Cardiovascular Drugs and Therapy
https://doi.org/10.1007/s10557-024-07614-9

REVIEW ARTICLE

Levosimendan: A New Therapeutical Strategy in Patients with Renal Insufficiency

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Accepted: 28 July 2024

Abstract

Levosimendan, a Ca2 + sensitizer with positive inotropic effects, is primarily employed for the short-term treatment of acute decompensated heart failure (ADHF). Levosimendan exerts renal function protection through various mechanisms, including anti-apoptosis, anti-inflammatory, and antioxidant effects in vivo. Additionally, levosimendan may have a protective effect on individuals with heart failure and renal insufficiency, as well as on renal function impairment after cardiac surgery. However, the application of levosimendan in patients with severe renal dysfunction remains controversial. This article delves into the use of levosimendan in severe renal insufficiency, explores its impact on renal function, and provides a comprehensive overview of its impact on renal function after cardiac surgery.

Keywords Levosimendan · Kidney · Heart failure · Cardiac surgery

Introduction

Levosimendan, a Ca2 + sensitizer interacting with cardiac troponin C, induces a positive inotropic effect without escalating myocardial oxygen consumption or affecting ventricular relaxation. Additionally, it activates the K + channel in vascular smooth muscle, leading to the dilation of tissue blood vessels [1, 2]. Levosimendan is particularly advantageous for patients with ischemic cardiomyopathy, including those with acute coronary syndrome (ACS) and heart failure with reduced ejection fraction (HFrEF) [3, 4]. Notably, renal dysfunction often accompanies heart failure, affecting approximately 50% of acute or chronic heart failure patients, in contrast to 5% in the general population. Renal impairment has been associated with reduced survival in patients with heart failure (HF) [5].

The vast majority of research documents present a wealth of clinical and preclinical evidence that not only substantiates the cardiorenal protective effects of levosimendan but also highlights its safety profile [6, 7]. However, a contentious issue remains regarding its use in patients with severe renal insufficiency [3, 8, 9]. The renal protective effects

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Published online: 07 August 2024

of levosimendan are partially attributed to organ-specific actions [10–13]. These effects involve relaxing pre-glomerular blood vessels, increasing renal artery diameter, and enhancing renal blood flow, directly contributing to renal protection, especially in patients with heart failure or diabetes that results in renal hypoperfusion (Fig. 1). Notably, renal tissues contain abundant K-ATP channels [14], and the activation of these channels by levosimendan mitigates oxidative stress response, alleviates cell apoptosis, and reduces acute kidney injury (AKI) resulting from ischemia–reperfusion; K(ATP) channel agonists (but not antagonists) appear to be devoid of toxic proximal tubular cell effects [15, 16].

Levosimendan's Impact on Renal Function in Animal Experiments

In animal experiments, levosimendan exerts renal function protection effects through multiple mechanisms such as anti-apoptosis, anti-inflammatory, and antioxidant (Fig. 2). Ischemia/reperfusion (I/R) injury, a critical factor in acute renal failure, involves oxidative stress, inflammation, and cell apoptosis. Levosimendan significantly reduces plasma creatinine, decreases N-acetyl-β-D-Glucosaminidase (NAG) levels, and lowers thiobarbituric acid reactive substance concentrations, while simultaneously increasing creatinine clearance rate. These findings suggest that levosimendan has the potential for antioxidant and anti-apoptotic effects mediated through mitochondrial K (ATP) channels and NO-related mechanisms. NO is generated in the kidneys and regulates renal hemodynamics. In this study on the Levosimendan protection against kidney I/R injuries in anesthetized pigs, it was found that blocking the release of mitochondrial K (ATP) channels and NO aggravated renal injury. Levosimendan exerts antioxidant and anti-apoptotic effects by activating cell signaling pathway factors such as eNOS and cytochrome C, thereby protecting the kidneys [15]. In another study of levosimendan on endotoxin-induced acute renal failure(ARF), it was found that levosimendan had no effect on NO generation, but, levosimendan, an ATP-sensitive K (ATP) channel opener, completely blocked ANG II-induced MC contraction, an action likely to increase renal vasoconstriction ± reduced glomerular ultrafiltration coefficient, Kf; it can significantly prevent levosimendan induced ARF [16]. Furthermore, levosimendan can reduce malondialdehyde (MDA) levels and enhancing superoxide dismutase (SOD) and glutathione (GSH) activity, which demonstrating its protective role against renal ischemia–reperfusion injury through lipid peroxidation [17–19]. Additionally, levosimendan reduces inflammatory factors such as intercellular cell adhesion molecule-1 (ICAM-1), Tumor Necrosis Factor alpha (TNF-α), and Interleukin-6 (IL-6), improves renal arterial pressure, and alleviates renal I/R injury [18, 20].

Levosimendan also exhibits renal protection following cardiac arrest, leading to reduced mortality and AKI [21, 22]. Its underlying mechanism involves activating extracellular signal-regulated kinase(ERK) signaling, improving mitochondrial dysfunction, and exerting anti-inflammatory, anti-apoptotic, and antioxidant effects. In rat models of AKI post-cardiac arrest and cardiopulmonary resuscitation (CPR), levosimendan decreases levels of Interleukin-6 (IL-1), IL-6, TNF, BCL2-associated X Protein (Bax), Caspase 3, and Caspase-9, while increasing B-cell leukemia/lymphoma-2 (bcl-2) expression levels [21].

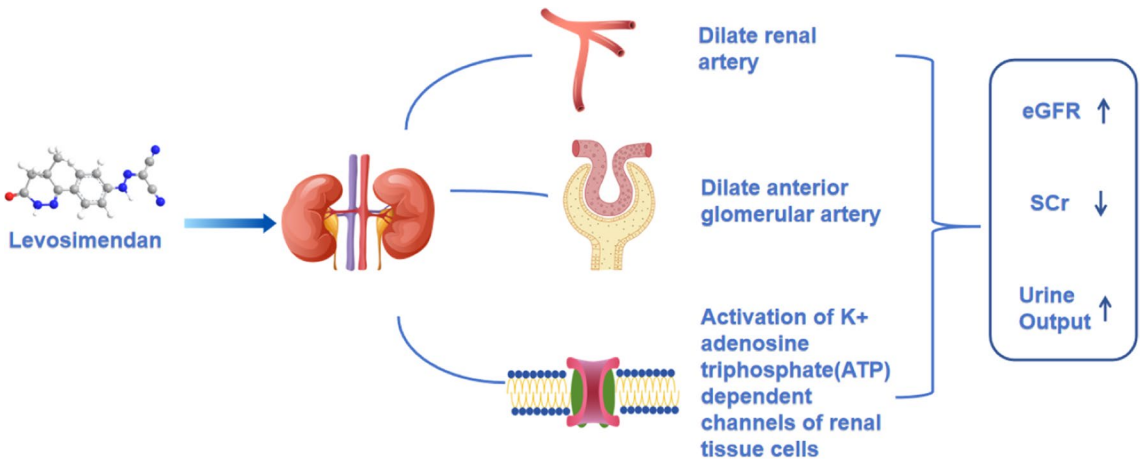

Fig. 1 Mechanism of renal function protection of levosimendan. The protective effect of levosimendan on the kidneys is primarily achieved through several mechanisms. It dilates the renal artery and glomerular artery blood vessels, which in turn increases renal blood flow and improves renal circulation. Furthermore, levosimendan activates renal tissue K-ATP channels. As a result of these actions, the glomerular filtration rate increases, serum creatinine levels decrease, and urine output is enhanced

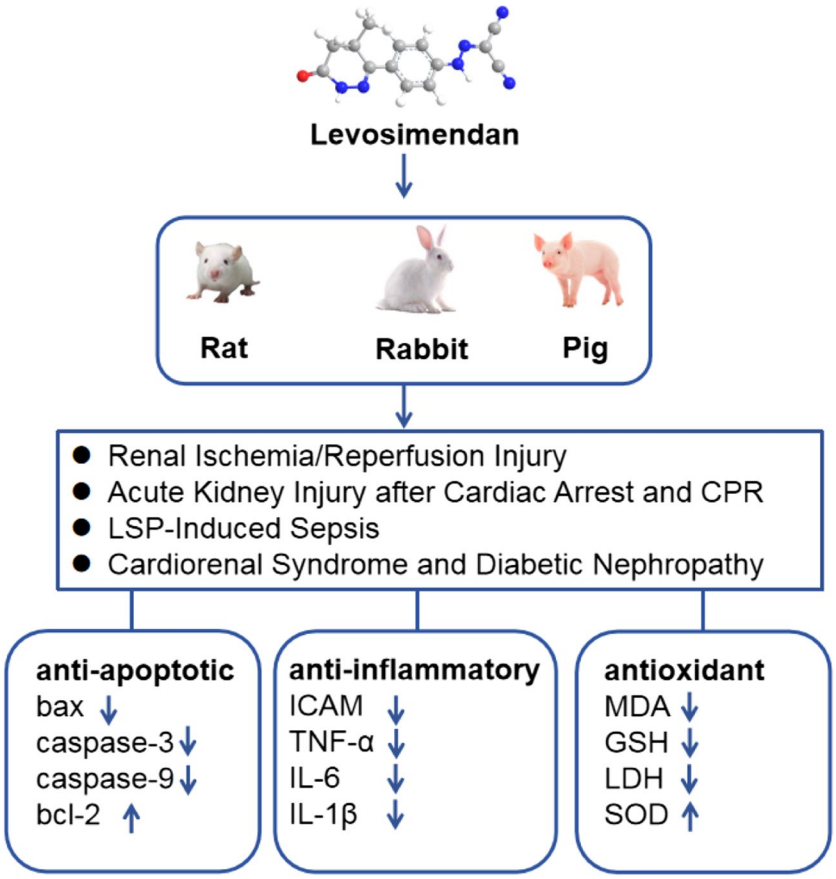

Fig. 2 Effect of levosimendan on renal function in animal experiments. Levosimendanhas shown protective effects on renal ischemia/reperfusion injury and acute kidney injury after cardiac arrest and CPR in various animals such as mice, rabbits, and pigs. The mechanisms mainly involve anti-apoptotic, anti-inflammatory, and antioxidant effects. Levosimendan increases the expression of anti-apoptotic protein Bcl-2 and reduces the expression of apoptotic proteins Bax, Caspase-3, and Caspase-9. Levosimendan reduces inflammatory factors such as ICAM-1, TNF-α, IL-6, IL-1β; levosimendan decreases MDA levels and SOD and GSH activity. bax = BCL2 associated X Protein, bcl-2 = B-cell leukemia/lymphoma-2, ICAM = The intercellular adhesion molecule, TNF-α = Tumour Necrosis Factor alpha, IL-6 = Interleukin-6, IL-1β = Interleukin-1beta, MDA = malonaldehyde, GSH = glutathione, LDH = lactate dehydrogenase, SOD = superoxidase dismutase

Protective Effect of Levosimendan on Renal Function in Heart Failure Patients

Levosimendan enhances renal function in patients with acute decompensated heart failure (ADHF) via boosting glomerular filtration rate (GFR) compared to dobutamine after 24 and 72 h, emphasizing its superiority over dobutamine in preserving renal function [23]. Another investigation, focusing on hospitalized patients with decompensated heart failure and renal insufficiency, revealed a substantial and sustained elevation in estimated GFR (eGFR) levels following levosimendan treatment [24]. The observed increase remained consistent for a duration of 14 days, signifying a sustained protective effect. Fedele et al. conducted a randomized double-blind experiment, affirming the direct renal protective effect of levosimendan in patients with ADHF and moderate renal dysfunction [25]. The study evaluated the effectiveness of levosimendan in maintaining renal function through multiple dimensions such as eGFR, renal blood flow, creatinine urea nitrogen, and urine output. In the context of acute heart failure (AHF), levosimendan-treated patients with eGFR below 60 ml/min exhibited a notable difference in elevated serum creatinine (SCr) clearance rate compared to standard treatment [26]. Furthermore, a real-world study demonstrated elevated eGFR levels after levosimendan infusion in AHF patients with eGFR below 90.0 ml/min/m^2, reinforcing its positive impact on renal function [27]. In conclusion, levosimendan consistently exhibits a robust protective effect on renal function in heart failure patients, positioning it as a valuable therapeutic option in clinical practice.

Levosimendan's Impact on SCr Levels

Levosimendan demonstrates a noteworthy improvement in SCr levels among patients experiencing severe heart failure and renal function deterioration [28]. Particularly, in cases of renal function deterioration, intervention with levosimendan resulted in a significant decrease in SCr from 1.4 ± 0.16 to 1.21 ± 0.23 mg/dL ($p = 0.001$). However, in the absence of renal function deterioration, no significant improvement was observed, with SCr ranging from 1.29 ± 0.33 to 1.37 ± 0.66 mg/dL ($p = 0.240$). In AHF patients with an eGFR < 60 ml/min (left ventricular ejection fraction (LVEF) less than 35%), there was a significant difference in SCr decrease between the levosimendan group and the standard treatment group (SCr decrease 0.13 ± 0.25 vs. 0.10 ± 0.58 mg/dL, $p < 0.05$). Additionally, the levosimendan group also exhibited a lower incidence of worsening renal function (WRF) (4% vs. 19%, $p < 0.05$) [26].

Levosimendan's Impact on Urine Output

In patients with ADHF, the levosimendan group not only increased eGFR significantly but also improved 24-h urine output compared to the dobutamine group [23]. However, in AHF patients with an eGFR < 60 ml/min (LVEF less than 35%), there was no difference in urine output between the levosimendan and the standard treatment groups (diuretics and other positive inotropic drugs) was observed [26].

Impact of Levosimendan in Patients with Severe Renal Insufficiency

The utilization of levosimendan in patients with severe renal insufficiency has sparked controversy, primarily due to the pharmacokinetic factors of this medicine. Levosimendan's primary effects are mediated by its circulating metabolites, specifically OR-1855 and OR-1896 (Fig. 3). While levosimendan is rapidly cleared from the plasma, the metabolites exhibit slower elimination, particularly in patients with severe chronic renal failure and end-stage renal disease (ESRD) undergoing hemodialysis [8, 9]. Caution and dose reduction are recommended when administering levosimendan in congestive heart failure patients with severe renal insufficiency.

A retrospective study based on data from a multi-institutional database challenges the prevailing belief that severe renal insufficiency is an absolute contraindication for levosimendan use [3]. The study found that levosimendan treatment in severe AHF patients, regardless of the presence of severe renal insufficiency (eGFR < 30 mL/min/1.73m2), did not significantly differ in mortality rates between 90 and 180 days when compared to patients receiving dobutamine treatment. Furthermore, a prospective, multicenter, real–world study provides additional evidence supporting the safety of levosimendan in patients with severe renal insufficiency, demonstrating remarkable improved eGFR levels following levosimendan infusion [27].

Nevertheless, a retrospective study comparing milrinone and levosimendan in patients with AHF and renal insufficiency raises cautionary concerns. Among patients receiving levosimendan, those with severe renal insufficiency exhibited clinical deterioration at 15 and 30 days compared to those treated with milrinone [29]. These findings prompt a reevaluation of levosimendan as an initial positive inotropic therapy for AHF patients with severe renal insufficiency. Due to limited data on the elimination of active metabolites in patients with renal dysfunction, special caution should be exercised when using levosimendan for patients with mild to moderate renal dysfunction. Renal dysfunction may lead to an increase in the concentration of active metabolites, resulting in more significant and long-lasting hemodynamic effects. The

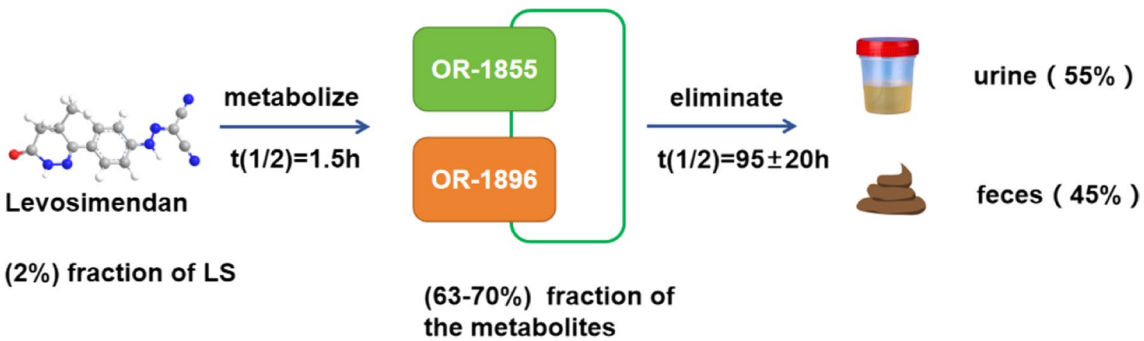

Fig. 3 Metabolic transformation and elimination pathways of levosimendan and its active metabolites. LS cannot be dialyzed, while the active metabolites can be dialyzed, but the dialysis filtration is low (8–23 ml/min), and the 4-h dialysis period has little effect on the total exposure of these metabolites. LS = levosimendan. LS cannot be dialyzed, while the active metabolites can be dialyzed, but the dialysis filtration is low (8–23 ml/min), and the 4-h dialysis period has little effect on the total exposure of these metabolites

current clinical consensus is still that patients with severe renal function injury (eGFR < 30 mL/min/1.73m^2) should not use levosimendan.

Impact of Levosimendan on Renal Function in Patients Undergoing Cardiac Surgery

Levosimendan presents a multifaceted influence on renal function across diverse cardiac surgery scenarios, highlighting its potential as a reno-protective agent within specific patient populations and surgical contexts (Table 1).

Impact of Levosimendan on Extracorporeal Circulation Cardiac Surgery and Coronary Artery Bypass Grafting (CABG)

Levosimendan demonstrates favorable effects in patients undergoing extracorporeal circulation cardiac surgery by enhancing postoperative cardiac output. It relaxes preglomerular resistance blood vessels, enhancing renal blood flow and eGFR without compromising renal oxygenation [30]. In a randomized placebo-controlled study, the levosimendan group exhibited significant increases in renal blood flow (12%, $p < 0.05$) and eGFR (21%, $p < 0.05$), along with reduced renal vascular resistance (18%, $p < 0.05$), while filtration fraction, renal oxygen consumption, and renal oxygen uptake remained unchanged. Levosimendan, safely administered in ESRD patients undergoing CABG alone [31], did not result in serious adverse reactions. However, it is important to note that renal function monitoring indicators were not part of the experimental assessment. Furthermore, in patients with impaired heart function undergoing extracorporeal circulation CABG, levosimendan did not exhibit any discernible effect on postoperative renal function [32]. Plasma creatinine, serum cystatin C, and urine NAG remained consistent between the placebo and levosimendan groups throughout the 5-day measurement period after surgery.

Impact of Levosimendan on Mitral Valve Surgery

Levosimendan exhibits a renal protective effect in patients with chronic kidney disease who undergo mitral valve surgery and experience perioperative myocardial dysfunction. In a multicenter randomized trial [33], the levosimendan group demonstrated a lower incidence of postoperative AKI and major complications compared to the placebo group. Additionally, another trial reported lower SCr levels and higher eGFR values in the levosimendan group undergoing mitral valve surgery with low ejection fraction [26]. Preoperative administration of levosimendan also protects renal function in high-risk patients undergoing heart valve surgery [34].

Table 1 Effect of levosimendan on renal function in patients undergoing cardiac surgery

Author	Year	Sample size (*N*)	Study design	Groups	Type of surgery	Renal parameter
Zemljic [40]	2007	40	RCT	LS vs standard therapy	Heart transplantation	eGFR↑; SCr ↓
Knezevic [39]	2014	94	RCT	LS vs standard therapy	Heart transplantation	eGFR↑; AKI ↓
Treskatsch [36]	2015	157	OS	LS (preoperative vs postoperative)	CABG,VR	Incidence postoperative renal dysfunction ↓; RRT↓
Guerrero-Orriach [44]	2020	60	RCT	LS vs dobutamine	CABG,VR	Renal function↑
Guerrero-Orriach [42]	2019	100	RCT	LS vs beta-agonist drugs	CABG,VR	Incidence of AKI kidney failure↓
Balzer [35]	2014	46	OS	LS (preoperative vs postoperative)	CABG,VR	Incidence postoperative renal dysfunction ↓
Tholén [43]	2021	28	RCT	LS vs placebo	CABG,VR	Renal blood flow↑; eGFR↑; renal vascular resistance↓
Bragadottir [3]	2013	30	RCT	LS vs placebo	CPB	Renal blood flow↑; eGFR↑; renal vascular resistance↓;
Guerrero [34]	2017	15	OS	LS (postoperative vs preoperative)	CPB、mitral valve surgery	SCr↑; BUN↓; AKIN ↑
Zangrillo [33]	2018	90	RCT	LS vs placebo	mitral valve surgery	AKI ↓
Baysal [26]	2014	128	RCT	LS vs standard therapy	mitral valve surgery	eGFR↑; SCr ↓

LS, levosimendan; *RCT*, randomized clinical trial; *OS*, observational study; *CABG*, coronary artery bypass graft; *VR*, valve reconstrution and/or replacement; *CPB*, cardiopulmonary bypass; *AKI*, incidence of acute kidney injury; *AKIN*, acute kidney injury network scores; *SCr*, serum creatinine; *BUN*, blood urea nitrogen; *eGFR*, estimating glomerular filtration rate; *RRT*, renal replacement therapy

The Impact of Levosimendan Administration Timing and Renal Function in Patients undergoing Bypass Grafting or Valve Surgery

Early administration of levosimendan is associated with improved renal function after cardiac surgery (bypass grafting and valve replacement) [35]. Patients who received levosimendan after anesthesia induction exhibited a significantly lower incidence of postoperative renal dysfunction compared to those who received levosimendan after admission to the ICU. A retrospective study investigating the timing of levosimendan administration on cardiac surgery outcomes revealed a marked reduction in the rates of in-hospital replacement therapy, mortality and morbidity among patients receiving preoperative levosimendan, as opposed to intraoperative or postoperative administration [36, 37].

Levosimendan's Impact in Patients Undergoing Myocardial Infarction Surgery

For patients with acute myocardial infarction-related interventricular septal rupture undergoing cardiac surgery, levosimendan did not significantly affect the incidence of renal function injury (≥ stage III) compared to the control group [38]. However, it is important to note that the condition of AMI-VSR is complex, and the recruited patients in the study might not fully represent the clinical reality, potentially introducing some limitations.

Levosimendan's Impact in Patients Undergoing Heart Transplant Surgery

Levosimendan demonstrates a positive impact on early renal function after heart transplantation [39]. In heart transplant recipients, the levosimendan group exhibited a greater increase in relative eGFR during the first week post-transplantation (62% vs. 12%, $p = 0.002$) and a lower incidence of AKI (28% vs. 6%, $p = 0.001$) compared to the standard treatment group. These beneficial effects extend to patients with advanced chronic heart failure awaiting heart transplantation, where levosimendan contributes to improved long-term renal function [40]. Furthermore, research indicates that levosimendan treatment does not pose a risk factor for AKI requiring renal replacement therapy in heart transplant patients with preserved renal function [41].

Acute Renal Injury After Surgery

Levosimendan demonstrates a protective effect on renal function in patients with low cardiac output syndrome undergoing cardiac surgery [42]. In patients with stable hemodynamics post-cardiac surgery, levosimendan dilates renal blood vessels, increases renal blood flow, and reduces renal vascular resistance. It significantly increases renal blood flow and decreases renal vascular resistance compared to placebo [43]. Additionally, levosimendan shows a a trend toward lower renal failure incidence in patients receiving it during surgery compared to those receiving it after surgery [44]. In a multicenter, randomized, placebo-controlled, phase 3 trial and a LEVO-CTS trial, although explicit reduction of postoperative AKI by levosimendan was not stated, it was demonstrated that the use of levosimendan is not associated with postoperative renal-replacement therapy or AKI [45, 46].

Conclusion

Levosimendan emerges as a reno-protective agent, improving renal outcomes through various mechanisms in heart failure, renal insufficiency, and diverse animal experiment conditions. Its positive impact extends to cardiac surgeries, AKI post-cardiac arrest, and sepsis-induced scenarios, underscoring its potential in managing renal complications across different clinical contexts.

Author Contribution All authors contributed to the study conceptualization and supervision. Data curation, formal analysis, and investigation were performed by Mengkai Lu, Yanna Yu, Nannan Shen, Haijiang Xia, and Jiana Shi. Funding acquisition was made by Xinwen Liu, Jiana Shi, Yongping Fu, and Ying Hu. The original draft of the manuscript was written by Xinwen Liu and Ying Hu; Xia Yongping and Ying Hu reviewed and edited the final manuscript. All authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Funding The authors gratefully acknowledge the financial support provided by National Natural Science Foundation of China, Youth Science Foundation Project (No. 72204073), Zhejiang Medical and Health Science and Technology (No. 2023KY491), the Science and Technology Projects in the Zhejiang Province Department of Education (No. Y202146979, Y202249053), Shaoxing Health Science and Technology Plan Project (No. KY2022066), and Zhejiang Medical Association Clinical Medicine Project (2023ZYC-A55, 2022ZYC-Z37), the Ministry of Education Industry-University Cooperative Education Project (No. 22087043124451).

Declarations

Ethics Approval Not applicable.

Consent to Participate Not applicable.

Consent to Publication Not applicable.

Competing Interests The authors declare no competing interests.

References

1. Yokoshiki H, Katsube Y, Sunagawa M, Sperelakis N. Levosimendan, a novel Ca2+ sensitizer, activates the glibenclamide-sensitive K+ channel in rat arterial myocytes. Eur J Pharmacol.

1997;333:249–59. https://doi.org/10.1016/s0014-2999(97)01108-4.
2. Pataricza J, Hõhn J, Petri A, Balogh A, Papp JG. Comparison of the vasorelaxing effect of cromakalim and the new inodilator, levosimendan, in human isolated portal vein. J Pharm Pharmacol. 2000;52:213–7. https://doi.org/10.1211/0022357001773715.
3. Chan CC, Lee KT, Ho WJ, Chan YH, Chu PH. Levosimendan use in patients with acute heart failure and reduced ejection fraction with or without severe renal dysfunction in critical cardiac care units: a multi-institution database study. Ann Intensive Care. 2021;11:27. https://doi.org/10.1186/s13613-021-00810-y.
4. Bouchez S, Fedele F, Giannakoulas G, et al. Levosimendan in acute and advanced heart failure: an expert perspective on posology and therapeutic application. Cardiovasc Drugs Ther. 2018;32:617–24. https://doi.org/10.1007/s10557-018-6838-2.
5. Damman K, Valente MA, Voors AA, O'Connor CM, van Veldhuisen DJ, Hillege HL. Renal impairment, worsening renal function, and outcome in patients with heart failure: an updated meta-analysis. Eur Heart J. 2014;35:455–69. https://doi.org/10.1093/eurheartj/eht386.
6. Cholley B, Bojan M, Guillon B, et al. Overview of the current use of levosimendan in France: a prospective observational cohort study. Ann Intensive Care. 2023;13:69. https://doi.org/10.1186/s13613-023-01164-3.
7. Honore PM, Redant S, Moorthamers S, et al. What should clinicians know about the renal effect and the mechanism of action of levosimendan? Expert Opin Drug Saf. 2021;20:1459–61. https://doi.org/10.1080/14740338.2021.1986483.
8. Puttonen J, Laine T, Ramela M, et al. Pharmacokinetics and excretion balance of OR-1896, a pharmacologically active metabolite of levosimendan, in healthy men. Eur J Pharm Sci : Off J Eur Fed Pharma Sci. 2007;32:271–7. https://doi.org/10.1016/j.ejps.2007.08.003.
9. Puttonen J, Kantele S, Kivikko M, et al. Effect of severe renal failure and haemodialysis on the pharmacokinetics of levosimendan and its metabolites. Clin Pharmacokinet. 2007;46:235–46. https://doi.org/10.2165/00003088-200746030-00004.
10. Damman K, Voors AA. Levosimendan improves renal function in acute decompensated heart failure: cause and clinical application. Editorial to "Levosimendan improves renal function in patients with acute decompensated heart failure: comparison with dobutamine by Yilmaz et al." Cardiovasc Drugs Ther. 2007;21:403–4. https://doi.org/10.1007/s10557-007-6070-y.
11. Honore PM, Gutierrez LB, Redant S, Kaefer K, Gallerani A, De Bels D. How levosimendan can improve renal function? Crit Care. 2019;23:331. https://doi.org/10.1186/s13054-019-2642-z.
12. Gamilla-Crudo AK, Kadambi PV, Prough DS. Test driving levosimendan as the new "kidney protector": first impressions. Crit Care Med. 2013;41:2445–6. https://doi.org/10.1097/CCM.0b013e3182963fdc.
13. Masarone D, Kittleson M, Pollesello P, Tedford RJ, Pacileo G. Use of levosimendan in patients with pulmonary hypertension: what is the current evidence? Drugs. 2023;83:195–201. https://doi.org/10.1007/s40265-022-01833-w.
14. Burkhoff D, Rich S, Pollesello P, Papp Z. Levosimendan-induced venodilation is mediated by opening of potassium channels. ESC heart failure. 2021;8:4454–64. https://doi.org/10.1002/ehf2.13669.
15. Grossini E, Molinari C, Pollesello P, et al. Levosimendan protection against kidney ischemia/reperfusion injuries in anesthetized pigs. J Pharmacol Exp Ther. 2012;342:376–88. https://doi.org/10.1124/jpet.112.193961.
16. Zager RA, Johnson AC, Lund S, Hanson SY, Abrass CK. Levosimendan protects against experimental endotoxemic acute renal failure. Am J Physiol Renal Physiol. 2006;290:F1453–62. https://doi.org/10.1152/ajprenal.00485.2005.
17. Tawfik MK, Makary S, Keshawy MM. Upregulation of antioxidant nuclear factor erythroid 2-related factor 2 and its dependent genes associated with enhancing renal ischemic preconditioning renoprotection using levosimendan and cilostazol in an ischemia/reperfusion rat model. Arch Med Sci : AMS. 2021;17:1783–96. https://doi.org/10.5114/aoms/111373.
18. Yakut N, Yasa H, Bahriye Lafci B, et al. The influence of levosimendan and iloprost on renal ischemia-reperfusion: an experimental study. Interact Cardiovasc Thorac Surg. 2008;7:235–9. https://doi.org/10.1510/icvts.2007.161356.
19. Gecit I, Kavak S, Yüksel MB, et al. Effect of short-term treatment with levosimendan on oxidative stress in renal tissues of rats. Toxicol Ind Health. 2014;30:47–51. https://doi.org/10.1177/0748233712451773.
20. Onody P, Aranyi P, Turoczi Z, et al. Levosimendan administration in limb ischemia: multicomponent signaling serving kidney protection. PLoS ONE. 2016;11:e0163675. https://doi.org/10.1371/journal.pone.0163675.
21. Tian L, Wang S, Zhao L, et al. Renoprotective effects of levosimendan on acute kidney injury following cardiac arrest via anti-inflammation, anti-apoptosis, and ERK activation. FEBS Open Bio. 2021;11:2236–44. https://doi.org/10.1002/2211-5463.13227.
22. Zhao L, Tian L, Wang S, Yang W, Lu X, Zhu C. Levosimendan in rats decreases acute kidney injury after cardiopulmonary resuscitation by improving mitochondrial dysfunction. Transl Androl Urol. 2021;10:3010–20. https://doi.org/10.21037/tau-21-443.
23. Yilmaz MB, Yalta K, Yontar C, et al. Levosimendan improves renal function in patients with acute decompensated heart failure: comparison with dobutamine. Cardiovasc Drugs Ther. 2007;21:431–5. https://doi.org/10.1007/s10557-007-6066-7.
24. Hou ZQ, Sun ZX, Su CY, et al. Effect of levosimendan on estimated glomerular filtration rate in hospitalized patients with decompensated heart failure and renal dysfunction. Cardiovasc Ther. 2013;31:108–14. https://doi.org/10.1111/1755-5922.12001.
25. Fedele F, Bruno N, Brasolin B, Caira C, D'Ambrosi A, Mancone M. Levosimendan improves renal function in acute decompensated heart failure: possible underlying mechanisms. Eur J Heart Fail. 2014;16:281–8. https://doi.org/10.1002/ejhf.9.
26. Zangrillo A, Alvaro G, Belletti A, et al. Effect of levosimendan on renal outcome in cardiac surgery patients with chronic kidney disease and perioperative cardiovascular dysfunction: a substudy of a multicenter randomized trial. J Cardiothorac Vasc Anesth. 2018;32:2152–9. https://doi.org/10.1053/j.jvca.2018.02.039.
27. Zhang H, Jiang L, Fu R, et al. Impact of levosimendan on efficacy and renal function in acute heart failure according to renal function: a perspective, multi-center, real-world registry. Front Cardiovasc Med. 2022;9:986039. https://doi.org/10.3389/fcvm.2022.986039.
28. Zorlu A, Yücel H, Yontar OC, et al. Effect of levosimendan in patients with severe systolic heart failure and worsening renal function. Arq Bras Cardiol. 2012;98:537–43. https://doi.org/10.1590/s0066-782x2012005000048.
29. Cui X, Wang Z, Dong X, et al. Comparative effectiveness and safety of milrinone and levosimendan as initial inotrope therapy in patients with acute heart failure with renal dysfunction. J Cardiovasc Pharmacol. 2022;79:781–90. https://doi.org/10.1097/FJC.0000000000001255.
30. Bragadottir G, Redfors B, Ricksten SE. Effects of levosimendan on glomerular filtration rate, renal blood flow, and renal oxygenation after cardiac surgery with cardiopulmonary bypass: a randomized placebo-controlled study. Crit Care Med. 2013;41:2328–35. https://doi.org/10.1097/CCM.0b013e31828e946a.
31. Atalay H, Temizturk Z, Altinsoy HB, et al. Levosimendan use increases cardiac performance after coronary artery bypass grafting in end-stage renal disease patients. Heart Surg Forum. 2016;19:E230–6. https://doi.org/10.1532/hsf.1426.

32. Ristikankare A, Pöyhiä R, Eriksson H, Valtonen M, Leino K, Salmenperä M. Effects of levosimendan on renal function in patients undergoing coronary artery surgery. J Cardiothorac Vasc Anesth. 2012;26:591–5. https://doi.org/10.1053/j.jvca.2012.01.035.
33. Guerrero-Orriach JL, Ariza-Villanueva D, Florez-Vela A, et al. Cardiac, renal, and neurological benefits of preoperative levosimendan administration in patients with right ventricular dysfunction and pulmonary hypertension undergoing cardiac surgery: evaluation with two biomarkers neutrophil gelatinase-associated lipocalin and neuronal enolase. Ther Clin Risk Manag. 2016;12:623–30. https://doi.org/10.2147/TCRM.S102772.
34. Guerrero Orriach JL, Galán Ortega M, Ramírez Fernandez A, et al. Assessing the effect of preoperative levosimendan on renal function in patients with right ventricular dysfunction. J Clin Monit Comput. 2017;31:227–30. https://doi.org/10.1007/s10877-016-9827-7.
35. Balzer F, Treskatsch S, Spies C, et al. Early administration of levosimendan is associated with improved kidney function after cardiac surgery - a retrospective analysis. J Cardiothorac Surg. 2014;9:167. https://doi.org/10.1186/s13019-014-0167-8.
36. Treskatsch S, Balzer F, Geyer T, et al. Early levosimendan administration is associated with decreased mortality after cardiac surgery. J Crit Care. 2015;30(859):e1-6. https://doi.org/10.1016/j.jcrc.2015.03.008.
37. Schiefenhövel F, Berger C, Penkova L, et al. Influence of timing of levosimendan administration on outcomes in cardiac surgery. Front Cardiovasc Med. 2023;10:1213696. https://doi.org/10.3389/fcvm.2023.1213696.
38. Li ZS, Wang K, Pan T, et al. The evaluation of levosimendan in patients with acute myocardial infarction related ventricular septal rupture undergoing cardiac surgery: a prospective observational cohort study with propensity score analysis. BMC Anesthesiol. 2022;22:135. https://doi.org/10.1186/s12871-022-01663-z.
39. Knezevic I, Poglajen G, Hrovat E, Oman A, Pintar T, Wu JC, et al. The effects of levosimendan on renal function early after heart transplantation: results from a pilot randomized trial. Clin Transplant. 2014;28:1105–11. https://doi.org/10.1111/ctr.12424.
40. Zemljic G, Bunc M, Yazdanbakhsh AP, Vrtovec B. Levosimendan improves renal function in patients with advanced chronic heart failure awaiting cardiac transplantation. J Cardiac Fail. 2007;13:417–21. https://doi.org/10.1016/j.cardfail.2007.03.005.
41. M'Pembele R, Roth S, Stroda A, et al. Risk factors for acute kidney injury requiring renal replacement therapy after orthotopic heart transplantation in patients with preserved renal function. Journal of clinical medicine. 2021;10. https://doi.org/10.3390/jcm10184117.
42. Guerrero Orriach JL, Navarro Arce I, Hernandez Rodriguez P, et al. Preservation of renal function in cardiac surgery patients with low cardiac output syndrome: levosimendan vs beta agonists. BMC Anesthesiol. 2019;19:212. https://doi.org/10.1186/s12871-019-0888-2.
43. Tholén M, Ricksten SE, Lannemyr L. Effects of levosimendan on renal blood flow and glomerular filtration in patients with acute kidney injury after cardiac surgery: a double blind, randomized placebo-controlled study. Critical care (London, England). 2021;25:207. https://doi.org/10.1186/s13054-021-03628-z.
44. Guerrero-Orriach JL, Malo-Manso A, Ramirez-Aliaga M, et al. Renal and neurologic benefit of levosimendan vs dobutamine in patients with low cardiac output syndrome after cardiac surgery: clinical trial FIM-BGC-2014-01. Front Pharmacol. 2020;11:1331. https://doi.org/10.3389/fphar.2020.01331.
45. Mehta RH, Leimberger JD, van Diepen S, et al. Levosimendan in patients with left ventricular dysfunction undergoing cardiac surgery. N Engl J Med. 2017;376:2032–42. https://doi.org/10.1056/NEJMoa1616218.
46. Jawitz OK, Stebbins AS, Raman V, et al. Association between levosimendan, postoperative AKI, and mortality in cardiac surgery: insights from the LEVO-CTS trial. Am Heart J. 2021;231:18–24. https://doi.org/10.1016/j.ahj.2020.10.066.