Review

Inotropes are not linked to Increased Mortality in Heart Failure

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Abstract

How to use inotropes is one of the most controversial topics in the management of heart failure. While most clinicians use these drugs, and recognize the state of inotrope dependency, current guidelines recommend them onlu as a bridge or palliation. Thus, inotropes are considered either neutral or detrimental in terms of outcomes. Meanwhile, properly designed randomized clinical trials testing the outcomes on inotropes, have never been performed and it is unlikely that they will ever be attempted. These trials would require randomizing patients with advanced heart failure, low output syndrome, and impaired end-organ perfusion into groups that received or not received inotropes, or received inotropes or placebo. Many physicians would consider this design unethical so the trials would be challenging to implement. But if it is unethical to deny inotropes to this subset of patients, we have to admit that inotropes do not only improve quality of life, but prolong it, or decrease mortality. Otherwise, we consider it unethical to deny the medication which increases mortality.

In this review, we analyze the current evidence relating to inotropes and outcomes. We demonstrate that the original trials were performed with agents that are no longer in use, or on patients without an indication for inotropes, or at a time before automatic cardio-defibrillators were recommended for primary prevention. We conclude that current guidelines for inotropes are misleading in their interpretation of outcomes in patients with advanced heart failure. The guidelines should be revised to adequately reflect the evidence.

Keywords

Inotropes; heart failure

Introduction

The role of inotropes in management of heart failure (HF) is changing. Mechanical circulatory support (MCS) offers increased survival and improved quality of life, far beyond the potential of inotropes. Nevertheless, many cardiologists still use them. It is much easier for the patient to accept continuous intravenous infusion of another drug, than to agree to an open heart surgery with implantation of hardware which requires serious maintenance and chronic anticoagulation. With rare exceptions, the left ventricular assist device (LVAD) implant is irreversible. Unlike medicine, it changes the lifestyle for a long time, till heart transplant, or forever. To the contrary, being on an inotrope is much less demanding. Because so many patients still remain on inotropes for months or even years, we want to clarify the issue of increased mortality, linked to the inotrope use.

At present, the use of inotropic agents in the management of HF is controversial. On one hand, specialists who manage patients with advanced HF utilize them widely. 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].

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 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 on 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, inotropes can 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.
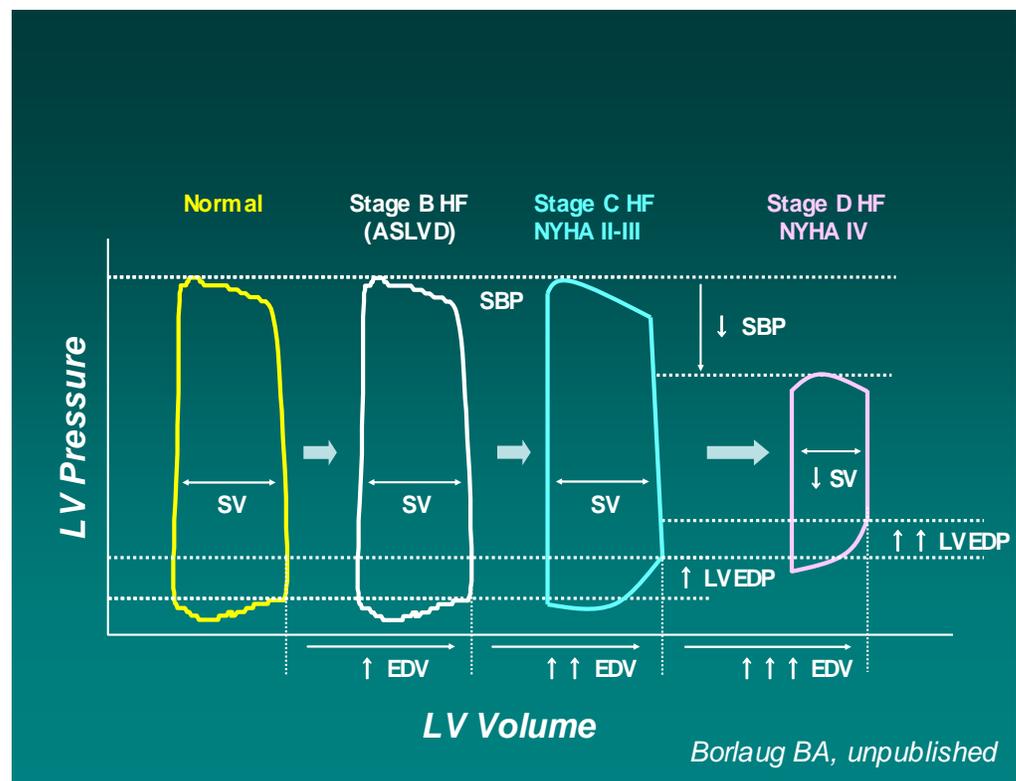
Figure 1. Hemodynamics in Heart Failure: a Progression (from Barry Borlaug, with permission)

Inotropes: Hemodynamic Effects

Milrinone and dobutamine are currently the only two inotropes approved for use in the United states and both exert their actions by increasing the intracellular level of cyclic adenosine monophosphate [9]. Dobutamine achieves this effect indirectly through adrenergic agonism while milrinone, a phosphodiesterase inhibitor, directly blocks cyclic monophosphate breakdown [10]. We reviewed the mechanism of action of both drugs in previously published paper [11].

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]	Cardiogenic shock, until definitive therapy (e.g., coronary revascularization, MCS, heart transplantation) or resolution of the acute precipitating problem	I	C
	"Bridge therapy" in stage D refractory to guideline determined medical therapy and device therapy, while awaiting MCS or cardiac transplantation	IIA	B
	Severe systolic dysfunction with low blood pressure and significantly depressed cardiac output in hospitalized patients	IIB	B
	Palliative therapy for symptom control in select patients with stage D despite optimal guideline determined therapy, not eligible for either MCS or cardiac transplantation	IIB	B
	Long-term IV inotropes, in the absence of specific indications or for reasons other than palliative care, are potentially harmful	III	B
	Inotropes in hospitalized patients without 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]	Inotropes should be considered in patients with hypotension (systolic blood pressure <85 mmHg) and/or hypoperfusion	IIA	C
	Inotropes are NOT recommended unless there is hypotension (systolic blood pressure <85 mmHg), hypoperfusion, or shock because of safety concerns (atrial and ventricular arrhythmias, myocardial ischaemia, and death).	III	C
Heart Failure Society of America 2010 [4]	IV inotropes may be considered to relieve symptoms and improve end-organ function in HF with LV dilation, reduced LVEF, and diminished peripheral perfusion or end-organ dysfunction (low output syndrome), particularly if systolic blood pressure is <90 mm Hg, in symptomatic hypotension despite adequate filling pressure, or unresponsiveness/intolerance of IV vasodilators.	may be consi-dered	C
	Inotropes may be considered in similar patients with evidence of fluid overload if they respond poorly to IV diuretics or have diminished/ worsening renal function.	may be consi-dered	C
	IV inotropes are not recommended unless left heart filling pressures are elevated or cardiac index is severely impaired	not re-commen-ded	C
International Society for Heart and Lung Transplantation 2006 [6]	In patients with decompensated HF 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

The magnitude of hemodynamic effects of the 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 [12]. However, greater response is common, with a twofold increase in cardiac index commonly observed [13].

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 profile at baseline derived the most benefits [12].

Most of hemodynamic effects of dobutamine and milrinone are similar [14]. Both dobutamine and milrinone

- Increase cardiac output
- Cause peripheral vasodilation
- Decrease pulmonary capillary wedge pressure

There are some differences between dobutamine and milrinone [15-18]

Dobutamine, in comparison with milrinone, causes
- Greater increase in heart rate
- Greater increase in myocardial oxygen consumption
- Greater proarrhythmic effect, including ventricular tachycardia [19,20]
- 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 drip, especially in the presence of renal dysfunction
- Greater hemodynamic effects in general when the patient is on beta blockers

In direct comparison of dobutamine and milrinone, Colucci et al.[17] found that milrinone caused a significantly greater reduction in left and right heart filling pressures and mean arterial pressure than did dobutamine, and for any given increase in dP/dt, milrinone caused a greater reduction in systemic vascular resistance than did dobutamine. Hemodynamic effects of dobutamine were blunted in patients with severe HF and elevated serum norepinephrine, most likely due to desensitization of myocardial beta 1 adrenoreceptors.

The biggest difference between the two especially in our expanding health care system may be cost. Dobutamine is cheaper [21,22]. For a course of in-hospital

inotrope therapy, total acquisition cost of milrinone was significantly higher than that of dobutamine (16,270 dollars +/- 1334 versus 380 dollars +/- 533 P <.00001)[21].   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% [12].

Overall, hemodynamic properties of inotropes seem to be optimal for low output, or "cold" HF patients, especially if they are also "wet"[23], i.e. have volume overload and increased intracardiac pressures. It is well known that this type of HF patients has the worst prognosis [24]. Besides, increase in cardiac output and decrease in congestion frequently results in improved urine output, a phenomenon widely known to HF doctors [16,25].

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

Table 2. Properties of dobutamine and milrinone

Inotrope	Dose	Onset and Duration of action	Side effects
Dobutamine	2.5 to 20 µg/kg/min IV	Onset of action is 1 to 10 min, peak effect 10 to 20 min. The half-life is 2 min	Ventricular ectopy, tachycardia, hypotension, angina, palpitations, fever, headache, nausea
Milrinone	0.25 to 0.75 µg/kg/min IV	Onset of action is 5 to 15 min. The half-life is 2.5 hours	Ventricular and supraventricular arrhythmias, angina, hypotension, headache

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 [26]. It is recognized that

symptoms and not purely the values of re-measured hemodynamic parameters have to be considered when deciding on inotrope dependence [26].

The inotrope dependency is particularly important when determination of the need for advanced HF therapies such as heart transplantation or ventricular assist device. Profile one, or "crush and burn", includes patients who rapidly decline despite inotropes, profile two patients decline more gradually but still "Sliding on inotropes." Profile three includes most stable patients who still need to be on inotropes, with the description "stable blood pressure, organ function, nutrition, and symptoms on continuous intravenous inotropic support (or a temporary circulatory support device or both), but demonstrating repeated failure to wean from support due to recurrent symptomatic hypotension or renal dysfunction: "dependent stability."[27]

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"[28]. The best definition of inotrope dependency we found in the paper by Hershberger et al.[28]: "Inotropic dependence was defined as the failure to wean from inotropes because of imminent (minutes to hours) worsening of the patient's clinical status (combined objective [eg, blood pressure, level of consciousness, confusion, change in creatinine, oxygenation] and subjective [eg, dyspnea, confusion, weakness]), 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 [28].

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 on inotropes versus placebo or inotrope versus no inotrope. The only comparison possible is one inotrope versus another, or inotropes versus a different mean of inotropic support, like in the REMATCH (Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure) trial [2]. Indeed, Lynne Stevenson wrote in 2003 [16] 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 [28]. 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. In the past, some inotropes were also used orally in the outpatient setting. Below, we briefly summarize non-randomized studies based on the setting of infusion. The studies where patients were randomized into inotrope versus placebo or inotrope versus no inotrope, regardless of the setting where infusion was performed, are summarized in Tables 3-5 in the end of the manuscript. 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 three-day dobutamine infusion in 29 patients resulted in hemodynamic and metabolic improvement, including elevation of sodium and improvement in renal function [29]

- 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 10 patients who responded to therapy during the subsequent year compared with the year before treatment (4 +/- 17 versus 17 +/- 15) [30].

- Intermittent infusions of either dobutamine (43 patients) or nitroprusside was given to a total of 113 patients for about a month. There was a higher re-hospitalization rate (86% versus 57%, p<0.02) and higher mortality (58% versus 28%) 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 [31].

- 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 [32].

This last study was designed to compare the outcomes in patients with 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 number 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. [31] is 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 [21].

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 per ACC/AHA[3]. We summarized the outcomes in our previous article [11]. Randomized controlled trials are included into Tables 3-5.

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 [33].

- Continuous home infusion of dobutamine or milrinone in 24 and 7 patients, respectively, resulted in improvement in NYHA functional class from 4.0+/-0.0 to 2.7+/-0.9 (p<0.0001), decrease of 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 control period preceding the therapy [34].

- 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 [35].

- Continuous home infusion of milrinone was given to 29 heart transplant candidates and resulted in hemodynamic and symptomatic improvement [36]

- Continuous home infusion of milrinone (8 patients) or dobutamine (12 patients) given as a bridge to cardiac transplantation, resulted in improvement of functional status, serum creatinine, better hemodynamic parameters, and decreased number of hospitalizations during positive inotropic infusion therapy when compared with pre-treatment baseline [37]

- Continuous home infusion of dobutamine (4 patients), dopamine (13 patients), or the combination of both (6 patients) resulted in reduction of the number of days spent in the hospital [38]

- Continuous (4 patients) and intermittent (7 patients) home infusion of dobutamine in 11 patients resulted in symptomatic improvement [39]

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 randomized control studies 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, six month mortality in patients with HF receiving inotropes during hospitalization reached 19% [40], while the analysis of the Medicare data indicated that in patients treated with continuous home inotrope infusion, a six month mortality exceeded 40% [33]. Analysis of the Acute Decompensated Heart Failure National Registry (ADHERE), showed that inotropic treatment with dobutamine and milrinone was associated with a 200% increase of in-hospital mortality in comparison to vasodilators [41]. However, baseline characteristics of the patients on inotropes, such as systolic blood pressure over 120 mmHg, demonstrate that they did not have low output syndrome. Only 8% of patients, started on inotropes, had systolic blood pressure less than 90 mmHg.

Moreover, the Flolan International Randomized Survival Trial (FIRST), determined that six month mortality among patients on dobutamine was 70%, with dobutamine being the strongest independent predictor of mortality in the study [42]. Use of dobutamine or milrinone was consistent with very poor prognosis, even in comparison with other intravenous vasoactive drugs like vasodilators [41]. The addition of more than one inotrope is associated with further mortality increase [43]. 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. [44] failed to demonstrate increased mortality on inotropes, while another meta-analysis on phosphodiestherase-3 inhibitors showed poorer outcomes on these agents [45]. In another retrospective study, no mortality difference was found between dobutamine and milrinone at home in a single center experience [46], 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 [47].

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 randomized, controlled trial, 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 [42]. 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 [48,49], oral vesnarinone [50], oral ibopamine [51], oral milrinone [51,52], and beta agonist xamoterol. Vesnarinone was associated with a dose-dependent increase in mortality mostly due to arrhythmic death [50]. None of these inotropes is currently in use, for the very reason of being associated with high mortality, 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 [50]. Meanwhile, all the above studies were conducted before the time when implantation of automatic cardioverters-defibrillators had become the routine. Today, many of

the patients on inotropes are implanted with defibrillators by the time they are inotrope dependent, and they 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% versus 18%) and 1-year (36% versus 9%) survival rates were significantly higher (p = 0.001 for both), and functional status was better, in patients on inotropes and amiodarone [53]. Earlier, the same group of authors demonstrated similar results in a randomized placebo controlled study (see Tables 3-5) [54].

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 [55]. Post hoc subgroup analysis did reveal an increase in a composite of death or re-hospitalization in patients with coronary artery disease treated with milrinone versus placebo (42% versus 36%), although no difference was found between the two groups in non-ischemic patients [56]. The ESSENTIAL trial examined the effect of low dose enoximone on patients with advanced HF on optimal medical therapy, and also showed no mortality difference [57]. In another study, oral enoximone used for weaning from intravenous inotropes, did not affect the mortality [58]. Other authors [59-65] 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 studied agents are not currently in use and therefore not very pertinent: enoximone [58,66], vesnarinone [67], amrinone [68]. 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 hazard ratio of 0.403 (95% confidence intervals 0.164 -0.992; p = 0.048).

But 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 [55]. Therefore, the 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 randomized controlled trials with inotropes share 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 cardioverters-defibrillators were not recommended for primary prevention, and an excess of sudden death may not be pertinent to current situation when the 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.

Conclusions

Randomized controlled trials with inotropes share certain common features: they were performed with inotropes that are not currently in use; they were performed before the time when automated cardioverter-defibrilators became standard of care for primary prevention of sudden cardiac death; and they were performed on patients without evidence of low output heart failure and without indications for inotropes. Thus, these studies may not be generalizable to our current clinical practice.

Currently, there is no evidence to suggest that in patients with low output syndrome, treated according to the current guidelines, and protected by implantable cardioverters-defibrillators, inotropes increase mortality. To the contrary, recognition of the state of inotrope dependency is incompatible with the statement that inotropes increase mortality.

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Table 3. Randomized control trials of inotropes in heart failure: poor outcomes of inotropes

Source, design	N	Follow-up	Inotrope	Cardiac index at baseline	Mortality	Other Outcomes in the Inotrope group versus Placebo
Cohn et al, 1998 [53] Vesnarinone Trial, randomized to vesnarinone in two different doses and placebo	3833	286 days	Vesnarinone, oral	Not reported	Mortality: Vesnarinone lower dose: 21% Vesnarinone higher dose: 22.9% Placebo: 18.9%, p<0.02 (versus placebo), the difference is presumably due to sudden (arrhythmic) death.	Improved quality of life
Cowley et al., 1994 [52] The Enoximone trial A randomized, double blind, placebo controlled trial: Enoximone vs placebo	151	One year	Enoximone, oral	Not reported	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 [51] Enoximone trial Double-blind, randomized, placebo-controlled Enoximone vs placebo	102	4 months	Enoximone, oral	Not reported	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[54] Randomized, placebo-controlled Ibopamine vs placebo	1906	About one year	Ibopamine, oral	Not reported	Mortality: Ibopamine: 232 (25%) Placebo:193 (20%) Relative risk 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 [55] Prospective Randomized Milrinone Survival Evaluation (PROMISE) trial Double blind, randomized Oral milrinone vs placebo	1 088	6 months	Oral milrinone	Not reported	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 [74]. Randomized, double-blind, placebo-controlled Randomization: xamoterol vs placebo	516	13 weeks	Xamoterol, oral (beta receptor agonist)	Not reported	Mortality: Xamoterol 9.1% Placebo: 3.7%, p=0.02	

Table 4. Randomized control trials of inotropes in heart failure: neutral outcomes of inotropes

Source, design	N	Follow-up	Inotrope	Cardiac index at baseline	Mortality	Other Outcomes in the Inotrope group versus Placebo
Cuffe et al., 2002 [58] Outcomes of a Prospective Trial of Intravenous Milrinone for Exacerbations (OPTIME-HF) trial: randomized, double-blind, placebo-controlled. Milrinone vs placebo	951	60 days	IV milrinone	Not reported	In-hospital mortality Milrinone: 3.8% Placebo: 2.3% 60-day mortality Milrinone: 10.3% Placebo: 8.9% No difference	Composite incidence of death or readmission: no difference Milrinone: 35% Placebo: 35.3% The median number of days hospitalized for cardiovascular causes within 60 days after randomization: No difference
Metra et al., 2009 [60] The Studies of Oral Enoximone Therapy in Advanced HF (ESSENTIAL), two identical, randomized, double-blind, placebo-controlled trials differed only by location	1854	17 months	Enoximone, oral	Not reported	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
Colucci et al., 1993 [62] Two randomized placebo controlled trials: milrinone vs placebo	140	3-6 months	Milrinone, oral	Not reported	No mortality difference. Trials terminated prematurely because of the release of the unfavorable results of the other trial	Improved exercise capacity on milrinone
Dibianco et al., 1984 [75] Randomized double-blind withdrawal study Patients who responded to amrinone in the first phase of the trial, were randomized to continue amrinone or to change to placebo	52	3 months		Not reported		No difference in cardiac performance or in rehospitalizations or functional status

Study	N	Duration	Drug	CO	Mortality	Other outcomes
Elis et al., 1998 [63] Randomized, double blind, placebo controlled Dobutamine vs placebo over a 24-hour period every 2 to 3 weeks.	19	6 months	Dobutamine IV, intermittent	Not reported	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 [64] Dobutamine vs placebo	20	4 weeks	Dobutamine, IV intermittent	Not reported	No mortality difference	Dobutamine: exercise duration increase, body weight decreased Placebo: no change
Oliva et al., 1999 [66] DICE (Dobutaminanell'Insufficienza Cardiaca) trial: Dobutamine vs standard treatment	38	6 months	IV dobutamine, intermittent	1.89 +/- 0.1 L/min/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 [65] Double-blind, placebo-controlled Amrinone vs placebo	99	12 weeks	Amrinone, oral	Not reported	No mortality difference	Exercise tolerance: no difference
Narahara, 1991 [67] The Western Enoximone Study Randomized, placebo controlled Enoximone vs placebo	164	12 weeks	Enoximone, oral	Not reported	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 [68] The Dutch Ibopamine Multicenter Trial Double-blind placebo-controlled, randomized Ibopamine vs digoxin vs placebo	161	6 months	Ibopamine, oral	Not reported	No mortality difference	

Table 5. Randomized control trials of inotropes in heart failure: good outcomes of inotropes

Source, design	N	Follow-up	Inotrope	Cardiac index at baseline	Mortality	Other Outcomes in the Inotrope group versus Placebo
Dubourg et al., 1990 [69] A double-blind, randomized trial Enoximone vs. placebo	30	31 days	Enoximone, oral	2.17 +/- 0.7 L/min/m2	Mortality Enoximone: 1 Placebo: 3	Symptoms improvement on enoximone
Feldman et al, 2007 [61]. EMOTE trial (Enoximone in Intravenous Inotrope-Dependent Subjects Study Enoximone or placebo. Enoximone was used to wean patients from IV inotropes	201	6 months	Oral enoximone	Not reported	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.	
Feldman et al., 1993 [70] Vesnarinone Study Randomized, double-blind, placebo-controlled Vesnarinone vs placebo	477	6 months	Vesnarinone, oral	Not reported	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	Vesnarinone: quality of life improved to a greater extent than in the placebo group over 12 weeks (P = 0.008)

					among the patients receiving vesnarinone	
Nanas et al., 2004 [57] Randomized, double-blind, placebo-controlled clinical trial. Dobutamine vs placebo	30	6 months	Dobutamine, IV Intermittent, plus amiodarone	2.3 ± 0.7 L/min/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 [71] 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+/- 0.2L/min/ m2		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 [76] 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/min/m2 (after Enoximo ne IV)		Enoximone: left ventricular ejection fraction improved from 30.1 +/- 6.8% to 33.9 +/- 9.9% Placebo: unchanged

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