BD, Zisman LS, Ferguson DA, Bristow MR. Combined oral positive inotropic and beta-blocker therapy for treatment of refractory class IV heart failure. *J Am Coll Cardiol* 1998;31:1336–1340.
65. Yoshikawa T, Baba A, Suzuki M, Yokozuka H, Okada Y, Nagami K, Takahashi T, Mitamura H, Ogawa S, for the Keio Interhospital Cardiology Study (KICS) Group. Effectiveness of carvedilol alone versus carvedilol + pimobendan for severe congestive heart failure. *Am J Cardiol* 2000;85:1495–1497, A1497.
66. Kumar A, Choudhary G, Antonio C, Just V, Jain A, Heaney L, Papp MA. Carvedilol titration in patients with congestive heart failure receiving inotropic therapy. *Am Heart J* 2001;142:512–515.
67. Stevenson LW. Clinical use of inotropic therapy for heart failure: looking backward or forward? Part II: chronic inotropic therapy. *Circulation* 2003;108:492–497.
68. Leier CV, Huss P, Lewis RP, Unverferth DV. Drug-induced conditioning in congestive heart failure. *Circulation* 1982;65:1382–1387.
69. Dies F, Krell MJ, Whitlow P. Intermittent dobutamine in ambulatory outpatients with chronic cardiac failure. *Circulation* 1986;74(suppl II):II-38.
70. Erlemeier HH, Kupper W, Bleifeld W. Intermittent infusion of dobutamine in the therapy of severe congestive heart failure: long-term effects and lack of tolerance. *Cardiovasc Drugs Ther* 1992;6:391–398.
71. Adamopoulos S, Piepoli M, Qiang F, Pissimissis E, Davies M, Bernardi L, Forfar C, Sleight P, Coats A. Effects of pulsed beta-stimulant therapy on beta-adrenoceptors and chronotropic responsiveness in chronic heart failure. *Lancet* 1995;345:344–349.
72. Oliva F, Latini R, Politi A, Staszewsky L, Maggioni AP, Nicolis E, Mauri F. Intermittent 6-month low-dose dobutamine infusion in severe heart failure: DICE multicenter trial. *Am Heart J* 1999;138:247–253.
73. Elis A, Bental T, Kimchi O, Ravid M, Lishner M. Intermittent dobutamine treatment in patients with chronic refractory congestive heart failure: a randomized, double-blind, placebo-controlled study. *Clin Pharmacol Ther* 1998;63:682–685.
74. Lubsen J, Just H, Hjalmarsson AC, La Framboise D, Remme WJ, Heinrich-Nols J, Dumont JM, Seed P. Effect of pimobendan on exercise capacity in patients with heart failure: main results from the Pimobendan in Congestive Heart Failure (PICO) trial. *Heart* 1996;76:223–231.
75. Hampton JR, van Veldhuisen DJ, Kleber FX, Cowley AJ, Ardia A, Block P, Cortina A, Cserhalmi L, Follath F, Jensen G, et al, for the Second Prospective Randomised Study of Ibopamine on Mortality and Efficacy (PRIME II) Investigators. Randomised study of effect of ibopamine on survival in patients with advanced severe heart failure. *Lancet* 1997;349:971–977.
76. Cohn JN, Goldstein SO, Greenberg BH, Lorell BH, Bourge RC, Jaski BE, Gottlieb SO, McGrew F III, DeMets DL, White BG, for the Vesnarinone Trial Investigators. A dose-dependent increase in mortality with vesnarinone among patients with severe heart failure. *N Engl J Med* 1998;339:1810–1816.
77. Califf RM, Adams KF Jr, McKenna WJ, Gheorghiade M, Uretsky BF, McNulty SE, Darius H, Schulman K, Zannad F, Handberg-Thurmond E, et al. A randomized controlled trial of epoprostenol therapy for severe congestive heart failure: the Flolan International Randomized Survival Trial (FIRST). *Am Heart J* 1997;134:44–54.
78. Hunt SA, Baker DW, Chin MH, Cinquegrani MP, Feldman AM, Francis GS, Ganiats TG, Goldstein S, Gregoratos G, Jessup ML, 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): developed in collaboration with the International Society for Heart and Lung Transplantation; endorsed by the Heart Failure Society of America. *Circulation* 2001;104:2996–3007.
79. Nieminen MS, Bohm M, Cowie MR, Drexler H, Filippatos GS, Jondeau G, Hasin Y, Lopez-Sendon J, Mebazaa A, Metra M, et al. Executive summary of the Guidelines on the Diagnosis and Treatment of Acute Heart Failure: the Task Force on Acute Heart Failure of the European Society of Cardiology. *Eur Heart J* 2005;26:384–416.