R E V I E W

Inotropes do not increase mortality in advanced heart failure

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Abstract: Inotrope use is one of the most controversial topics in the management of heart failure. While the heart failure community utilizes them and recognizes the state of inotrope dependency, retrospective analyses and registry data have overwhelmingly suggested high mortality, which is logically to be expected given the advanced disease states of those requiring their use. Currently, there is a relative paucity of randomized control trials due to the ethical dilemma of creating control groups by withholding inotropes from patients who require them. Nonetheless, results of such trials have been mixed. Many were also performed with agents no longer in use, on patients without an indication for inotropes, or at a time before automatic cardio-defibrillators were recommended for primary prevention. Thus, their results may not be generalizable to current clinical practice. In this review, we discuss current indications for inotrope use, specifically dobutamine and milrinone, depicting their mechanisms of action, delineating their patterns of use in clinical practice, defining the state of inotrope dependency, and ultimately examining the literature to ascertain whether evidence is sufficient to support the current view that these agents increase mortality in patients with heart failure. Our conclusion is that the evidence is insufficient to link inotropes and increased mortality in low output heart failure.

Keywords: inotropes, dobutamine, milrinone, heart failure

Introduction

It is widely recognized that decreased cardiac output is the trigger of a pathologic chain of events that results in the clinical syndrome of systolic heart failure (HF). Treatments that increase cardiac output, such as cardiac transplantation or left ventricular assist devices, are curative. A similar effect should be expected of inotropes because they, too, increase cardiac output.

At present, however, the use of inotropic agents in the management of HF is largely controversial. On one hand, almost everyone who manages patients with advanced HF utilizes them. The Acute Heart Failure Global Survey of Standard Treatment (ALARM-HF) global survey of 666 hospitals in nine countries showed that inotropes were used in 39% of all admissions for acute HF.[1] In the Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure (REMATCH) trial, 72% of patients in the medical arm and 65% of patients in the ventricular assist device arm were on inotropes.[2] Indeed, the HF community uniformly recognizes the state of "inotrope dependency". On the other hand, current guidelines caution that these drugs may be potentially detrimental: "Despite improving hemodynamic compromise, positive inotropic agents have not demonstrated improved outcomes in patients with HF in either the hospital or outpatient setting".[3]

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The purpose of this paper is to present a thorough review of the evidence on inotrope use in HF, and to ascertain whether the strength of the evidence is sufficient to support the current view that long-term use of these agents may lead to increased rates of mortality among HF patients. We grouped the evidence, separating the sources demonstrating inotrope benefit from those indicating their detriment. Moreover, due to their availability in the US, this review will focus mainly on dobutamine and milrinone.

Current guidelines on inotropes

Guidelines of the American College of Cardiology Foundation/American Heart Association (ACCF/AHA) (2013),[3] Heart Failure Society of America (2010),[4] European Society of Cardiology (2012),[5] and International Society for Heart and Lung Transplantation[6–8] have recommendations on inotropes. While the guidelines on mechanical circulatory support (2013)[7] and the guidelines for the care of heart transplant recipients (2010)[8] address very specific indications of post-left ventricular assist device implantation right ventricular failure[7] and acute cellular or antibody-mediated rejection and hemodynamic support in the early post-operative period,[8] respectively, the rest make recommendations on the use of positive inotropic agents in HF. The recommendations of various societies are summarized in Table 1. In general, inotropes are indicated in the presence of acute or chronic hemodynamic compromise with end organ dysfunction due to low output, and are considered to be detrimental and contraindicated if this syndrome is not present.

Specifically, the ACCF/AHA guidelines state that use of parenteral inotropic agents in hospitalized patients without documented severe systolic dysfunction, low blood pressure, or impaired perfusion, and evidence of significantly depressed cardiac output, with or without congestion, is potentially harmful.[3]

These recommendations are based on profound understanding of the pathophysiology of HF. As the disease progresses over time, the heart maintains normal cardiac output, but at the cost of rising left ventricular end diastolic pressure (Figure 1). The mainstay intervention at these stages is diuretic therapy, which decreases intracardiac filling pressures (congestion), along with medications favoring left ventricular reverse remodeling such as angiotensin-converting enzyme inhibitors. Eventually, compensatory mechanisms fail, and cardiac output decreases. Only at this advanced stage can inotropes be beneficial. Because low output is not present at the earlier stages, administration of inotropes cannot be favorable but can certainly cause harm because of side effects.

Inotropes: mechanism of action and hemodynamic effects

Milrinone and dobutamine are currently the only two inotropes approved for use in the US and both exert their actions by increasing the intracellular level of cyclic adenosine monophosphate (cAMP).[9] Dobutamine achieves this effect indirectly through adrenergic agonism while milrinone, a phosphodiesterase inhibitor, directly blocks cAMP breakdown.[10]

Dobutamine is a sympathomimetic amine, which acts on beta-1, beta-2, and alpha-1 adrenergic receptors. The stimulation of these receptors produces a relative strong additive inotropic effect and a relatively weak chronotropic effect.[11] Alpha-1 agonist activity in the vasculature causes vasoconstriction, which balances the beta-2 vasodilatory effect, permitting relatively unchanged blood pressure with administration.[12] Dobutamine increases myocardial contractility, with accompanying reflex reduction in sympathetic tone. In HF patients, its use has actually been shown to cause a dose-dependent decrease in plasma norepinephrine.[13] Overall, this leads to an increase in cardiac output by selective augmentation of stroke volume with a decrease in systemic vascular resistance. Because of its adrenergic properties, the use of dobutamine is problematic in patients who take beta blockers.

Milrinone is a bipyridine derivative of amrinone with 10–75 times more positive inotropic effect; additionally, unlike its parent drug, it has direct vasodilatory properties.[14] Milrinone works by inhibiting phosphodiesterase 3 (PDE3), which in turn prevents the degradation of cAMP and ultimately leads to an increase in protein kinase A (PKA). PKA increases contractility of the left ventricle through cAMP dependent-PKA, which phosphorylates calcium channels, leading to a trans-sarcolemmal influx of calcium, increasing the rate that the sarcoplasmic reticulum uptakes calcium. PKA also causes the phosphorylation of myofilament proteins which facilitates the action of actin and myosin, and therefore increases cardiac contractility and cardiac output.[15]

Milrinone thus functions as an inodilator, both increasing cardiac contractility and reducing afterload with a consequent reduction in left ventricular filling pressures. When compared with adrenergic inotropic drugs such as dobutamine, milrinone has been shown to exert

Table 1 Guideline recommended indications for inotropic agents in heart failure

Guidelines		Strength	Level of evidence
American College of Cardiology Foundation/American Heart Association 2013[3]	Until definitive therapy (eg, coronary revascularization, mechanical circulatory support, heart transplantation) or resolution of the acute precipitating problem, patients with cardiogenic shock should receive temporary intravenous inotropic support to maintain systemic perfusion and preserve end-organ performance.	I	C
	Continuous intravenous inotropic support is reasonable as "bridge therapy" in patients with stage D refractory to guideline determined medical therapy and device therapy who are eligible for and awaiting mechanical circulatory support or cardiac transplantation.	IIA	B
	Short-term, continuous intravenous inotropic support may be reasonable in those hospitalized patients presenting with documented severe systolic dysfunction who present with low blood pressure and significantly depressed cardiac output to maintain systemic perfusion and preserve end-organ performance.	IIB	B
	Long-term, continuous intravenous inotropic support may be considered as palliative therapy for symptom control in select patients with stage D despite optimal guideline determined medical therapy and device therapy who are not eligible for either mechanical circulatory support or cardiac transplantation.	IIB	B
	Long-term use of either continuous or intermittent, intravenous parenteral positive inotropic agents, in the absence of specific indications or for reasons other than palliative care, is potentially harmful in the patient with HF.	III	B
	Use of parenteral inotropic agents in hospitalized patients without documented severe systolic dysfunction, low blood pressure, or impaired perfusion, and evidence of significantly depressed cardiac output, with or without congestion, is potentially harmful.	III	B
European Society of Cardiology 2012[5]	An intravenous infusion of an inotrope (eg, dobutamine) should be considered in patients with hypotension (systolic blood pressure <85 mmHg) and/or hypoperfusion to increase cardiac output, increase blood pressure, and improve peripheral perfusion.	IIA	C
	Inotropic agents are not recommended unless the patient is hypotensive (systolic blood pressure <85 mmHg), hypoperfused, or shocked because of safety concerns (atrial and ventricular arrhythmias, myocardial ischemia, and death).	III	C
Heart Failure Society of America 2010[4]	Intravenous inotropes (milrinone or dobutamine) may be considered to relieve symptoms and improve end-organ function in patients with advanced HF characterized by LV dilation, reduced LVEF, and diminished peripheral perfusion or end-organ dysfunction (low output syndrome), particularly if these patients have marginal systolic blood pressure (<90 mmHg), have symptomatic hypotension despite adequate filling pressure, or are unresponsive to, or intolerant of, intravenous vasodilators.	May be considered	C
	These agents may be considered in similar patients with evidence of fluid overload if they respond poorly to intravenous diuretics or manifest diminished or worsening renal function.	May be considered	C
	Intravenous inotropes (milrinone or dobutamine) are not recommended unless left heart filling pressures are known to be elevated or cardiac index is severely impaired based on direct measurement or clear clinical signs.	Not recommended	C
International Society for Heart and Lung Transplantation Guidelines for Management of Heart Transplant Candidates 2006[6]	In patients with decompensated heart failure and hypoperfusion in spite of adequate filling pressures, inotropic or pressor therapy should be used.	I	C
	Long-term use of inotropic therapy should only be used as a pharmacologic bridge to transplantation or for palliation.	I	C

Abbreviations: HF, heart failure; LV, left ventricle; LVEF, left ventricular ejection fraction.
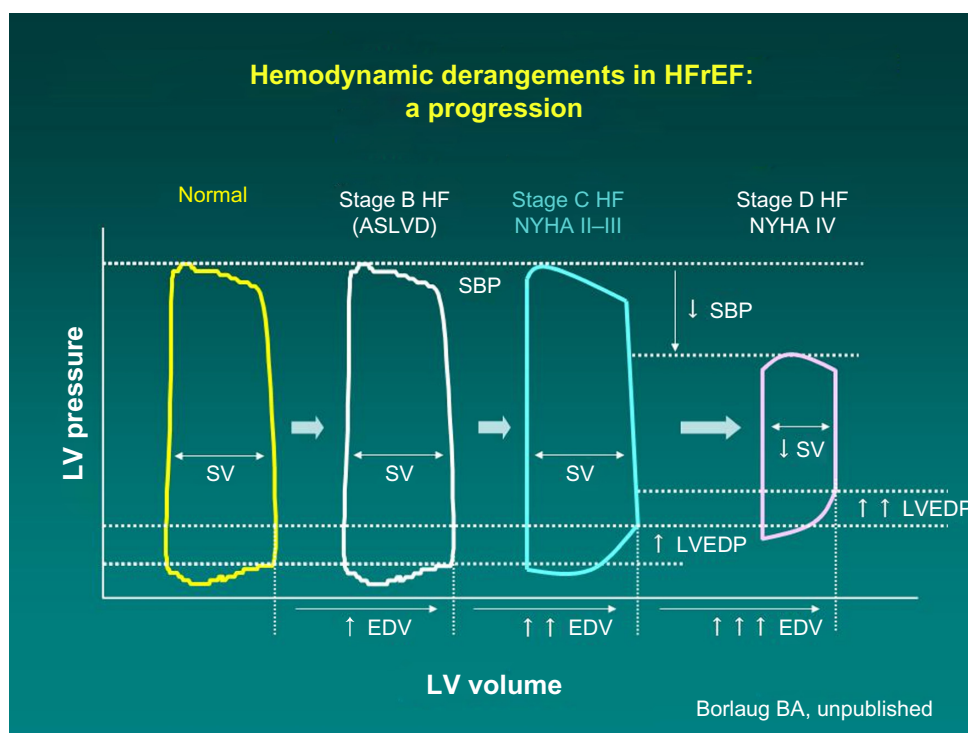
Figure 1 Progression of hemodynamic derangements in heart failure (Barry Borlaug, with permission).
Abbreviations: ASLVD, asymptomatic systolic left ventricular dysfunction; EDV, end-diastolic volume; HF, heart failure; HFrEF, heart failure with reduced ejection fraction; LV, left ventricle; LVEDP, left ventricular end diastolic pressure; NYHA, New York Heart Association; SBP, systolic blood pressure; SV, stroke volume.

these hemodynamic effects with less myocardial oxygen consumption.[14,16] Besides, milrinone can be used in patients on beta blockers, because its effects are not dependent on beta adrenoreceptors.

Milrinone not only acts as a systemic but also a pulmonary vasodilator. It was found to lower pulmonary vascular resistance in HF patients awaiting transplant by decreasing mean pulmonary arterial pressures, in addition to significantly lowering pulmonary capillary wedge pressure.[17] Effects were more pronounced in severe pulmonary hypertension.[18] Its actions on the pulmonary vasculature are comparable to sildenafil, as both medications increase the levels of cyclic nucleotides to exert an effect.[19] Sildenafil causes mainly PDE5 inhibition, increasing cyclic guanosine monophosphate levels, while milrinone inhibits PDE3, causing an increase in cAMP as previously mentioned. Sildenafil lacks direct inotropic effects, due to relatively low concentrations of PDE5 in the myocardium. In a study of New York Heart Association (NYHA) class IV patients, Botha et al[19] concluded that while both milrinone and sildenafil caused similar reductions in systemic and pulmonary vascular resistance, milrinone caused two times greater reduction in mean pulmonary artery pressure and significantly greater reduction of the pulmonary

capillary wedge pressure, suggesting that milrinone may be the preferred agent in patients with pulmonary hypertension and HF. Milrinone also produced more cardio-specific effects due to the widespread distribution of PDE3 throughout the myocardium, resulting in lower filling pressures and higher heart rates in comparison.[19]

The magnitude of the hemodynamic effects of inotropes on cardiac index and cardiac output is remarkable. Insurance carriers look for a 20% increase in cardiac index or a similar decrease in pulmonary wedge pressure, in order to issue an approval for continuous home inotropes.[20] However, greater response is common, with a two-fold increase in cardiac index commonly observed.[21]

Milrinone in currently approved doses typically increases cardiac index by 24%–42%, decreases pulmonary capillary wedge pressure by 24%–33%, and reduces systemic vascular resistance by 15%–31%, with dose-dependent effect. The drug is effective in most patients, and those with the worst hemodynamic profiles at baseline derive the most benefits.[20]

Most of the hemodynamic effects of dobutamine and milrinone are similar.[22] Both dobutamine and milrinone:
- increase cardiac output;
- cause peripheral vasodilation;

Table 2 Properties of dobutamine and milrinone

Inotrope	Dose	Onset and duration of action	Side effects	Comments
Dobutamine	2.5–20 µg/kg/minute IV	Onset of action is 1–10 minutes, peak effect 10–20 minutes. The half-life is 2 minutes.	Ventricular ectopy, tachycardia, hypotension, angina, palpitations, fever, headache, nausea.	
Milrinone	0.25–0.75 µg/kg/minute IV	Onset of action is 5–15 minutes. The half-life is 2.5 hours.	Ventricular and supraventricular arrhythmias, angina, hypotension, headache.	A 50 mcg/kg bolus is sometimes recommended,[17] although it may increase the risk of side effects and does not add to beneficial hemodynamic effects.[84]

Abbreviation: IV, intravenous.

- and decrease pulmonary capillary wedge pressure.

There are some differences between dobutamine and milrinone.[16,23–25]

Dobutamine, in comparison with milrinone, causes:

- greater increase in heart rate;
- greater increase in myocardial oxygen consumption;
- greater proarrhythmic effect, including ventricular tachycardia;[26,27]
- and effects are attenuated in patients who receive beta blockers.

Milrinone, in comparison with dobutamine, causes:

- more hypotension;
- greater reduction in left and right heart filling pressures;
- greater reduction in mean arterial pressure;
- greater reduction in pulmonary arterial pressure;
- longer duration of action after discontinuation of the intravenous infusion, especially in the presence of renal dysfunction;
- and greater hemodynamic effects in general when the patient is on beta blockers.

The biggest difference between the two, especially in our expanding health care system, may be cost. Dobutamine is cheaper.[28,29] For a course of in-hospital inotrope therapy, total acquisition cost of milrinone was significantly higher than that of dobutamine (US \$16,270± \$1,334 vs US \$380± \$533, $P<0.00001$).[28] In terms of arrhythmogenicity, dobutamine causes atrial and ventricular arrhythmias more commonly than milrinone, although both agents have proarrhythmic potential and hence both require continuous rhythm monitoring, at least while in the hospital. Milrinone causes nonsustained ventricular tachycardia in 3.7% of patients and sustained ventricular tachycardia in 0.5%.[20]

Overall, hemodynamic properties of inotropes seem to be optimal for low output, or "cold" HF patients, especially if they are also "wet",[30] ie, have volume overload and increased intracardiac pressures. It is well-known that this type of

HF patient has the worst prognosis.[31] Besides, increase in cardiac output and decrease in congestion frequently results in improved urine output, a phenomenon widely known to HF doctors.[24,32]

It is quite counterintuitive that drugs with such remarkable hemodynamic effects can be detrimental in advanced HF.

Inotrope dependency

The term "inotrope dependent" is used liberally in the guidelines, without a formal definition. Patients are characterized as inotrope dependent if they cannot be weaned off inotropes at an experienced HF center.[4] Inotrope dependence means that withdrawal of inotropes leads to symptomatic hypotension, recurrent congestive symptoms, or worsening renal function.[33] It is recognized that symptoms and not purely the values of re-measured hemodynamic parameters have to be considered when deciding on inotrope dependence.[33]

Meanwhile, if we admit that there is a subset of patients who depend on inotropes, we have to logically conclude that inotropes prolong life. And indeed, the HFSA guidelines state that "these agents may help relieve symptoms due to poor perfusion and preserve end-organ function in patients with severe systolic dysfunction and dilated cardiomyopathy".[4] End organ function in HF is usually related to hepatic and renal function. If inotropes help preserve liver and kidney function, they ought to prolong life, or to "avoid imminent death".[34] The best definition of inotrope dependency we found in the paper by Hershberger et al.[34] "Inotropic dependence was defined as the failure to wean from inotropes because of imminent (minutes to hours) worsening of the patient's clinical status … such that death appeared imminent, and the patient was deemed highly unlikely to survive inotrope withdrawal to permit hospital discharge". The authors state further that the attempted withdrawal of inotropic support in this cohort of patients can be acutely life-threatening.[34]

If we recognize that patients on inotropes cannot be weaned off of them, we have to admit that inotropes reduce mortality in this terminal end-stage HF population. Otherwise, the term "inotrope dependent" becomes oxymoranical.

Inotrope dependency is the condition which makes it unfeasible and ethically unacceptable to conduct any randomized controlled trials (RCTs) on inotropes versus placebo or inotrope versus no inotrope. The only comparison possible is one inotrope versus another, or inotropes versus a different means of inotropic support, like in the REMATCH trial.[2] Indeed, Lynne Stevenson wrote in 2003[24] that randomized trials performed with and without inotropic infusions during HF hospitalizations have selected patients in whom intravenous therapy was not considered essential for management. Hershberger et al also wrote that a randomized clinical trial designed to remove dobutamine from patients deemed inotrope dependent would cause considerable discomfort from an ethical perspective.[34] Ten years later, this statement still holds true. But if you enroll only patients in whom the intervention is not essential, you cannot establish the value of the very intervention that is tested.

Patterns of inotrope use

There are three distinct patterns of intravenous inotrope use: confined to hospital admission, intermittent home infusions (usually several times per week at the infusion center), and the infusions started in the hospital and continued at home continuously, weeks to months and even years in duration. Besides, some inotropes were used orally in the outpatient setting. Below, we briefly summarize non-randomized studies based on the setting of infusion. Randomized studies, where patients are randomized into inotrope versus placebo or inotrope versus no inotrope, regardless of the setting where infusion was performed, are summarized in Table 3. All studies, in the text and in the table, include patients with symptomatic HF and decreased left ventricular ejection fraction.

Hospital infusions

- Some studies report the experience with in-hospital inotrope infusions when the patients were admitted not because of hemodynamic compromise and low output syndrome, but electively. A 3-day dobutamine infusion in 29 patients resulted in hemodynamic and metabolic improvement, including elevation of sodium and improvement in renal function.[35]
- Intravenous milrinone given to 14 patients resulted in improved hemodynamics and allowed higher doses of

diuretics and other HF medications. Oral angiotensin-converting enzyme inhibitor and diuretic doses were increased by 318% and 89%, respectively. NYHA functional class improved from 3.8±0.4 to 2.6±0.6 following therapy, and there was a reduction in hospital admissions in ten patients who responded to therapy during the subsequent year compared with the year before treatment (4±17 versus [vs] 17±15).[36]

- Intermittent infusions of either dobutamine (43 patients) or nitroprusside were given to a total of 113 patients for about 1 month. There was a higher rehospitalization rate (86% vs 57%, $P<0.02$) and higher mortality (58% vs 28%, $P<0.006$) in the dobutamine group. The decision of using dobutamine versus nitroprusside was made by individual physicians. Baseline systolic blood pressure was 90 mmHg in the dobutamine group and 95 mmHg in the nitroprusside group; there is no indication whether this difference was significant. Heart transplantation was done in 78% of those on dobutamine and only in 48% of those on nitroprusside.[37]
- In 261 patients, in-hospital infusion of nesiritide in two different doses was compared with dobutamine. Six-month mortality was lower in the nesiritide groups.[38]

This last study was designed to compare the outcomes in patients with an infusion of nesiritide in a lower and higher dose versus any other vasoactive drug, at the discretion of the investigator, and patients were randomized into these three arms. Some patients in the arm with vasoactive drug were on dobutamine. The comparison between nesiritide and dobutamine was therefore a comparison between non-randomized groups, with very limited numbers of baseline characteristics and no invasive hemodynamic information. Moreover, mean baseline systolic blood pressure was 120 mmHg, and blood pressure below 90 mmHg was an exclusion criterion. Consequently, the study omitted all patients with low output HF syndrome, fundamentally excluding the only patients with an indication for dobutamine use. This essential design flaw makes the study inconclusive. The study of Capomolla et al[37] was also inconclusive due to lack of randomization.

Comparison of dobutamine versus milrinone in hospitalized patients, awaiting heart transplantation, did not show a clear advantage of one or the other in terms of right heart hemodynamics, death, need for additional vasodilator/inotropic therapy, need for mechanical cardiac support before transplantation, or ventricular arrhythmias requiring increased antiarrhythmic therapy.[28]

Table 3 Randomized controlled trials of inotropes in heart failure

Source, design	N	Follow-up	Inotrope	Cardiac index at baseline	Mortality	Other outcomes in the inotrope group vs placebo
Poor outcomes						
Cohn et al, 1998[67] Vesnarinone Trial, randomized to vesnarinone in two different doses and placebo	3,833	286 days	Vesnarinone, oral	NR	Mortality: Vesnarinone lower dose: 21% Vesnarinone higher dose: 22.9% Placebo: 18.9%, $P<0.02$ (vs placebo), the difference is presumably due to sudden (arrhythmic) death	Improved quality of life
Cowley et al, 1994[66] The Enoximone Trial, a randomized, double-blind, placebo-controlled trial: enoximone vs placebo	151	One year	Enoximone, oral	NR	Number of deaths: Enoximone: 27 Placebo: 18, $P<0.05$ Sudden deaths: Enoximone: 11 Placebo: 5 Progressive HF death: Enoximone: 12 Placebo: 11 The trial was ended early because of an excess mortality in the patients treated with enoximone	Improved quality of life
Uretsky et al, 1990[65] Enoximone trial Double-blind, randomized, placebo-controlled enoximone vs placebo	102	4 months	Enoximone, oral	NR	Mortality: Enoximone: 5 patients Placebo: 0 patients, $P<0.05$ Two deaths were sudden, two were from progressive HF, and one was from acute myocardial infarction	No differences in symptoms or exercise duration at the end of 4 months
Hampton et al, 1997[68] Randomized, placebo-controlled ibopamine vs placebo	1,906	About 1 year	Ibopamine, oral	NR	Mortality: Ibopamine: 232 (25%) Placebo: 193 (20%) RR: 1.26 (95% CI: 1.04–1.53), $P=0.017$. The trial was stopped early, because of an excess of deaths in the ibopamine group	
Packer et al, 1991[69] Prospective Randomized Milrinone Survival Evaluation (PROMISE) trial Double-blind, randomized oral milrinone vs placebo	1,088	6 months	Oral milrinone	NR	Mortality from all causes: Milrinone: 30% Placebo: 24% (A 28% increase in all cause mortality, $P=0.038$, and a 34% increase in cardiovascular mortality, $P=0.016$). The trial stopped prematurely because of survival compromise on milrinone	Hospitalizations: Milrinone 44% Placebo 39%, $P=0.041$
The Xamoterol in Severe Heart Failure Study, 1990[85] Randomized, double-blind, placebo-controlled Randomization: xamoterol vs placebo	516	13 weeks	Xamoterol, oral (beta receptor agonist)	NR	Mortality: Xamoterol: 9.1% Placebo: 3.7%, $P=0.02$	
Metra et al, 2009[75] The Studies of Oral Enoximone Therapy in Advanced HF (ESSENTIAL), two identical, randomized, double-blind, placebo-controlled trials that differed only by geographic location	1,854	17 months	Enoximone, oral	NR	All-cause mortality: no difference	The 6-minute walk distance increased with enoximone, compared with placebo, in ESSENTIAL-I ($P=0.025$, not reaching, however, the pre-specified criterion for statistical significance of $P<0.020$)

(*Continued*)

Table 3 (*Continued*)

Source, design	N	Follow-up	Inotrope	Cardiac index at baseline	Mortality	Other outcomes in the inotrope group vs placebo
Elis et al, 1998[47] Randomized, double-blind, placebo-controlled dobutamine vs placebo over a 24-hour period every 2 to 3 weeks	19	6 months	Dobutamine IV, intermittent	NR	The median survival: Dobutamine: 4.6 months Placebo: 8 months No difference	No difference between the number of admissions for HF
Erlemeier et al, 1992[48] Dobutamine vs placebo	20	4 weeks	Dobutamine, IV intermittent	NR	No mortality difference	Dobutamine: exercise duration increase, body weight decreased Placebo: no change
Oliva et al, 1999[49] DICE (Dobutaminanell'Insufficienza Cardiaca) trial: dobutamine vs standard treatment	38	6 months	IV dobutamine, intermittent	1.89±0.1 L/ minute/m^2	Dobutamine: 5 deaths, 2 heart transplants Standard treatment: 3 deaths No difference	Hospitalizations for all causes: no difference Dobutamine: 11 (7 for HF) Standard treatment: 17 (11 for HF) No difference in NYHA class and in 6-minute walking test
Massie et al, 1985[78] Double-blind, placebo-controlled amrinone vs placebo	99	12 weeks	Amrinone, oral	NR	No mortality difference	Exercise tolerance: no difference
Narahara, 1991[79] The Western Enoximone Study Randomized, placebo-controlled enoximone vs placebo	164	12 weeks	Enoximone, oral	NR	No mortality difference	Enoximone: greater increases in exercise time than placebo treatment at weeks 4 and 8 but not after 12 weeks
Van Veldhuisen et al, 1993[80] The Dutch Ibopamine Multicenter Trial Double-blind placebo-controlled, randomized ibopamine vs digoxin vs placebo	161	6 months	Ibopamine, oral	NR	No mortality difference	
Good outcomes						
Dubourg et al, 1990[81] A double-blind, randomized trial Enoximone vs placebo	30	31 days	Enoximone, oral	2.17±0.7 L/ minute/m^2	Mortality: Enoximone: 1 Placebo: 3	Symptoms improvement on enoximone
Feldman et al, 2007[76] EMOTE trial (Enoximone in Intravenous Inotrope-Dependent Subjects Study) Enoximone vs placebo Enoximone was used to wean patients from IV inotropes	201	6 months	Oral enoximone	NR	Alive and free of IV inotropes at 30 days: Enoximone: 62 (61.4%) Placebo: 51 (51%) At 60 days Enoximone: 46.5% Placebo: 30%, *P*=0.016 Time to death or re-initiation of IV inotropes: At 6 months: HR: 0.76 (95% CI: 0.55–1.04) At 60 days: HR: 0.62 (95% CI: 0.43–0.89), *P*=0.009 At 90 days: HR: 0.69 (95% CI: 0.49–0.97), *P*=0.031, favoring enoximone	

(*Continued*)

Table 3 (*Continued*)

Source, design	N	Follow-up	Inotrope	Cardiac index at baseline	Mortality	Other outcomes in the inotrope group vs placebo
Feldman et al, 1993[82] Vesnarinone Study Randomized, double-blind, placebo-controlled vesnarinone vs placebo	477	6 months	Vesnarinone, oral	NR	Mortality plus worsening HF: Vesnarinone: 26 Placebo: 50, $P=0.003$ A 62% reduction (95% CI: 28%–80%) in the risk of dying from any cause among the patients receiving vesnarinone	Vesnarinone: quality of life improved to a greater extent than in the placebo group over 12 weeks ($P=0.008$)
Nanas et al, 2004[71] Randomized, double-blind, placebo-controlled clinical trial Dobutamine vs placebo	30	6 months	Dobutamine, IV intermittent, plus amiodarone	2.3 ± 0.7 L/ minute/m^2	Survival: Dobutamine plus amiodarone vs placebo plus amiodarone HR: 0.403 (95% CI: 0.164–0.992; $P=0.048$) 1-year survival estimate: Dobutamine plus amiodarone: 69% Placebo plus amiodarone: 28%, $P<0.05$ 2-year survival estimate: Dobutamine plus amiodarone: 44% Placebo plus amiodarone: 21%, $P<0.05$	
Likoff et al, 1984[83] Randomized, double-blind, placebo-controlled After being stabilized on amrinone, patients were randomized into continuation on amrinone or withdrawal of amrinone	9	Two 13-week stages	Amrinone, IV	1.9 ± 0.2 L/ minute/m^2		Placebo: 7 patients had a significant deterioration of symptoms or exercise tolerance, or both. After 4 weeks of readministration of amrinone, clinical status improved
Khalife et al, 1987[87] Double-blind, randomized, placebo-controlled Randomization: after the first phase when IV enoximone was given to all patients, they were randomized into oral enoximone or placebo	17	12 weeks	Enoximone, IV and oral, in a 2-part study	3.42 ± 0.72 L/minute/ m^2 (after enoximone IV)		Enoximone: LVEF improved from $30.1\%\pm6.8\%$ to $33.9\%\pm9.9\%$ Placebo: unchanged

Abbreviations: CI, confidence interval; HR, hazard ratio; IV, intravenous; NR, not reported; NYHA, New York Heart Association; RR, relative risk; LVEF, left ventricular ejector fraction; HF, heart failure; vs, versus.

Intermittent home infusions

Historically, intermittent infusions of inotropes were used as a treatment for end-stage HF with severe symptoms (NYHA III/IV). This practice is no longer supported and is a Class III recommendation as per ACC/AHA.[3]

No randomized trials are available, but there were several published series summarizing the outcomes.

- Intravenous amrinone, given as intermittent infusions initially at the hospital, and then at home, to 41 patients, over the period of 51 months, resulted in improvement in NYHA class in 66% of patients, and a 50% reduction in number of days spent in the hospital and number of hospital admissions in the 6 months following the beginning of therapy, compared to the 6 months before the therapy.[39]

- Intravenous dobutamine in four patients and milrinone in 32 patients, given as intermittent home infusions over the period of 294 days, resulted in a reduced number of hospital admissions, days spent in the hospital, and emergency room visits, compared with similar data from the year before entry in the program for each patient.[40]

- Intravenous milrinone given as intermittent infusions at home for a short period of time (four cycles of 3 days per week) resulted in improved hemodynamics which was sustained throughout the treatment period and for 4 months after its discontinuation (mean pulmonary arterial pressure, pulmonary capillary wedge pressure, systemic vascular resistance, and pulmonary vascular resistance were significantly decreased and cardiac index was significantly increased).[41]

- Intravenous intermittent dobutamine in 13 patients resulted in improved hemodynamics (a 25% increase in cardiac output) and, in seven patients, an improvement in functional class.[42]
- Intravenous intermittent dobutamine in eleven patients for a period of time ranging 1.8–24 (mean: 7.8) months, resulted in significant increases in cardiac index and in NYHA functional class (3.8±0.4 to 2.8±0.7, $P<0.01$).[43]
- Intermittent home infusions of milrinone in ten patients resulted in a four-fold decrease in hospitalizations during the study and symptomatic improvement.[44]
- Intermittent dobutamine infusions in eleven patients for 3–24 months resulted in symptomatic improvement and a mean of 1.2 reduction in NYHA functional class.[45]
- Intermittent dobutamine or milrinone infusions given to 73 patients resulted in subjective improvement.[46]

RCTs on intermittent home inotropes are included in Table 3. Elis et al[47] did not demonstrate either a morbidity or mortality advantage of intermittent intravenous dobutamine. Erlemeier et al[48] and Oliva et al[49] also did not find any mortality difference, although the sample size was small in all three studies, with 19, 20, and 38 patients, respectively.

Multiple episodes of ventricular tachycardia have been reported on intermittent dobutamine infusion.[26]

The data on mortality are very variable. One study reported that only three out of 17 patients survived the 26-week study period of intermittent dobutamine, with six patients experiencing sudden death, and three other patients dying of progressive HF,[42] while others reported no mortality at all.[41,44] Because patients' selection and infusion drugs, as well as the protocols, were not standardized, no conclusions on mortality are possible.

Continuous home infusions

Continuous inotrope infusion at home is more relevant to today's practice than intermittent treatments. Such infusion may be used to improve symptoms and to better quality of life in hospice patients, in addition to acting as a bridge to cardiac transplant in candidates awaiting a donor. A decrease in the need for HF hospitalizations after initiation of continuous home inotrope infusions was suggested by the analysis of the Medicare data.[50]

- Continuous home infusion of dobutamine or milrinone in 24 and seven patients, respectively, resulted in improvement in NYHA functional class from 4.0±0.0 to 2.7±0.9 ($P<0.0001$), decrease in the number of hospital admissions and length of stay from 20.9±12.7 to 5.5±5.4 days ($P=0.0004$), as well as a 16% reduction in

cost of care in comparison to the control period preceding the therapy.[51]
- Continuous home infusion of milrinone was used in 60 heart transplant candidates and resulted in hemodynamic and symptomatic improvement as well as cost reduction, with 88.3% of patients eventually undergoing heart transplant.[52]
- Continuous home infusion of milrinone was given to 29 heart transplant candidates and resulted in hemodynamic and symptomatic improvement.[53]
- Continuous home infusion of milrinone (eight patients) or dobutamine (twelve patients) given as a bridge to cardiac transplantation, resulted in improvement of functional status, serum creatinine, better hemodynamic parameters, and decreased numbers of hospitalizations during positive inotropic infusion therapy when compared with pre-treatment baseline.[54]
- Continuous home infusion of dobutamine (four patients), dopamine (13 patients), or the combination of both (six patients) resulted in a reduction of the number of days spent in the hospital.[55]
- Continuous (four patients) and intermittent (seven patients) home infusion of dobutamine in eleven patients resulted in symptomatic improvement.[56]

The number of reported deaths while on inotropes varied greatly among the studies, but since there were no control groups, and same patients' historical data were used as control, no conclusion about mortality can be derived.

Mortality data and randomized studies

There is a relative paucity of RCTs on the mortality effect of inotropes in HF. Thus, to date, much of the data on the subject has been drawn from retrospective analysis. Overall, the data suggests that mortality of patients treated with intravenous inotropes is high. In the Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness (ESCAPE) trial, 6-month mortality in patients with HF receiving inotropes during hospitalization reached 19%,[57] while the analysis of the Medicare data indicated that in patients treated with continuous home inotrope infusion, 6-month mortality exceeded 40%.[50] Analysis of the Acute Decompensated Heart Failure National Registry (ADHERE), showed inotropic treatment with dobutamine and milrinone was associated with a 200% increase of in-hospital mortality in comparison to vasodilators.[58] Moreover, the Flolan International Randomized Survival Trial (FIRST), determined that 6-month mortality among patients on dobutamine was 70%,

with dobutamine being the strongest independent predictor of mortality in the study.[59] Use of dobutamine or milrinone was consistent with very poor prognosis, even in comparison with other intravenous vasoactive drugs like vasodilators.[58] The addition of more than one inotrope is associated with further mortality increase.[60] High mortality rate alone, however, does not in itself prove that inotropes are detrimental. Indeed, mortality is expected to be high by virtue of the advanced disease states in those who require inotropes.

Meta-analyses and retrospective analyses examining the mortality effect of inotropes in HF have been largely mixed. A meta-analysis of multiple placebo-controlled trials by Thakray et al[61] failed to demonstrate increased mortality on inotropes, while another meta-analysis on phosphodiestherase-3 inhibitors showed poorer outcomes on these agents.[62] In another retrospective study, no mortality difference was found between dobutamine and milrinone at home in a single center experience,[63] although milrinone was deemed more effective as a bridge to transplant, allowing more patients to be bridged by inotropes alone, without the need for mechanical circulatory support. Also, renal and hepatic function improved on milrinone.[64]

Some suggestions of increased mortality on inotropes come from post-hoc analyses of trials not designed to test the outcomes on inotropes where no randomization on inotrope versus no inotrope or placebo was conducted. For example, the FIRST trial was a RCT, designed to test the effects of continuous intravenous epoprostenol plus conventional therapy versus conventional therapy alone in patients with advanced HF. Some patients who entered the trial were also on intravenous dobutamine.[59] The analysis of the outcomes depending on the use of dobutamine is therefore flawed because the patients who required inotropes were sicker (89% in NYHA IV) than those who did not (53%).

We grouped the randomized trials on inotropes into three categories: trials that demonstrate negative effects of inotropes on clinical outcomes, those that show neutral effects, and those that show beneficial effects of inotropes (Table 3).

Increased mortality was found on oral enoximone,[65,66] oral vesnarinone,[67] oral ibopamine,[68] oral milrinone,[68,69] and beta agonist xamoterol. Vesnarinone was associated with a dose-dependent increase in mortality, mostly due to arrhythmic death.[67] None of these inotropes is currently in use, and hence none of these outcomes are pertinent to the effects of intravenous dobutamine or milrinone. Besides, inotropes are proarrhythmic, and sudden cardiac death is considered the main mechanism responsible for excess mortality on inotropes.[67] Meanwhile, all the above studies were conducted

before the time when implantation of automated cardioverter-defibrillators had become the routine. Today, many of the patients on inotropes are implanted with defibrillators by the time they are inotrope dependent and are largely protected from arrhythmic death.

Indirectly, this consideration is confirmed by the study of Drakos et al. Due to concern that arrhythmia might contribute to inotrope-induced mortality; they compared end-stage HF patients on intermittent inotropes versus conventional medical management, adding oral amiodarone to both groups (inotropes were represented by either dobutamine or levosimendan). The study was not randomized. The 6-month (51% vs 18%) and 1-year (36% vs 9%) survival rates were significantly higher ($P=0.001$ for both), and functional status was better, in patients on inotropes and amiodarone.[70] Earlier, the same group of authors demonstrated similar results in a randomized, placebo-controlled study (Table 3).[71] Interestingly, the survival benefit with this strategy was superior for ischemic compared to non-ischemic etiology of HF.[72]

The majority of randomized studies are neutral, demonstrating neither benefit nor detriment of inotropes. In the Outcomes of a Prospective Trial of Intravenous Milrinone for Exacerbations (OPTIME-CHF) trial of 951 patients admitted for acute decompensated HF, there were no significant differences of in-hospital mortality, 60-day mortality, or combined 60-day death when comparing milrinone versus placebo.[73] Post-hoc subgroup analysis did reveal an increase in a composite of death or rehospitalization in patients with coronary artery disease treated with milrinone versus placebo (42% vs 36%), although no difference was found between the two groups in non-ischemic patients.[74] The Studies of Oral Enoximone Therapy in Advanced HF (ESSENTIAL) trial examined the effect of low-dose enoximone on patients with advanced HF on optimal medical therapy, and also showed no mortality difference.[75] In another study, oral enoximone used for weaning from intravenous inotropes, did not affect the mortality.[76] Other authors[47–49,77–80] also reported no difference in terms of mortality between inotropes and placebo.

Conversely, relatively few studies demonstrated beneficial effects of inotropes on mortality. Similarly to those trials showing increased mortality, most of these studied agents are not currently in use and are therefore not very pertinent: enoximone,[76,81] vesnarinone,[82] and amrinone.[83] The only study on dobutamine in this group used it in combination with amiodarone to negate potential proarrhythmic effects. Mortality reduction on dobutamine plus amiodarone versus placebo plus amiodarone had a hazard ratio of 0.403 (95% confidence interval [CI]: 0.16–40.992; $P=0.048$).

Nevertheless, the main observation from reading reports of inotrope use, randomized or not randomized, is that very few authors report the data on central hemodynamics. We saw in multiple sets of guidelines cited in the beginning of this review that the only indication for inotropes in HF is low output syndrome. Meanwhile, very few papers provide hemodynamic data. It means that in most studies, cardiac index/cardiac output were not even measured, and patients were enrolled based on symptomatic HF and decreased left ventricular ejection fraction, which is not an equivalent for low output syndrome. Moreover, in the OPTIME-CHF trial, patients were excluded if their doctors thought that inotropes were indicated.[73] It means that effects of inotropes were tested on patients who did not have indications for them, which is the best way to evaluate for side effects without therapeutic benefits.

In summary, most RCTs with inotropes share the following features:

- They were performed with pharmacologic agents that are currently not in use. The reason for them being no longer used is the fact that they increase mortality. This does not mean, however, that the effects of the drugs, which proved to be detrimental, can be extrapolated to currently used agents.
- They were performed in the years when automatic cardioverter-defibrillators were not recommended for primary prevention, and an excess of sudden death may not be pertinent to the current situation when patients with advanced cardiomyopathy are protected with implanted defibrillators.
- They were performed on patients who did not have any evidence of low output syndrome and therefore did not have indications for inotropes.

The controversy in understanding the role of inotropes is very visible in modern literature. In the recent review, Francis et al[88] acknowledge that use of inotropes "has been plagued by excessive mortality". On the other hand, they state that "there are clinical settings where inotropic support … may be lifesaving". These two statements are mutually exclusive. Either inotropes save lives, or they increase mortality. If patients cannot survive without inotropes, the inotropes are lifesaving. It is time to stop talking about "clear evidence that inotropic therapy increases mortality" and focus on definitions of the conditions where inotropes save lives.

Conclusion

In this review, we examined the quality of the current evidence, and found it insufficient to support the view that inotropes increase mortality in advanced heart failure patients with low output syndrome. Meta-analyses and randomized controlled trials results have been largely mixed, with inconclusive data. Moreover, randomized controlled trials have been scarce due to the ethical dilemma of withholding inotropes in patients who require them. Most randomized controlled trials shared certain common features: they were performed with inotropes that are not currently in use; they were performed before automated cardioverter-defibrillators were standard of care for primary prevention; and they were performed on patients without evidence of low output HF and without indications for inotropes. Thus, these studies may not be generalizable to our current clinical practice.

The use of inotropes should be limited to patients with systolic failure with evidence of hypoperfusion and inotrope dependence in whom weaning of inotropes may be life-threatening. Further studies should target these patient cohorts, using direct measurement of cardiac index/output as enrollment criteria, as they derive the most benefit from both acute and chronic inotrope therapy.

Disclosure

The authors report no conflicts of interest in this work.

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