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REVIEW ARTICLE

Renal Effects of Levosimendan: A Consensus Report

Mehmet B. Yilmaz · Elena Grossini · José C. Silva Cardoso · István Édes · Francesco Fedele · Piero Pollesello · Matti Kivikko · Veli-Pekka Harjola · Julia Hasslacher · Alexandre Mebazaa · Andrea Morelli · Jos le Noble · Anders Oldner · Ignacio Oulego Erroz · John T. Parissis · Alexander Parkhomenko · Gerhard Poelzl · Sebastian Rehberg · Sven-Erik Ricksten · Luís M. Rodríguez Fernández · Markku Salmenperä · Mervyn Singer · Sascha Treskatsch · Bojan Vrtovec · Gerhard Wikström

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Abstract Renal dysfunction is common in clinical settings in which cardiac function is compromised such as heart failure, cardiac surgery or sepsis, and is associated with high morbidity and mortality. Levosimendan is a calcium sensitizer and potassium channel opener used in the treatment of acute heart failure. This review describes the effects of the inodilator levosimendan on renal function. A panel of 25 scientists and clinicians from 15 European countries (Austria, Finland, France, Hungary, Germany, Greece, Italy, Portugal, the Netherlands, Slovenia, Spain, Sweden, Turkey, the United Kingdom, and Ukraine) convened

M. B. Yilmaz (✉)
Department of Cardiology, Cumhuriyet University School of Medicine, Sivas, Turkey
e-mail: cardioceptor@gmail.com

E. Grossini
Laboratorio di Fisiologia, Dipartimento di Medicina Traslazionale, Università degli Studi del Piemonte Orientale A. Avogadro, Piemonte, Italy
e-mail: grossini@med.unipmn.it

J. C. Silva Cardoso
Faculdade de Medicina, Alameda Prof. Hernâni Monteiro, Universidade do Porto, Porto, Portugal
e-mail: silvacardoso30@gmail.com

I. Édes
Institute of Cardiology, Medical and Health Science Center, University of Debrecen, Debrecen, Hungary
e-mail: edesi@med.unideb.hu

F. Fedele · A. Morelli
Department of Cardiovascular, Respiratory, Nephrological, and Geriatric Sciences, La Sapienza University of Rome, Rome, Italy

F. Fedele
e-mail: francesco.Fedele@uniroma1.it

A. Morelli
e-mail: andrea.morelli@uniroma1.it

P. Pollesello · M. Kivikko
Cardiology and Critical Care, Orion Pharma, Espoo, Finland

P. Pollesello
e-mail: piero.pollesello@orionpharma.com

M. Kivikko
e-mail: matti.kivikko@orionpharma.com

V.-P. Harjola
Departments of Cardiology, Helsinki University Hospital, Helsinki, Finland
e-mail: Veli-Pekka.Harjola@hus.fi

J. Hasslacher
Internistische Intensiv- und Notfallmedizin, Universitätsklinik für Innere Medizin, Innsbruck, Austria
e-mail: julia.hasslacher@i-med.ac.at

A. Mebazaa
Department of Anaesthesia and Intensive Care, INSERM UMR 942, Lariboisière Hospital, University of Paris, Paris, France
e-mail: alexandre.mebazaa@lrb.aphp.fr

J. le Noble
Department of Intensive Care, VieCuri Medical Center, Venlo, The Netherlands
e-mail: jlenoble@viecuri.nl

A. Oldner
Department of Physiology & Pharmacology, Section of Anaesthesiology & Intensive CareMedicine, Karolinska Institute, Stockholm, Sweden
e-mail: anders.oldner@ki.se

I. Oulego Erroz · L. M. Rodríguez Fernández
Department of Pediatrics, Complejo Asistencial Universitario de León, León, Spain

I. Oulego Erroz
e-mail: ignacio.oulego@gmail.com

L. M. Rodríguez Fernández
e-mail: luism@arrakis.es

J. T. Parissis
Heart Failure Unit, Attikon University Hospital, Athens, Greece
e-mail: jparissis@yahoo.com

and reached a consensus on the current interpretation of the renal effects of levosimendan described both in non-clinical research and in clinical study reports. Most reports on the effect of levosimendan indicate an improvement of renal function in heart failure, sepsis and cardiac surgery settings. However, caution should be applied as study designs differed from randomized, controlled studies to uncontrolled ones. Importantly, in the largest HF study (REVIVE I and II) no significant changes in the renal function were detected. As it regards the mechanism of action, the opening of mitochondrial K_{ATP} channels by levosimendan is involved through a preconditioning effect. There is a strong rationale for randomized controlled trials seeking beneficial renal effects of levosimendan. As an example, a study is shortly to commence to assess the role of levosimendan for the prevention of acute organ dysfunction in sepsis (LeoPARDS).

Keywords Levosimendan · Renal dysfunction

Abbreviations

HF	Heart failure
AHF	Acute heart failure
GFR	Glomerular filtration rate
eGFR	Estimated glomerular filtration rate
NYHA	New York Heart Association class
KATP channel	Adenosine triphosphate-dependent potassium channel
I/R	Ischemia-reperfusion
NAG	N-acetyl-β-glucosaminidase
L-NAME	Nω-nitro-L-arginine methyl ester
5-HD	5-hydroxydecanoate
RBF	Renal blood flow
CABG	Coronary artery bypass grafting
MAP	Mean arterial pressure
RPV	Renal parenchymal volume

Introduction

Renal dysfunction is common in patients with heart failure (HF) [1] and other clinical settings in which cardiac function is compromised such as cardiac surgery or sepsis [2, 3] and is associated with high morbidity and mortality. Due to the complex interactions underlying this cardiorenal syndrome, the kidneys can be affected in both the short- and long-term. Elevations of serum urea and creatinine levels are often encountered in congestive HF, secondary to reductions in renal blood flow and/or elevations in central venous pressure leading to a reduction in glomerular filtration rate (GFR). Conversely, impaired renal function has a significant impact on the prognosis of patients with compromised heart function. For instance, in a broad spectrum of patients with chronic HF in the CHARM study [4], renal dysfunction was independently associated with increased risk of death, cardiovascular death, and hospitalization due to HF. In advanced chronic HF, renal impairment was a stronger predictor of mortality than either left ventricular ejection fraction or New York Heart Association class [5].

Levosimendan is a calcium sensitizer and adenosine triphosphate-dependent potassium (K_{ATP}) channel opener developed for treating acute HF. Its positive inotropic, vasodilating and cardioprotective properties have been extensively investigated in experimental studies [6] and clinical trials [7] not only in the context of HF but also in surgery

A. Parkhomenko
Strazhesko Institute of Cardiology, National Scientific Centre, Kiev, Ukraine
e-mail: aparkhomenko@yahoo.com

G. Poelzl
Department of Cardiology, Medical University Innsbruck, Innsbruck, Austria
e-mail: gerhard.poelzl@uki.at

S. Rehberg
Department of Anesthesiology, Intensive Care and Pain Medicine, University of Muenster, Muenster, Germany
e-mail: Sebastian_Rehberg@ukmuenster.de

S.-E. Ricksten
Department of Cardiothoracic Anesthesia and Intensive Care, Sahlgrenska University Hospital, Gothenburg, Sweden
e-mail: sven-erik.ricksten@aniv.gu.se

M. Salmenperä
Department of Anesthesiology and Intensive Care Medicine, Helsinki University Hospital, Helsinki, Finland
e-mail: markku.salmenpera@hus.fi

M. Singer
Intensive Care Medicine, University College London, London, UK
e-mail: m.singer@ucl.ac.uk

S. Treskatsch
Department of Anesthesiology and Intensive Care Medicine, Charité - University Medicine Berlin, Campus Charité Mitte and Campus Virchow-Klinikum, Berlin, Germany
e-mail: sascha.treskatsch@charite.de

B. Vrtovec
Advanced Heart Failure and Transplantation Center, Department of Cardiology, Ljubljana University Medical Center, Ljubljana, Slovenia
e-mail: bojan.vrtovec@gmail.com

G. Wikström
Kardiologkliniken, Akademiska Sjukhuset, Uppsala, Sweden
e-mail: gerhard.wikstrom@medsci.uu.se

settings and in critical care patients. Levosimendan increases myocardial contractility, reduces filling pressure, and dilates arterial, venous and coronary vessels [6]. In contrast to other inotropic agents, the enhanced cardiac contractility seen with levosimendan is not accompanied by large increases in oxygen consumption [8]. Levosimendan has an active metabolite, OR-1896, that has similar pharmacological properties to levosimendan. As this metabolite is formed and eliminated slowly, it offers at least 7 days of added benefit [9].

This paper examines available data on the effect of levosimendan on renal function also in comparison with other available inotropes and vasodilators.

Methods

In the systematic analysis of the literature data sources were PubMed, Index Medicus, Excerpta Medica, Reference Update, BIOSIS, Science Citation Index. Pertinent papers were independently identified by two trained investigators (updated October 20, 2012). Papers and abstracts found by searching (levosimendan AND (renal OR kidney*)) were selected according to the search strategy described in Figure 1. For the synthesis of the data a panel of 25 scientists and clinicians from 15 European countries (Austria, Finland, France, Hungary, Germany, Greece, Italy, Portugal, the Netherlands, Slovenia, Spain, Sweden, Turkey, the United Kingdom, and Ukraine) convened on October 25, 2012. The members of the panel were invited on the basis of their authorship of scientific papers which described the renal effects of levosimendan. Even if a paper did describe neutral or negative effects the first author was invited to attend and discuss his/her data. The panel reached a consensus on the current interpretation of the renal effects of levosimendan and its putative mechanisms of action.

Evidence from Animal Models

Pre-clinical data on renal perfusion effects are scant and sometimes contradictory (Table 1). In healthy dogs, levosimendan increased renal medullary blood flow [10], yet did not affect either the renal macro- or the micro-circulation under septic conditions in pigs and rabbits [11, 12]. In these studies, levosimendan improved cardiac function but also reduced arterial blood pressure; both of these factors will influence renal perfusion. Grossini et al. [13] investigated the renal effects of levosimendan in anesthetized pigs undergoing an ischemia-reperfusion injury, under conditions of 'renal isolation'. Here, direct administration into the renal artery during 90 min of ischemia did not influence the subsequent change in renal blood flow on reperfusion [13].

The rationale for the use of levosimendan in lipopolysaccharide-induced acute renal failure was the assumption that calcium sensitization specifically offsets sepsis-induced reductions in myocardial function, and thus improves systemic and renal hemodynamics and mitigates the lipopolysaccharide-induced inflammatory state. Studies in endotoxemic mice [14] and ovine septic shock [15] found beneficial renal effects in conjunction with improved hemodynamics rather than immunomodulation [14]. In an endotoxemic pig model, where levosimendan did not improve hemodynamics, no beneficial effects on renal function were observed [15]. These findings are, however, not consistent.

In a study of porcine endotoxemia levosimendan markedly improved cardiac output and splanchnic but not renal blood flow [12].

Ischemia-reperfusion (I/R) injury in the kidneys is a significant problem in critically ill patients, e.g. after hemorrhage and/or trauma, as it is an important cause of acute renal failure due to oxidative, inflammatory and apoptotic mechanisms. I/R injury can result in the development of a marked systemic inflammatory response and multiple organ dysfunction,

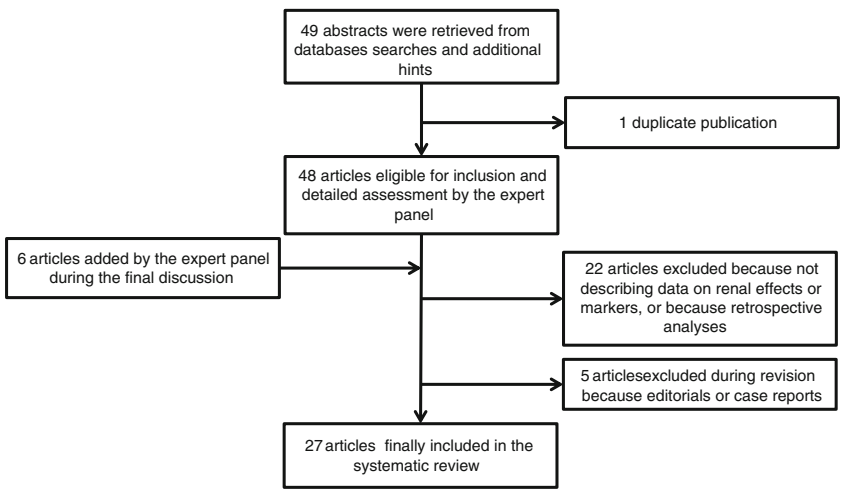

Fig. 1 Flow diagram for selection of the articles included in this systematic review

Table 1 Effects of levosimendan or its metabolite OR-1896 on renal tissue and/or function in in vivo animal experiments

Study	Animal model	Disease model	Comparator	Main levosimendan effects on renal tissue and/or function
Grossini [13]	Pig	Renal I/R	Levosimendan without or with Custodiol® vs placebo	Better protection against renal I/R injury in terms of antioxidant, anti-apoptotic and pro-survival actions, and improvement of renal function (creatinine clearance, plasma creatinine, microalbuminuria, albumin/creatinine ratio). Role of mitochondrial K_{ATP} channels and NO
Rehberg [42]	Sheep	Sepsis	Vasopressin and norepinephrine ± levosimendan	Improved renal function (surrogate parameters: creatinine, plasma urea, dieresis, urinary protein/creatinine ratio)
Yakut [23]	Rabbit	Renal I/R	Levosimendan vs placebo or iloprost	More pronounced reduction in renal I/R injury
Zager [14]	Mouse	Endotoxemic acute renal failure	Levosimendan vs placebo	Protection against endotoxemic acute renal failure due to vasoactive effects
Faivre [11]	Rabbit	Sepsis	Levosimendan with vasopressin vs levosimendan with norepinephrine	No altered systolic or diastolic renal blood flow or cortical or medullary perfusion
Oldner [12]	Pig	Sepsis	Levosimendan vs placebo	Renal blood flow unaffected
Pagel [10]	Dog	Healthy	Levosimendan vs pimobendan or milrinone	Greater increase in blood flow to the renal medulla and decreased renal medullary and cortical vascular resistance
Gecit [50]	Rat	Enzyme activities in healthy rats	Levosimendan vs placebo	Reduction of oxidative stress
Louhelainen [24]	Rat	Salt-induced hypertension	OR 1896 vs placebo	No effects on albuminuria or tissue morphology
Chew [51]	Pig	Sepsis	Levosimendan vs placebo	No effects on renal and liver function (serum creatinine, urea, bilirubin, AST, ALT)

I/R ischemia/reperfusion; *Custodiol®* multi-organ histidine-tryptophan-ketoglutarate preservation solution; *NO* nitric oxide; *AST* aspartate aminotransferase; *ALT* alanine aminotransferase

leading to an approximate 30-40 % mortality rate [16, 17]. The anti-inflammatory and anti-apoptotic properties of levosimendan make it an interesting candidate for treatment of this condition. Indeed it has provided protection through a preconditioning effect [18–20] and a reduction in inflammatory and oxidative stress profiles [21, 22]. In a rabbit renal I/R injury model, a levosimendan infusion commenced 30-min pre-ischaemia provided similar renal protection as iloprost against oxidative stress [23]. Likewise, in a pig model, levosimendan infused into the renal artery during 90 min of ischemia followed by 120-min of reperfusion provided renal protection with a reduction in renal damage (N-acetyl-β-glucosaminidase [NAG]), oxidative stress (malonyldialdehyde) and apoptosis [13]. Renal function was preserved to a higher degree, and cell survival and antioxidant systems were activated to a greater extent. These benefits could be prevented by pre-treatment with the non-specific nitric oxide synthase blocker, N^{ω}-nitro-L-arginine methyl ester (L-NAME), or with the mitochondrial K_{ATP} channel inhibitor, 5-hydroxydecanoate (5-HD). Finally, using a model of salt-sensitive hypertensive Dahl/Rapp rats, the levosimendan metabolite OR-1896 prevented salt-induced cardiovascular mortality and ameliorated cardiac hypertrophy and function, but without providing any significant renal protection [24].

Consensus Opinion on Current Preclinical Data Regarding Renal Effects of Levosimendan

Data obtained in pre-clinical studies suggest that the anti-oxidant and anti-apoptotic effects of levosimendan could be related to protection against renal ischemic reperfusion injury. As seen in the cardiac muscle, the opening of the mitochondrial K_{ATP} channels may be involved through a preconditioning effect, and nitric oxide may play a significant role. All in all, animal data on the effect of Levosimendan on renal function are not consistent. In fact, experimental data obtained in different renal injury models are quite different, but are still consistent within the individual models. In septic models there seems to be predominant improvements in hemodynamics by levosimendan, whereas the organ-protective effect of the drug dominates in case of I/R injury. It should be noted there are no experimental data on renal effects in animal models of heart failure. Animal data on the

effect of levosimendan on renal function do not provide definitive evidence as to whether the observed reno-protective effects are mediated by increases in renal perfusion and/or GFR, or other mechanisms.

Clinical Evidence

Decompensated Heart Failure

Renal effects of levosimendan have been evaluated in several clinical studies in patients with severe systolic HF. The LIDO randomized controlled trial compared levosimendan and dobutamine in patients with low-output HF [25]. Apart from an overall clinical outcome benefit, renal function (defined as a decrease in serum creatinine) improved over 24 h in the levosimendan arm, as compared to the control group (−9 and −1 μM/l, respectively, p=0,03). In parallel, the non-randomized PORTLAND study assessed the efficacy and safety of levosimendan in the treatment of acute HF in everyday clinical practice [26]. Diuresis rapidly improved in previously oliguric patients after initiation of levosimendan, along with a reduction in serum creatinine levels that persisted on day five. We must highlight, however, that in the PORTLAND study there was not a control arm.

In a single-centre prospective study of patients with advanced chronic HF awaiting cardiac transplantation, at 3 months there was significant improvement in creatinine clearance in the levosimendan arm, with little or no change in the control group [27]. A fall in serum creatinine levels ≥0.5 mg/dL occurred in 50 % of levosimendan patients, compared to 10 % of controls (p=0.005).

Yilmaz et al. [28] investigated 88 consecutive patients with acutely decompensated HF (NYHA III-IV) who required inotropic therapy. Patients were randomized to receive either levosimendan or dobutamine. While left ventricular ejection fraction increased significantly in both treatment groups, the levosimendan group showed significant improvement in GFR after 24 h (+15.3 %), while the dobutamine arm showed no difference (−1.33 %). At 72 h, GFR was significantly increased from baseline levels in levosimendan- (+45.45 %), but not in dobutamine- (+0.09 %) treated patients, although both drugs improved 24-h urinary output. The same group also compared the effects of levosimendan and dobutamine on right ventricular function in 40 consecutive patients with severe chronic biventricular HF [29]. Again, levosimendan improved both 24-h urine output and creatinine levels, whereas dobutamine produced only a small increase in urine output and no improvement in creatinine levels. Levosimendan patients also required less diuretic therapy and were discharged sooner.

Zorlu et al. [30] studied the effect of levosimendan in patients with severe systolic heart failure and worsening renal function and subclassified the patients into those without and with worsening renal function, defined as an increase in serum creatinine >0.3 mg/dL. Levosimendan significantly improved renal function (creatinine, GFR) in those with worsening renal function but not in those with stable renal function.

Finally, Caira et al. [31] showed that levosimendan improves renal function, systemic and renal hemodynamic parameters in patients with acute heart failure and moderate renal impairment by measuring renal blood flow, glomerular filtration rate, blood urea nitrogen, creatinine, urinary output, sodium excretion and plasma sodium.

During a late revision of this text the results of the phase III studies REVIVE I and II were published [32] containing further data on the effect of levosimendan on renal function: worsening of renal function occurred in 12/350 patients in the levosimendan arms, and 16/350 patients in the placebo arm (n.s.), thus no significant improvement of renal function was found.

Cardiac Surgery

A limited number of clinical studies assessed the renal effects of levosimendan in the context of cardiac surgery. Bragadottir et al. [33] investigated the short-term effects of levosimendan on renal blood flow, GFR, renal oxygen consumption, and oxygenation in 30 patients with normal preoperative serum creatinine levels after uncomplicated surgery. Compared to placebo, levosimendan increased cardiac output, promoted renal vasodilatation and increased renal blood flow and GFR, suggestive of selective dilatation of pre-glomerular resistance vessels. The renal oxygen supply–demand relationship was however unaffected.

Levosimendan facilitated the weaning from the cardiopulmonary bypass in a placebo-controlled study in 60 patients with left ventricular ejection fraction <50 % undergoing coronary artery bypass grafting surgery [34]. In a substudy of the same population the postoperative renal function was assessed [35] and no significant differences between levosimendan and placebo groups were detected in terms of creatinine, cystatin C and urine N-acetyl-β-glucosaminidase (NAG). Eight (26.6 %) levosimendan patients and 13 (43.3 %) placebo patients experienced renal incidents (as defined by the authors), though this difference did not reach statistical significance (p=0.167).

Four additional studies on the use of levosimendan in cardiac surgery included some benefits on renal endpoints (mainly postoperative renal dysfunction or failure). Al-Shawaf et al. [36] studied type 2 diabetic patients with depressed myocardial function who underwent elective surgery for coronary artery disease. Among the postoperative events, renal dysfunction was noticed in 2/14 patients treated with levosimendan vs 5/16 patients treated with milrinone. Alvarez et al. [37] compared levosimendan to dobutamine in cardiac surgery patients developing low cardiac output syndrome. The authors reported 1/15 renal failure in the levosimendan group vs 0/15 in the

Table 2 Clinical reports of the effects of levosimendan on renal function

Study	Setting	Sample size	Study type	Cohorts/comparator(s)	Levosimendan effects on renal markers, function or status
Cardiology settings					
Follath [25]	Low-output HF	200	Blinded	Levosimendan *vs* placebo (1:1)	↓serum creatinine
Cardoso [26]	Acute systolic HF	129	Consecutive	Levosimendan on top of standard of care	rapid ↑ urine output, ↓serum creatinine for 5 day
Yilmaz [29]	Severe low-output systolic HF	40	Open-label	Levosimendan *vs* dobutamine (2:1)	↓creatinine, ↑ urine output
Yilmaz [28]	Acutely decompensated HF	88	Blinded	Levosimendan *vs* dobutamine (2:1)	↑GFR
Zorlu [30]	Severe acutely decompensated systolic HF	45	Consecutive	Levosimendan in worsening or non-worsening renal function	↓creatinine, ↑ GFR, in patients with worsening renal function
Zemljic [27]	Advanced chronic HF	40	Blinded	Levosimendan *vs* placebo (1:1)	↓creatinine, ↑creatinine clearance over 3 months
Caira [31]	Acute HF	10	Consecutive	All on levosimendan	↑renal blood flow velocity, ↑renal artery output
Packer [32]	Acute HF (REVIVE I and II)	700	Blinded	Levosimendan *vs* placebo on top of standard of care(1:1)	↔worsening of renal function
ICU settings					
Hasslacher [52]	Acute HF and septic shock	25	Consecutive, all received LS for 2 h	Acute HF (16) and septic cardiac failure (9) patients	↔ urea, ↔ creatinine, ↔ serum cystatin
Morelli [40]	Septic shock	30	Blinded	Levosimendan versus dobutamine (1:1)	↑creatinine clearance, ↑ urinary output
Operative settings					
Bragadottir [33]	Uncomplicated surgery, no HF	30	Blinded	Levosimendan *vs* placebo	↑ renal vasodilatation, ↑ renal blood flow. ↑ GFR, ↔ renal oxygen demand/supply
Ristikankare [35]	On-pump CABG	60	Blinded	Levosimendan *vs* placebo (1:1)	↔ serum cystatin C, ↔plasma creatinine, ↔ N-acetyl-β-glucosaminidase, ↔ GFR
Al-Shawaf [36]	Type-2 diabetic patients undergoing elective coronary artery surgery	30	Blinded	Levosimendan *vs* milrinone (1:1)	↔ (numerically lower) postoperative renal dysfunction (as per author definition)
Alvarez [37]	Scheduled cardiac surgery with cardiopulmonary bypass	30	Blinded?	Levosimendan *vs* dobutamine (1:1)	↔ risk of postoperative acute renal failure (as per author definition)
Barisin [38]	Off-pump CABG	31	Blinded	Levosimendan low dose or high dose *vs* placebo (1:1:1)	postoperative renal failure (no events occurred)
Levin [39]	Postoperative low cardiac output syndrome	137	Blinded	Levosimendan *vs* dobutamine (1:1)	↓ risk of postoperative acute renal failure (defined as ↑ creatinine >50 %)
Meta-analysis					
Landoni [7] based on 4 studies [36–39]	Cardiac surgery	228 (from 4 studies)	Meta-analysis	Levosimendan *vs* various comparators	↓ risk of postoperative acute renal failure (as per author definition)

CABG coronary artery bypass grafting; *GFR* glomerular filtration rate

comparator group. Barisin et al. [38] did not notice any post-operative acute renal failure event in either the levosimendan or placebo arm when the treatment was administered preoperatively in patients undergoing off-pump CABG. Finally, Levin et al. [39] reported 5/69 and 21/68 episodes of renal failure in the levosimendan and dobutamine arms of their randomized study on the treatment of patients who develop post-operative low cardiac output syndrome after CABG with cardiopulmonary bypass. The data of these four studies are summarized in a recent meta-analysis by Landoni et al. [7].

Sepsis

A study by Morelli et al. reports data on the renal effect of levosimendan in septic patients. [40] Patients with persisting left ventricular dysfunction related to septic shock after 48 h of conventional treatment including dobutamine (5 μg/kg per minute) were randomized after 48 h of conventional treatment to receive a 24-h infusion of either levosimendan (0.2 μg/kg per min, n=15) or dobutamine (5 μg/kg per min, n=13). Among other effects, levosimendan increased gastric mucosal flow, creatinine clearance, and urinary output while it decreased lactate concentrations.

Consensus Opinion on the Renal Effects of Levosimendan in a Clinical Setting

Most reports on the effect of levosimendan indicate an improvement of renal function in heart failure, sepsis and cardiac surgery settings (Table 2). However, caution should be applied as study designs differed from randomized, controlled studies to uncontrolled ones. These studies are mainly confined to patients with severe systolic HF and some degree of renal dysfunction, and provide additional information on renal biomarkers and function. Importantly, in the largest HF study (REVIVE I and II) no significant changes in the renal function were detected. Data from the surgical setting are also heterogeneous, ranging from no effect in patients with normal renal function to clinical benefit in those requiring mechanical assist devices for post-cardiotomy HF. Larger studies in different clinical settings (mainly acute HF, septic shock, cardiac surgery) are warranted to clarify the renal effects of levosimendan.

Potential Mechanisms of Renal Protection

The K_{ATP} channel opening effects of levosimendan in vascular smooth muscle is linked to organ-preserving effects in several preclinical and clinical investigations [6]. As these channels are present in organ beds other than the myocardium, this mechanism may offer organ protection extending beyond the heart. Together with its hemodynamic effects, Morelli et al. [41] suggested levosimendan may also be protective for lung, kidney, liver, gastrointestinal mucosa, brain and vascular endothelium.

Timely intervention with levosimendan may reverse the ongoing processes of renal dysfunction through several protective mechanisms involving macro- or microcirculation. Renal blood flow depends on renal vascular resistance, as well as, arterial and venous pressures. Of note, central venous pressure is an important independent predictor of eGFR in patients with HF [42].

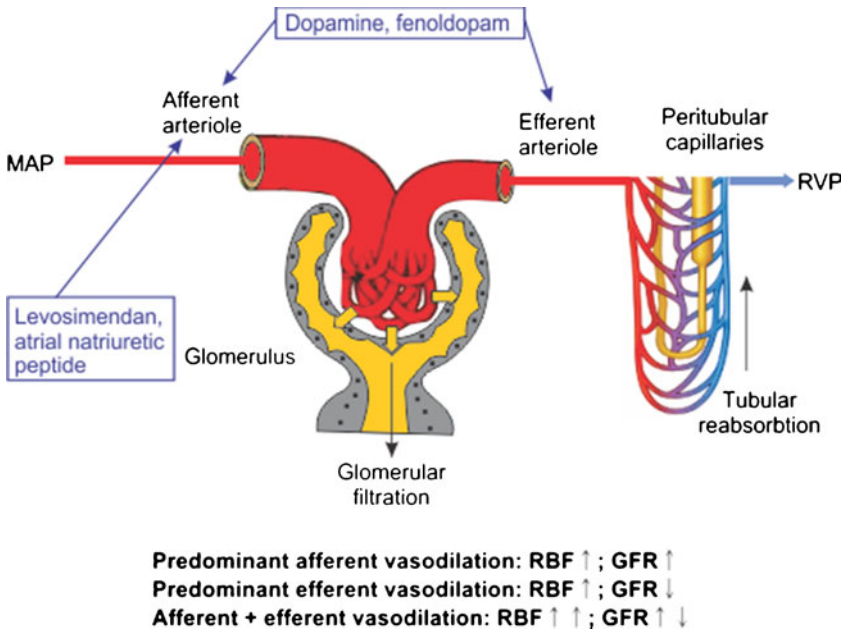

Fig. 2 Differential effects of renal vasodilators on preglomerular (afferent arteriole) and postglomerular (efferent arteriole) vascular resistance sections. *RBF* renal blood flow; *MAP* mean arterial pressure; *RPV* renal parenchymal volume; *GFR* glomerular filtration rate

When compared to traditional inotropes, levosimendan provides functional improvement of the right ventricle and significant reductions in right-sided pressures, including central venous and pulmonary artery wedge pressures [43–45]. This potentially alleviates the increased renal vein pressure that may impair renal function through a decreased perfusion pressure and a decrease in GFR.

Furthermore, Bragadottir et al. [33] found that levosimendan induced a preglomerular vasodilation (with an increase in both RBF and GFR), suggesting that the potential beneficial renal effects of levosimendan in patients with heart failure and impaired renal function, may not only be caused by an increase in cardiac output, but also by a specific renal vasodilatory action. In fact, K_{ATP} channels are also present in afferent arterioles [46] and may play a role in the effects of levosimendan on renal blood flow (see Fig. 2). In contrast, in cardiac surgery patients, dopamine dilates both pre- and postglomerular resistance vessels, with a pronounced increase in renal blood flow but with no change in GFR [47].

With regard to the microcirculation, levosimendan may augment renal perfusion via vasodilatation arising from its K_{ATP} channel agonism. Furthermore, it may reverse angiotensin-2-mediated mesangial cell contraction [14], thereby increasing glomerular capillary surface area [48]. This provides a further rationale for the use of levosimendan in septic shock where renal vasoconstriction is mediated at least in part by angiotensin-2 [40]. Other potentially beneficial mechanisms within the kidney relate to preconditioning, anti-inflammatory and anti-apoptotic effects [6].

Future Studies

The panel agreed that it would be useful, although a very demanding task, to compare systematically the renal effects of other i.v. drugs used in acute cardiac care (in all settings) such as recombinant natriuretic peptides, nitrates, other K_{ATP} channels openers, catecholamines, and phosphodiesterase inhibitors (see the recent data associating milrinone to an increase of acute kidney injury risk in cardiac surgery [49]).

Ideally, large randomized controlled trials seeking beneficial renal effects of levosimendan in different clinical settings should be performed.

In this regard, it is worth to mention that a 500-patient study sponsored by the NIHR-EME program is shortly to commence in the UK (led by Dr Anthony Gordon in conjunction with the Imperial Clinical Trials Unit) assessing the role of Levosimendan for the Prevention of Acute oRgan Dysfunction in Sepsis (LeoPARDS). This double-blind randomised placebo-controlled trial will test if levosimendan, when added to normal care, can reduce multiple organ failure, which will then hopefully lead to better outcomes and survival rates for patients.

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