Current Status of Inotropes in Heart Failure

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KEYWORDS

• Inotropes • Heart failure • Cardiogenic • Shock • Palliative care • Milrinone • Dobutamine • Dopamine

KEY POINTS

- In the contemporary era, inotrope use has increased and indications have broadened. Survival with chronic inotrope use has also improved compared with the previous era.
- Inotropes are indicated in acute decompensated heart failure or cardiogenic shock with evidence of hypoperfusion; in cardiogenic shock after myocardial infarction; as a bridge to other therapies, including mechanical circulatory support or cardiac transplantation; to improve renal perfusion in cardiorenal syndrome; in right ventricular heart failure; and as palliative inotrope therapy in end-stage heart failure.
- Selection of an inotropic agent is dictated predominantly by the clinical scenario and the desired physiologic effects. Milrinone and dobutamine are the most commonly used inotropes. Dopamine and digoxin are also useful adjuncts. Newer agents, including levosimendan, omecamtiv mecarbil, and istaroxamine, are being evaluated.
- Inotrope therapy has been noted to alleviate symptoms, improve quality of life, decrease hospitalizations, and reduce length of stay in end-stage heart failure. It has also been shown to be cost-effective as a palliative option.

HISTORY OF INOTROPES

Although the first mentions of edema and dyspnea can be found in Greek and Roman texts from antiquity, the modern age of the study of heart failure began in the twentieth century when advances in hemodynamic study and later heart catheterization allowed for newfound insight into cardiovascular function.[1,2] Effective treatment, however, lagged with early focus directed toward the discovery of improved diuretics.

Digitalis, or digoxin, was the first inotrope to be successfully implemented in the treatment of heart failure.[3] William Withering postulated its usefulness more than 200 years ago when giving herbal remedies containing the foxglove plant,[3] with digoxin being isolated from it as the active metabolite in the 1930s.[4]

Meanwhile, at the University College in London, England, George Oliver and Edward Albert Shäfer began studying the effects of the suprarenal gland, first witnessing the direct actions of catecholamines.[5,6] The Japanese chemist Jokichi Takamine isolated epinephrine in pure crystal form in 1901.[5,7] Over the next 60 years, the various other catecholamines and hundreds of sympathomimetic substances were discovered and purified. Our knowledge of their mechanisms of action was elucidated with the first uses of this group in heart failure and cardiogenic shock (CS) occurring in the 1960s to 1970s.[8]

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Beginning toward the end of this period, the next big breakthroughs arrived. With the catecholamine pathway elucidated, phosphodiesterase inhibitors became a novel treatment by altering downstream targets in this conduit.[9] More recently, sarcoplasmic reticulum calcium ATPase isoform 2a (SERCA2a) stimulators, myosin/actin cross-bridge enhancers, and calcium sensitizers have come to show significant promise.

FROM THEN TO NOW: CURRENT INDICATIONS FOR INOTROPES

In the contemporary era, inotrope use has increased and indications have broadened. Survival with chronic inotrope use has also improved compared with the previous era before the early 2000s. Current guidelines suggest their utilization in CS or in hypotension/hypoperfusion due to heart failure (**Box 1**).[10,11] Their usefulness extends to after a myocardial infarction (MI); perioperatively during cardiac surgery; as a bridge to advanced therapies, including transplantation; and as chronic palliative inotrope therapy in end-stage heart failure (**Box 2**). Selection of an inotropic agent in advanced heart failure is dictated predominantly by clinical scenario and the desired physiologic effects.[12] The major indications of inotropes are reviewed next.

Acute Decompensated Heart Failure/ Cardiogenic Shock

Inotropic therapy may be beneficial in patients with severely depressed cardiac output, systemic hypoperfusion, and end-organ dysfunction. Milrinone and dobutamine are the commonly used inotropes for patients with acutely decompensated heart failure. Several studies show improvement in heart failure symptoms with the use of dobutamine and milrinone at continuous infusion doses; however, there is associated increased mortality and it should be used only if evidence of hypoperfusion.[12,13]

The OPTIME (Outcomes of a Prospective Trial of Intravenous Milrinone for Exacerbations of Chronic Heart Failure) study of short-term milrinone use in patients with acute decompensated heart failure without CS suggested a more favorable response in patients with nonischemic cardiomyopathy compared with ischemic cardiomyopathy on subgroup analysis.[14] Overall, milrinone use did not show a benefit in days spent hospitalized for cardiovascular cause, short-term to midterm mortality, nor a composite of death or readmission and was associated with increased rates of atrial arrhythmias and sustained hypotension requiring intervention.[14] These results

Box 1
Current guidelines regarding oral and intravenous inotrope use in heart failure

American College of Cardiology Foundation/ American Heart Association 2013

- Acute CS to maintain end-organ perfusion until definitive therapy or resolution of acute cause (*class I, level C)*
- Stage D heart failure refractory to standard therapy as a bridge to ventricular assist devices or transplantation *(class IIa, level B)*
- Patients with stage D heart failure refractory to standard therapy who are not candidates for ventricular assist devices or transplantation as a palliative measure *(class IIa, level B)*
- Documented severe systolic heart failure presenting with low blood pressure and worsened cardiac output as a short-term therapy to maintain end-organ perfusion *(class IIa, level B)*
- Low-dose dopamine infusion to loop diuretics in the decompensated heart to preserve renal function and improve diuresis *(class IIb, level B)*
- Digoxin in reduced left ventricular ejection fraction and persistent heart failure symptoms despite optimal medical therapy *(class IIa, level B)*

European Society of Cardiologists 2016

- Acute heart failure complicated by hypotension (SBP <85 mm Hg), hypoperfusion, and/ or shock (*class IIb, level C)*
- Levosimendan or phosphodiesterase inhibitor in patients with hypotension, hypoperfusion, or shock thought to be due to over beta-blockade *(class IIa, level C)*
- Digoxin in concomitant NYHA class IV and atrial fibrillation with rapid ventricular rate in patients who are digoxin naive *(class IIa, level B)*
- Digoxin in concomitant NYHA class I to III and atrial fibrillation with inadequate response, intolerance, or contraindication to beta-blockers *(class IIa, level B)*
- Digoxin in reduced left ventricular ejection fraction and persistent heart failure symptoms despite ACE-I (or ARB), beta-blockers, and mineralocorticoid receptor agonist *(class IIb, level B)*

Abbreviations: ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin-receptor blocker; NYHA, New York Heart Association; SBP, systolic blood pressure.