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Review

Inotropes are linked to Increased Mortality in Heart Failure

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Introduction

With the advancement of technology and availability of mechanical circulatory support (MCS) devices for the treatment of acute decompensated systolic HF in the 21st century, the role of inotropes is becoming obsolete. Medical therapy for acute decompensated heart failure (HF) has not changed since 1960's, we still use supplemental oxygen, diuretics, vasodilators and inotropes to improve congestion, cardiac output, end organ perfusion and symptoms related to elevate filling pressures[1]. Despite demonstrated improvements in hemodynamics, the uses of inotropes have not demonstrated any improvements in mortality. Mechanical circulatory support (MCS) use is growing rapidly in the USA, in patients with stage D HF both as destination therapy and as a bridge to cardiac transplantation. In both, transplant-eligible and non-transplant-eligible patients, improvement in end-organ perfusion, functional capacity, quality of life and most importantly mortality have been demonstrated. In this perspective paper we are going to discuss the current lack of evidence for inotropic therapy and the evolving benefit of MCS in end-stage systolic HF patients.

Inotropes in End-Stage HF

Advanced HF with cardiogenic shock, are syndromes characterized in many patients by a reduction in myocardial contractile force. Medical therapy is still considered the mainstay for acute decompensated HF. The guidelines recommend diuretic therapy, which decreases intracardiac filling pressures and relieve congestion [2-4] This has to be accompanied with medications favoring left ventricular reverse remodeling such as angiotensin-converting enzyme inhibitors (ACEI) [5], angiotensin receptors blockers[6], beta blockers[7], aldosterone blockers[8], and nitrate/hydralazine [9]. As the disease progresses, compensatory mechanisms fail, and cardiac output decreases (stage D HF).

Inotropic therapies are utilized to stabilize acute decompensated HF patients with low cardiac output. The use of inotropes can be divided into three distinct patterns of use: hospital admission for patients presenting with acute decompensated HF and end organ involvement, intermittent home infusions (several times per week at the infusion center), and continuous home infusion as a bridge to cardiac transplantation or for palliation [10-12].

Inotropes have been used for more than fifty years and continues to be the used in patients presenting with low perfusion state due to cardiogenic shock. [1] The Acute HF 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[13]. Furthermore, in the mechanical circulatory support (MCS) studies, 72% of patients in the medical arm and 65% of patients in the ventricular assist device arm were on inotropes[14]. Inotropes successfully improve cardiac hemodynamics and patients' symptoms by increasing myocardial contractility mainly by increasing intracellular calcium concentrations. Inotropes are crucial in bridging selected patients to cardiac transplantation [15].

Despite improving hemodynamic compromise, inotropic agents are accompanied by increased morbidity and mortality due to increased tachycardia and myocardial oxygen consumption leading to arrhythmia, and myocardial ischemia [16]. This negative effect has been demonstrated in both the hospital and outpatient setting.[2] Beside digoxin, the current American College of Cardiology/American Heart Association, European Society of Cardiology and Heart Failure Society of America guidelines endorse that inotropic agents should be reserved for patients presenting with acute decompensated HF and low-output states and reduced end-organ perfusion, who typically are admitted to an intensive care unit [2-4]. Furthermore, the ACCF/AHA guidelines state specifically 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. This is based on multiple studies showing evidence for harm in patients with advanced HF [16].

Chronic HF patients who are not eligible for advanced therapies have been shown to have poor survival when treated with inotropes [17,18]. These finding

are based on retrospective studies and post hoc analysis of prospective studies [16]. However, despite the reduced survival, many patients prefer improved quality of life, even at the potential expense of a shorter survival. [18,19] The decision to use inotropic therapy and the selection of inotropic agent should reflect the realistic goals of therapy for the individual with HF. These goals should be discussed in great detail with the patient and family.

Evidence is sufficient to link inotropes to increased mortality

Based on the current studies that showed increased mortality in patients with advanced HF treated with inotropes, the use of inotropes should be limited to patients with advanced HF who are not candidates to MCS or heart transplantation. In the ADHERE (Acute Decompensated Heart Failure National Registry) study[17], Abraham et al. performed a retrospective analysis of observational patient data from the ADHERE registry where they reviewed over 65,000 cases admitted for acute decompensated HF from 263 US hospitals during October 2001 to July 2003 where they included patients whom had received nitroglycerin, nesiritide, milrinone or dobutamine (n= 15,230) therapy and assessed risk factor and propensity-adjusted odds ratios for in-hospital mortality. What they demonstrated was that use of inotropes doubled the in-hospital mortality compared to use of vasodilators; 12.3% and 13.9% for patients receiving milrinone and dobutamine, respectively, compared to 4.7% and 7.1% for patients receiving nitroglycerin and nesiritide, respectively. Moreover, they also found that length of stay was longer compared to those on vasodilator therapy, 10.9 and 10 days for patients receiving milrinone and dobutamine, respectively, compared to 7.1 and 7.9 days for patients receiving nitroglycerin and nesiritide, respectively.

Inotropic dependence is 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 impending, and the patient is deemed highly unlikely to survive inotrope withdrawal to permit hospital discharge [20]. In other words, withdrawal of inotropic support in this cohort of patients can be acutely life-threatening [2,20].

Furthermore, in the OPTIME-CHF (Outcomes of a Prospective Trial of Intravenous Milrinone for Exacerbations of Chronic HF) trial [21], Cuff et al. demonstrated in this prospective study that intravenous (IV) milrinone used in chronic HF patients, admitted for acute decompensated HF, increased morbidity associated with hypotension and new atrial arrhythmias but no significant difference in in-hospital mortality or 60-day mortality. As an extension of the OPTIME-CHF trial, Felker et al. [22]analyzed the interaction of the etiology of HF (ischemic vs. non-ischemic) with IV milrinone and found that patients with ischemic HF were not only hospitalized longer (13 days vs. 11.7 days) but also had increased 60-day mortality (11.6% vs. 7.5%) compared to patients with non-ischemic cardiomyopathy. In this study, 22% of patients were started on beta-blockers on admission. Thus, the "neutralizing" effect of beta-blockers for milrinone infusion was suspected. A post-hoc analysis was done looking into the

neutralizing effect of milrinone and showed decrease incidence of death or re-hospitalization in non-ischemic group suggesting neutralizing effect. However, the study had limitation since it was retrospective post-hoc analysis and authors did not clarify the definition of ischemic cardiomyopathy. Furthermore, double the patients in the non-ischemic cardiomyopathy group were lost to follow up [23].

In spite of increased mortality seen in the inpatient setting as seen in the ADHERE study, the consideration of intermittent inotropic therapy has also been studied in the outpatient setting. With a varying array of treatment regimens as well as administration from daily to weekly regimens, some with concomitant use of amiodarone as an antiarrhythmic, there has been some evidence of improved symptoms, decreased hospitalization and short term mortality, but the studies were small and observational in nature and failed to demonstrate "true" benefit of intermittent inotropic therapy [18,24,25].

Inotropes Use in Palliative and Hospice Care

Due to lack of evidence for mortality benefit association with inotropes in ADHF patients, inotropes were studies in hospice care and palliative care settings. [20] In one prospective study, the author suggested that intermittent infusion of intravenous inotropes is can modify end-stage HF symptoms, improve functional class and may also facilitate better utilization of hospice and palliative care resources among patients with end-stage heart. [26] The current HF guidelines suggest that long-term, continuous intravenous inotropic support may be considered as palliative therapy for symptom control in select patients with stage D HF despite optimal medical therapy and device therapy who are not eligible for either MCS or cardiac transplantation. [2]

Mechanical Circulatory Assist Devices – A Game Changer in End-Stage HF management

Prior to the advent of left ventricular assist devices (LVAD), patients with end-stage HF who were ineligible for heart transplant did not have many options except for palliative care or palliative inotropic therapy which was not a viable long term treatment strategy. To evaluate the efficacy of LVADs, the REMATCH (Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive HF) trial from May 1998 to July 2001 randomized 128 patients to either LVAD or optimal medical therapy [14]. Their findings were remarkable. Survival at one year was 52% in the device group and 25% in the medical group. The observed mortality of 75% at 1 year in the medical group approaches mortality rates seen in pancreatic cancer. Of note, however, patients in the device group were twice as likely to have a serious adverse effect, namely, infection, bleeding or malfunction of device, but overall had improved quality of life compared to medical group. Moreover, the INTrEPID (Investigation of Non-transplant Eligible Patients who are Inotropic Dependent) [27] trial which was a prospective nonrandomized clinical trial comparing LVAD to optimal medical therapy enrolled 55 patients between March 2000 and May 2003 who were inotropic dependent, demonstrated that survival at 6 months was 46% in the

device group and 22% in the medical group and survival at 1 year was 27% in the device group and 11% in the medical group. Further, 85% of the LVAD patients demonstrated either no symptoms or minimal HF symptoms compared to the medical group, whom experienced no improvement in functional NYHA class. Results of the REMATCH and INTrEPID trial demonstrated that patients with end-stage HF have dismal survival rates on optimal medical therapy, but do far much better with mechanical support as well as have improved quality of life.

With evidence of the benefits of mechanical support compared to inotropic therapy for end-stage HF, it is essential to consider mechanical support as the first line treatment in patients with end-stage HF, with inotropes being reserved to acutely stabilize the patient as a bridge to MCS or for palliation. Further, future research should not be directed to development of novel inotropic agents as by definition any drug that increases myocardial contractility will result in increase myocardial oxygen demand, which is associate with worse outcomes. Medical therapy in end stage HF is obsolete and this is the era of mechanical circulatory support. Although inotropes may be useful as a short-term strategy to help temporize acute hemodynamic instability in cardiogenic shock, the clear increase in mortality and morbidity with its use should be weighed against the benefit of a more durable, long-term treatment strategy with mechanical assist devices.

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