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The Role of Inotropic Agents in the Treatment of Heart Failure

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Abstract

Systolic heart failure (HF) is a systemic disease caused by reduced cardiac contractility. Though it would seem logical that this disease could be treated by employing strategies to directly improve contractility, inotropic therapies in the HF population have universally failed to live up to their expectations. Paradoxically, favorable outcomes can be achieved by administering drugs that acutely *reduce* contractility and block neurohormonal stimulation. The proven success of this latter approach, especially in combination with implantable cardioverter-defibrillator and cardiac resynchronization therapy (ICD-CRT), has drawn our attention away from addressing the root cause of the problem: reduced contractility. In this clinician update, we will discuss current options for inotropic therapy in HF, when it might be appropriate to employ inotropes in HF patients, and what steps can be taken to mitigate their risks while maximizing benefit.

Case 1 – Decompensated Heart Failure with Oliguria

A 68 year-old man with type II diabetes and ischemic cardiomyopathy (LVEF 25%) presents with dyspnea and increasing abdominal distension despite compliance with maximal medical therapy, adherence to fluid and sodium restrictions, and ICD-CRT. His creatinine has risen from 1.3 to 2.1 and his BUN from 20 to 52. Heart rate is paced at 70, blood pressure is 95/56, jugular venous pressure is 12 cm of H_2O, with moderate ascites and edema. You elect to admit him to the hospital for further treatment including intravenous loop diuretics.

Should you also discontinue his beta blocker and start dobutamine?

ANSWER TO CASE:

Most patients admitted with heart failure in the U.S., even those with systolic dysfunction, have normal blood pressure and clearly do not require inotropes. On the other hand, the patient described in this case represents a challenging population in which acute heart failure is associated with deterioration in renal function, i.e. cardiorenal syndrome.[1] There is no

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large randomized controlled trial supporting the use of β-agonists (e.g. dobutamine) or phosphodiesterase (PDE) inhibitors (e.g. milrinone) in such patients, even when the systolic blood pressure is in the 90's. On the contrary, these cAMP-stimulating therapies are associated with more adverse events during hospitalization and an increase in post-discharge mortality, and are thus Class III (contraindicated) per AHA/ACC guidelines.[2-8] The negative effects of these agents are likely a consequence of widespread phosphorylation of Ca handling proteins by cAMP. Although this provides inotropy by both increasing and synchronizing release of Ca sparks by couplons distributed throughout the cell (Figure 1), it can also lead to Ca overload of the sarcoplasmic reticulum (SR) and spontaneous release of Ca into the cytoplasm, thereby triggering arrhythmias.[9] cAMP stimulation has also been implicated in maladaptive remodeling.[10]

β-blockers should be maintained in this hemodynamically stable patient (a Class I indication),[8] as there is no evidence that routinely discontinuing β-blockers in this setting is beneficial.[11, 12] Patients such as this usually respond well to intravenous loop diuretics (avoiding the absorption issues of oral diuretics in the setting of intestinal edema), with improved renal function as preload is optimized. In patients who are truly refractory to diuretics, intravenous nitroglycerine or ultrafiltration can be helpful (Class IIa).[8] Though nesiritide is another Class IIa alternative to inotropes, there have been concerns about its negative effects on renal function.[13] In patients whose renal function declines in response to any of the above therapies (worsening cardiorenal syndrome), inotropes may be required transiently to allow reduction in right atrial and renal venous pressure to achieve effective diuresis and symptom relief. However, it must be understood that cAMP stimulation places these patients at immediate and long-term risk. Low (renal) dose dopamine has been advocated in this setting, but with little confirmed benefit by clinical trials. Since dopamine likely acts by increasing cardiac output rather than selectively increasing renal perfusion,[14] it exposes patients to the same risks as other β-agonists. Finally, if β-blockers are discontinued during hospitalization for acute decompensation, they should be restarted once the patient has been stabilized on oral agents.

Case 2-Very Low Cardiac Index and Pulmonary Hypertension

A 52 year-old woman with dilated non-ischemic cardiomyopathy and biventricular dysfunction, left ventricular ejection fraction 25%, and moderate mitral regurgitation is referred for heart transplant evaluation. Though ambulatory, she complains of progressive fatigue. Heart rate is 95 and blood pressure 86/60, which is her baseline. Creatinine is stable at 1.4. During evaluation, a pulmonary artery (PA) flotation catheter reveals a PA pressure of 65/28, pulmonary capillary wedge pressure of 25, right atrial pressure of 14, and cardiac output of 2.4 (cardiac index 1.4). Systemic vascular resistance is 1822 dynes/sec × cm^{-5}.

Should you start an inotrope?

ANSWER TO CASE:

No, as in the previous case, an inotrope is not indicated in the absence of clinical signs of hypoperfusion, despite what seem like alarming pulmonary pressures and cardiac output. Both the ADHERE registry[6] of HF patients and the ESCAPE trial[7] of severe decompensated HF patients demonstrated significantly higher in-hospital and 6-month mortality respectively when patients were treated with either dobutamine or milrinone instead of vasodilators. Afterload and preload reduction with intravenous nitroprusside and furosemide, followed by transition to an oral regimen, can lead to both acute and sustained benefit on hemodynamics and reduction in mitral regurgitation.[15, 16]

Case 3-Shock and Palliative Inotropic Therapy

A 70 year-old man with advanced prostate cancer and ischemic cardiomyopathy, left ventricular ejection fraction 18%, is brought to the emergency room after two episodes of near syncope. He is somnolent and falls asleep during the interview. He is on very low doses of ACE inhibitor and did not tolerate a β-blocker as an outpatient because of low blood pressure. His baseline creatinine is 1.8. Heart rate is paced at 70 and blood pressure is lower than usual at 72/55. Chest is clear, jugular venous pressure is normal. He has mitral and tricuspid regurgitation murmurs and an S3. His extremities are cool with trace edema and he is oliguric.

Should you start an inotrope?

ANSWER TO CASE:

Yes. Cardiogenic shock with organ dysfunction is a Class I indication for temporary inotropic therapy to support perfusion while revascularization or other definitive therapies are administered.[8] Unfortunately, this patient is not a candidate for heart transplantation because of his malignancy. In some patients it becomes difficult or impossible to wean inotropes because of dependence of blood pressure or renal perfusion on continued inotropic support. If these patients are not candidates for heart transplant or mechanical assist, it has become acceptable to prescribe chronic outpatient inotrope infusions, usually dobutamine or milrinone, purely as a palliative measure (a Class IIb indication).[8] Such infusions allow patients to be discharged home without congestive symptoms, and in a small percentage of patients the inotrope can be titrated off as an outpatient. Patients and their families must be educated, sometimes in consultation with palliative medicine specialists, that inotropic therapy is not curative and may increase the overall risk of death. Many patients will accept this risk in exchange for the opportunity to leave the hospital and spend their remaining time at home.

Non-randomized and retrospective data from small studies have suggested that PDE inhibitors like milrinone might be associated with superior pulmonary vasodilation, a more stable clinical course, and less inotrope “tolerance” than dobutamine; however, hemodynamic efficacy, arrhythmogenic potential, and outcomes of patients treated with dobutamine and milrinone are similar.[17, 18] Milrinone titration is also more challenging because of its longer half-life. On the other hand, several small studies have shown that β-blockers are well tolerated when added to treatment with PDE inhibitors, and may also portend a survival benefit.[19, 20] Thus it may be reasonable to add one of the approved β-blockers for HF if the patient requires continuous milrinone.

Case 4-Recurrent HF Admissions

A 62 year-old man with ischemic cardiomyopathy and an LVEF of 30% is seen in follow-up after his second hospitalization for HF this year. Despite adherence to maximal medications and strict sodium and fluid restriction, he continues to complain of exertional fatigue.

Should you add digoxin to his outpatient regimen?

ANSWER TO CASE:

Yes. Unlike β-agonists, digoxin has not been associated with worsening survival or maladaptive remodeling, possibly because digoxin does not activate G-protein associated pathways. Instead, digoxin loads the SR with Ca by blocking the sodium-potassium (Na-K) ATPase, raising intracellular sodium, and thereby reducing Ca efflux by sodium-calcium

exchange.[21] The DIG trial demonstrated that while digoxin provided no mortality benefit compared to placebo, it reduced the frequency of HF hospitalizations.[22] The lack of a mortality benefit was caused, in part, by an increase in death due to arrhythmias, consistent with Ca overload of the SR. The RADIANCE trial found that discontinuing digoxin in patients with low EF and HF resulted in worsening HF.[23] Current AHA/ACC guidelines classify digoxin use as IIA in patients with current or prior symptoms of HF and reduced LVEF to decrease hospitalizations for HF.[8] Importantly, digoxin levels should be maintained between 0.5 and 1.0 ng/ml. This lower target level may reduce the adverse effects of digoxin while preserving its benefits. It is important to remember that digoxin provides no mortality benefit, and therefore it is absolutely not a substitute for neurohormonal blockade.

Future Inotropic Therapy

Myofilament Calcium Sensitizers

Ca sensitizers are designed to improve contractility by enhancing binding of Ca to troponin C. One such sensitizer, levosimendan, has been well studied. Although the LIDO study suggested that levosimendan was more effective than dobutamine with fewer adverse effects,[24] the recent randomized controlled trial, SURVIVE, found no significant benefit of levosimendan over dobutamine in patients with acute HF and EF < 30%.[25] This may be in part due to PDE inhibition properties of levosimendan. At the present time, levosimendan is not approved in the U.S., but is available in Europe.

Other Therapies

Istaroxime is an investigational drug that blocks Na-K ATPase to raise intracellular sodium levels like digoxin, but also stimulates SERCA on the SR like a cAMP-mediated inotrope. An initial study (HORIZON-HF) suggested hemodynamic benefit,[26] but two larger phase I trials scheduled for enrollment in 2009 were withdrawn. Growth hormone may enhance Ca transients,[27] but has had variable results in clinical studies.[28] Thyroid hormone has been shown in animal models to enhance Ca handling proteins involved in CICR, and small nonrandomized clinical trials have suggested efficacy with minimal side effects.[29, 30] However, outcomes have not been studied in a large randomized controlled trial. The phytopharmaceutical, crataegus extract (hawthorn), raises intracellular Ca, prolongs the action potential, and may improve exercise capacity in mild HF. Though widely used in Europe by HF patients as a “natural” remedy, a randomized trial recently showed no benefit.[31] Current and investigational inotropes are summarized in Table 1, and an algorithm for appropriate use of inotropes in heart failure is provided in Figure 2.

Inotropes are clearly indicated in cardiogenic shock but also continue to be employed in decompensated heart failure, especially when patients have borderline blood pressure, or fail to respond to loop diuretics and vasodilators. However, there is no data demonstrating an outcome benefit of inotropes in the heart failure population, likely because of proarrhythmia and maladaptive remodeling. Future inotropic therapies should be designed with these problems in mind. One approach is to increase EC coupling efficiency, i.e. synchronizing Ca sparks, without increasing Ca load.[32] Until then, neurohormonal blockade and vasodilators should remain our preferred therapies.

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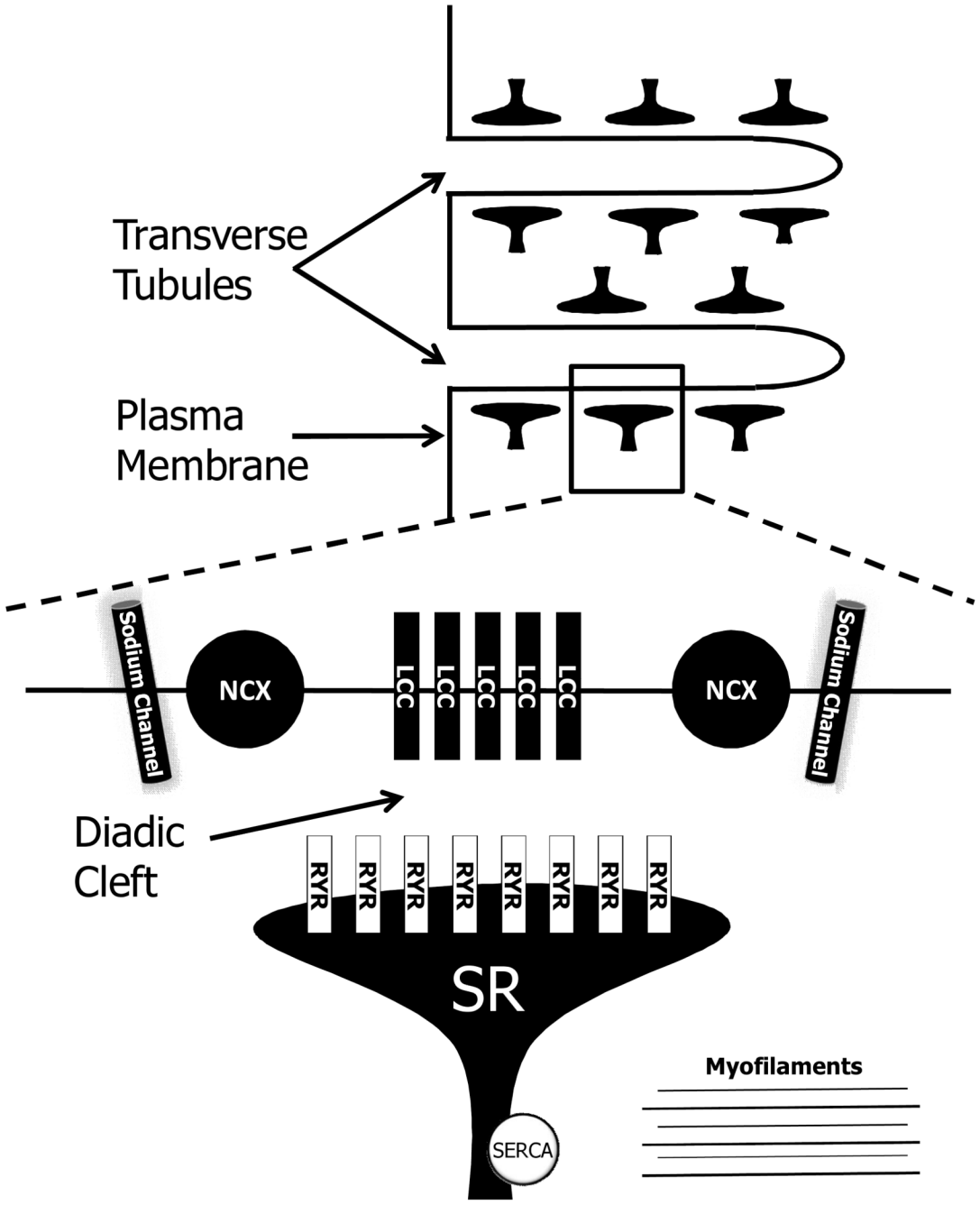

Figure 1.

During each action potential, voltage-dependent L-type calcium channels (LCCs) located on the plasma membrane open, and a relatively small amount of Ca enters the cell, crosses the diadic cleft, and triggers ryanodine receptors (RyRs) on the sarcoplasmic reticulum (SR) to open, thereby releasing a much larger amount of Ca from the SR store into the cytoplasm. LCCs and RyRs on the SR are organized into independent functional units, known as couplons, which are distributed along the transverse-tubules (upper panel). In healthy cells, couplons activate synchronously, and the released Ca diffuses to the myofilaments and activates contraction. In diastole, sodium-calcium exchange (NCX) removes about 20% of cytoplasmic Ca from the cell while the SR Ca ATPase (SERCA) pumps the other 80% back

into the SR. In failing cardiomyocytes, a reduction in both the rate and extent of Ca delivery to the myofilaments results in reduced contractility. For the purposes of this clinician update, the most important causes are a reduction in the number of couplons activated with each action potential and a loss of their synchronous activation.[33] These abnormalities are likely caused by a reduction in the open probability of LCCs, leading to defective triggering of RyRs.[34] Reduced SR Ca stores caused by increased NCX activity, reduced SERCA activity and leaky RyRs may also contribute to the reduction in Ca delivery to the myofilaments in heart failure.[35-37] The SR Ca load can be increased by blocking the sodium-potassium ATPase to raise intracellular sodium, thereby reducing Ca removal by NCX (e.g. digoxin), or by enhancing LCC and SERCA activity (e.g. β-agonists).

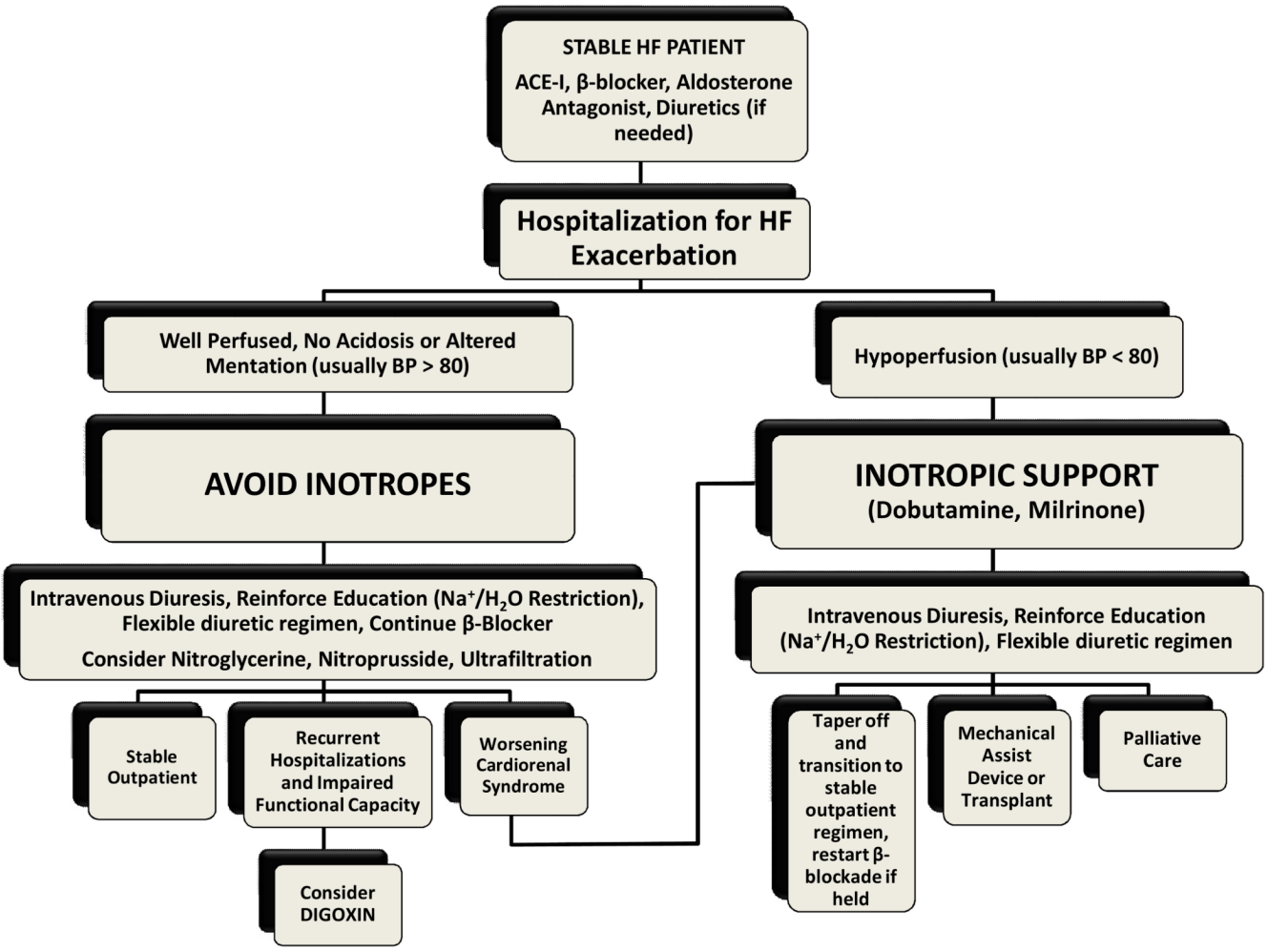

Figure 2.

Recommended approach to use of inotropic support in patients hospitalized with acute HF exacerbation. As long as patients appear clinically well-perfused, usually with a systolic blood pressure (BP) > 80, inotropes provide no outcome benefit and subject patients to significant risks of arrhythmia, remodeling and death. Well-perfused patients with impaired functional capacity and frequent hospitalizations for HF exacerbation may benefit from digoxin. In hospitalized patients with worsening cardiorenal syndrome despite intravenous diuretic and vasodilator therapy, it is reasonable to add an inotrope in an attempt to acutely rescue renal function. If patients are hospitalized with clinical evidence of shock, inotropic support is clearly indicated as a temporary measure until stabilized on oral agents, or bridged to transplant or mechanical assist device. Continuous home inotropes may also be considered for end stage patients as a palliative measure.

Table 1

Drug	Mechanism	Indication	Effect on Mortality
Digoxin	Na-K pump inhibitor, raises SR Ca	Recurrent HF Admissions	Neutral; increased mortality if chronic treatment discontinued
Dobutamine	β-agonist, widespread cAMP-dependent phosphorylation, increases Ca entry via LCCs, raises SR Ca, synchronizes Ca sparks, stimulates remodeling	Shock, palliative use in end-stage disease	Increased
Milrinone	PDE inhibitor, bypasses β receptor, otherwise mechanism same as dobutamine	Shock, palliative use in end-stage disease	Increased; possibly mitigated by concomitant use of β-blocker
Dopamine	β-agonist, widespread phosphorylation, raises SR Ca, stimulates remodeling	Shock	Increased
Levosimendan	Myofilament Ca sensitizer, PDE inhibitor	Shock; not available in U.S.	Increased
Istaroxime	Na-K pump inhibitor, PDE inhibitor	Under investigation	Unknown
Growth Hormone	Enhances Ca release by the SR	Under investigation	Unknown
Thyroid Hormone	Enhances Ca release by the SR	Under investigation	Unknown
Crataegus Extract (Hawthorn)	Raises intracellular Ca, prolongs the action potential	A “natural” therapy for stable outpatients with HF	Neutral

Na-K = sodium-potassium

PDE=phosphodiesterase

SR=sarcoplasmic reticulum