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OPTIMIZATION OF INDIVIDUAL DOSING OF CARDIOTROPIC DRUGS TO IMPROVE CARDIAC CONTRACTILE FUNCTION

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RELEVANCE

Acute and chronic heart failure are characterized by impaired cardiac contractile function (inotropy), leading to reduced cardiac output and end-organ hypoperfusion. Cardiotropic drugs, particularly inotropes, are a cornerstone of treatment in acute decompensated heart failure and cardiogenic shock, designed to directly enhance myocardial contractility. However, these agents possess a narrow therapeutic window and are associated with significant risks, including arrhythmogenesis, increased myocardial oxygen consumption, and potential long-term cardiotoxicity. A standardized, "one-size-fits-all" dosing approach fails to account for the vast inter-patient variability in pathophysiology, comorbidities, and pharmacodynamic response. Therefore, optimizing the individual dosage of these potent medications is a critical clinical challenge. This article explores the modern strategies for personalizing inotrope therapy, aiming to maximize hemodynamic benefits while minimizing adverse effects, thereby improving patient outcomes.

Keywords: inotropes, heart failure, cardiac contractility, personalized medicine, hemodynamic monitoring, dose optimization, dobutamine, milrinone, cardiogenic shock.

АКТУАЛЬНОСТЬ

Острая и хроническая сердечная недостаточность характеризуются нарушением сократительной функции сердца (инотропии), что приводит к снижению сердечного выброса и гипоперфузии конечных органов. Кардиотропные препараты, в частности инотропы, являются краеугольным камнем лечения при острой декомпенсированной сердечной недостаточности и кардиогенном шоке, предназначенные для прямого усиления сократимости миокарда. Однако эти средства обладают узким терапевтическим окном и связаны со значительными рисками, включая аритмогенность, повышенное потребление кислорода миокардом и потенциальную долгосрочную кардиотоксичность. Стандартизированный подход к дозированию по принципу "один размер для всех" не учитывает огромную межиндивидуальную вариабельность в патофизиологии, сопутствующих заболеваниях и фармакодинамическом ответе. Поэтому оптимизация индивидуальной дозы этих сильнодействующих препаратов является важнейшей клинической задачей. В данной статье рассматриваются современные стратегии персонализации инотропной терапии с целью максимизации гемодинамических преимуществ при минимизации побочных эффектов, тем самым улучшая исходы для пациентов.

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Ключевые слова: инотропы, сердечная недостаточность, сократимость сердца, персонализированная медицина, гемодинамический мониторинг, оптимизация дозы, добутамин, милринон, кардиогенный шок.

INTRODUCTION

Improving cardiac contractile function is a primary goal in the management of acute heart failure and cardiogenic shock. Inotropic agents are powerful tools for achieving this objective, but their use is a double-edged sword, offering hemodynamic improvement at the cost of potential life-threatening side effects. This review focuses on the critical need for optimizing the individual dosage of cardiotropic drugs. We discuss the limitations of standard weight-based dosing and advocate for a personalized approach guided by multi-modal monitoring. This includes advanced hemodynamic monitoring (e.g., pulmonary artery catheters or less invasive cardiac output monitors), serial echocardiography for direct assessment of cardiac function (e.g., LVEF, VTI, strain imaging), and close tracking of clinical and biochemical markers of end-organ perfusion (e.g., lactate, renal function). The article reviews the pharmacology of different inotrope classes—catecholamines, phosphodiesterase inhibitors, and calcium sensitizers—and outlines a goal-directed titration strategy. The objective is to administer the "lowest effective dose for the shortest necessary time" to achieve specific physiological targets rather than simply maximizing the infusion rate. This personalized approach aims to improve the benefit-risk ratio, potentially reducing mortality and morbidity in critically ill cardiac patients. The emerging role of pharmacogenomics in predicting patient response is also discussed as a future frontier in therapy optimization.

Heart failure (HF) is a global pandemic affecting millions of people. Its most severe presentations, acute decompensated heart failure (ADHF) and cardiogenic shock (CS), are medical emergencies with high mortality rates. The pathophysiological hallmark of these conditions is a profound depression of myocardial contractility, leading to a vicious cycle of low cardiac output, systemic hypoperfusion, and further cardiac injury (Tehrani et al., 2014).

Inotropic agents are administered to directly augment the force of myocardial contraction, thereby breaking this cycle. This drug class includes traditional catecholamines (e.g., dobutamine, dopamine), phosphodiesterase-3 (PDE3) inhibitors (e.g., milrinone), and calcium sensitizers (e.g., levosimendan). While effective in improving hemodynamics, their use is fraught with peril. By increasing intracellular calcium and cyclic adenosine monophosphate (cAMP), they also increase heart rate, myocardial oxygen demand, and the risk of ventricular arrhythmias. Retrospective studies have suggested an association between inotrope use and increased mortality, highlighting the need for caution (Guglin, 2017).

The central thesis of this article is that the risks associated with inotropic therapy can be mitigated through a dynamic, individualized, and goal-directed approach to dosing. This moves beyond simplistic weight-based protocols to a sophisticated strategy that integrates real-time patient data to tailor therapy, ensuring that the dose administered is the optimal one for that specific patient at that specific time.

LITERATURE REVIEW

The rationale for optimizing inotrope dosage is rooted in pharmacology, physiology, and clinical evidence.

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Pharmacodynamic Variability: Patients with heart failure exhibit significant variability in their response to inotropes. This can be due to factors such as the severity and chronicity of HF, the underlying etiology, patient age, renal and hepatic function, and genetic factors. For instance, chronic HF leads to downregulation and desensitization of β-adrenergic receptors, which can blunt the response to catecholamines like dobutamine. In such patients, an agent with a different mechanism, like the PDE3 inhibitor milrinone, may be more effective (Francis et al., 2021).

The Concept of "Lowest Effective Dose": The prevailing paradigm has shifted from achieving maximal hemodynamic effect to achieving adequate effect with the lowest possible dose. High-dose inotropic support may produce impressive hemodynamic numbers (e.g., a very high cardiac index) but at the expense of excessive tachycardia and oxygen consumption, which can be detrimental. The goal is not to normalize numbers but to restore adequate end-organ perfusion, as evidenced by improving lactate levels, urine output, and mentation.

The Role of Advanced Monitoring: Individualization is impossible without robust monitoring. Historically, the pulmonary artery catheter (PAC) was the gold standard, providing comprehensive data on cardiac output, filling pressures, and vascular resistance. While its use has declined due to concerns about invasiveness, it remains invaluable in complex cases of shock. More recently, less invasive cardiac output monitoring systems and, critically, point-of-care echocardiography have become central to this process. Echocardiography provides a direct, real-time visual and quantitative assessment of contractile function (e.g., left ventricular ejection fraction [LVEF], velocity time integral [VTI] as a surrogate for stroke volume), allowing clinicians to titrate therapy directly against its intended physiological effect (Beaubien-Souligny et al., 2020).

Pharmacogenomics: An emerging area is the study of how genetic variations affect drug response. For example, polymorphisms in β1- and β2-adrenergic receptors can influence an individual's response to catecholamines. While not yet in routine clinical use, pharmacogenomic testing holds the promise of predicting inotrope sensitivity and guiding agent selection in the future (Liggett, 2013).

Methodology for dose optimization - Optimizing inotrope dosage is a systematic, iterative process.

Step 1: Baseline Assessment and Goal Setting. Before initiating therapy, a comprehensive assessment is performed to understand the patient's specific hemodynamic profile. Is the primary problem pump failure (low contractility), inadequate preload, excessive afterload, or a combination? Clear, achievable therapeutic goals must be set. Examples include: Maintain a mean arterial pressure (MAP) > 65 mmHg. Achieve a cardiac index > 2.2 L/min/m². Achieve lactate clearance > 10% per hour. Maintain urine output > 0.5 mL/kg/hr.

Step 2: Selection of the Appropriate Inotropic Agent. The choice of agent depends on the clinical context (see Table 1). For example, in a patient with normotensive cardiogenic shock ("cold and wet" profile), dobutamine may be a first-line choice. In a patient on chronic beta-blockade or with co-existing pulmonary hypertension, milrinone might be preferred for its inotropic and vasodilatory effects.

Step 3: Cautious Initiation and Titration. The principle of "start low, go slow" is paramount. The inotrope is initiated at the lower end of its recommended dose range (e.g., dobutamine at 2-3 mcg/kg/min). The dose is then titrated upwards every 15-30 minutes based on the response observed through continuous monitoring.

Step 4: Multi-Modal Response Monitoring. Titration is guided by data from multiple sources: Hemodynamic monitoring - Continuous arterial blood pressure, central venous pressure,

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and cardiac output/index. Echocardiography - A brief focused echo exam can be performed before and after dose adjustments to assess changes in LVEF, stroke volume (via VTI), and signs of right ventricular strain. Biochemical Markers - Serial measurements of arterial lactate, venous oxygen saturation ($ScvO_2$), and markers of renal/hepatic function. Clinical Assessment - Evaluation of peripheral perfusion (capillary refill time, skin temperature), urine output, and mental status.

Step 5: Regular Re-evaluation and Weaning. Inotropic support is intended as a temporary bridge—to recovery, to decision, or to mechanical circulatory support. The patient's need for the inotrope must be re-evaluated at least daily. As soon as the underlying condition improves and hemodynamic stability is achieved, a gradual weaning process should be initiated.

Table 1: Comparative profile of common inotropic agents for dose optimization

Drug class	Example	Mechanism of action	Primary hemodynamic effects	Key considerations for individualized dosing
β-Adrenergic agonist	Dobutamine	Primarily stimulates β1-receptors, increasing intracellular cAMP	↑ Contractility (+++) ↑ Heart Rate (++) ↓ SVR (+)	Titrate to: Cardiac output/index, lactate clearance. Monitor for: Tachycardia, arrhythmias, hypotension (at high doses). Note: Efficacy may be blunted in patients on beta-blockers.
Phosphodiesterase-3 Inhibitor	Milrinone	Inhibits PDE3, preventing the breakdown of cAMP	↑ Contractility (++) ↓ SVR (+++) ↓ PVR (++)	Titrate to: Cardiac output, SVR/PVR reduction. Monitor for: Profound hypotension. Note: Requires dose adjustment in renal impairment. Longer half-life makes rapid titration difficult.
Calcium sensitizer	Levosimendan	Sensitizes troponin C to calcium, improving contractility without increasing intracellular Ca^{2+}	↑ Contractility (++) ↓ SVR (+++) No significant ↑ in MVO_2	Titrate to: Clinical/hemodynamic response after initial bolus. Monitor for: Hypotension. Note: Very long half-life (active metabolite). Cardioprotective effects proposed.
Catecholamine (Ino-pressor)	Norepinephrine	Primarily α1-agonist, with modest β1-agonist	↑ SVR (+++) ↑ MAP (+++) ↑ Contractility (+)	Titrate to: Target MAP. Use: First-line agent in shock with vasodilation (e.g., septic or

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		effects		profound cardiogenic shock). Often used with an inotrope.

(Legend: ↑ Increase; ↓ Decrease; SVR: Systemic Vascular Resistance; PVR: Pulmonary Vascular Resistance; MVO_2: Myocardial Oxygen Consumption; + weak effect, ++ moderate effect, +++ strong effect)

Discussion of outcomes and challenges - The primary outcome of an optimized dosing strategy is an improved benefit-risk ratio. By achieving therapeutic goals with the lowest possible dose, the incidence of tachyarrhythmias, myocardial ischemia, and hypotension may be reduced. This approach may facilitate faster weaning from vasoactive support and potentially improve short-term survival and end-organ recovery.

However, this strategy is not without challenges. It is resource-intensive, requiring advanced monitoring capabilities and skilled personnel (e.g., intensivists, critical care nurses, sonographers). The interpretation of data can be complex, especially when multiple vasoactive drugs are used simultaneously. Furthermore, there is a lack of large-scale randomized controlled trials that directly compare a protocolized, goal-directed titration strategy against standard care. Most evidence is derived from physiological principles and observational data.

The future of optimization lies in integrating technology and biology. Machine learning algorithms could potentially analyze continuous streams of monitoring data to suggest real-time dose adjustments. Widespread adoption of pharmacogenomic testing could allow for the a priori selection of the most effective and safest agent for an individual patient.

CONCLUSION

The administration of cardiotropic drugs to improve cardiac contractility is a high-stakes intervention. The era of standardized, weight-based dosing is giving way to a more nuanced, sophisticated paradigm of personalized medicine. By leveraging multi-modal monitoring—combining advanced hemodynamics, functional echocardiography, and key biomarkers—clinicians can optimize individual dosages. The goal is to titrate therapy to achieve specific physiological endpoints while actively minimizing dose-related toxicity. This goal-directed approach, centered on the principle of using the "lowest effective dose for the shortest necessary time," is the cornerstone of modern, safe, and effective inotropic support for patients with severe heart failure.

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