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REVIEW
Heart failure/cardiomyopathy

Rationale, experimental data, and emerging clinical evidence on early and preventive use of levosimendan in patients with ventricular dysfunction

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Acute ventricular dysfunction (AVD) is a complex condition with substantial morbidity and mortality, still featuring unique therapeutic challenges. Levosimendan is a calcium sensitizer and ATP-dependent potassium channel opener that was developed as an inodilating drug for the treatment of acute heart failure and cardiogenic shock. Differently from other more widely used inotropic agents, levosimendan has some exclusive characteristics, in terms of mechanisms of action, pharmacodynamic profile, and haemodynamic effects. This may have important clinical implications. In particular, in patients with AVD or in patients with pre-existing severe ventricular impairment undergoing planned myocardial stress, the administration of levosimendan before the onset of overt symptoms or before cardiovascular therapeutic procedures may have the potential to bridge the patient through the critical phase. In this review, we will focus on the rationale, the existing experimental data, and the emerging clinical experience supporting an early, even preventive use of levosimendan in severe ventricular dysfunction, beyond its recognized indications.

Keywords Levosimendan • Acute ventricular dysfunction • Myocardial oxygen consumption • Inotropic agents

Introduction

The aetiology of acute ventricular dysfunction (AVD) and of its clinical manifestations, acute heart failure (AHF) and cardiogenic shock, is mainly ischaemic, with acute coronary syndromes (ACS) and chronic coronary artery disease accounting for >50% of cases.[1,2] In AVD due to other aetiologies (arrhythmic, valvular, infective, etc.), myocardial ischaemia may still occur due to a mismatch between oxygen demand and supply, regardless of the presence of significant coronary artery stenosis.[1,2] Myocardial ischaemia, in turn, contributes to cardiac cell death, and it further impairs systolic and diastolic functions, resulting in a vicious cycle leading to pulmonary congestion and/or low output cardiac syndrome (*Figure 1*). Thus, irrespective of its cause, myocardial ischaemia is a major issue in AVD.

Levosimendan is a calcium sensitizer and adenosine triphosphate (ATP)-dependent potassium channel opener that was developed as an inodilating drug for the treatment of AHF and cardiogenic shock.[3] Differently from other inotropic agents, levosimendan has some peculiar characteristics, in terms of mechanisms of action, pharmacodynamic profile, haemodynamic effects, and impact on myocardial oxygen consumption.[3] Consequently, specific levosimendan indications may be foreseen in case of AVD (i.e. during ACS, myocarditis, takotsubo syndrome, acute valvular regurgitation, etc.) and of patients with pre-existing severe ventricular dysfunction undergoing a planned procedure implying 'acute myocardial stress' [surgery, percutaneous coronary intervention (PCI), ventricular tachycardia ablation, and weaning from mechanical circulatory and ventilatory supports]. In these clinical settings, the early administration of levosimendan before

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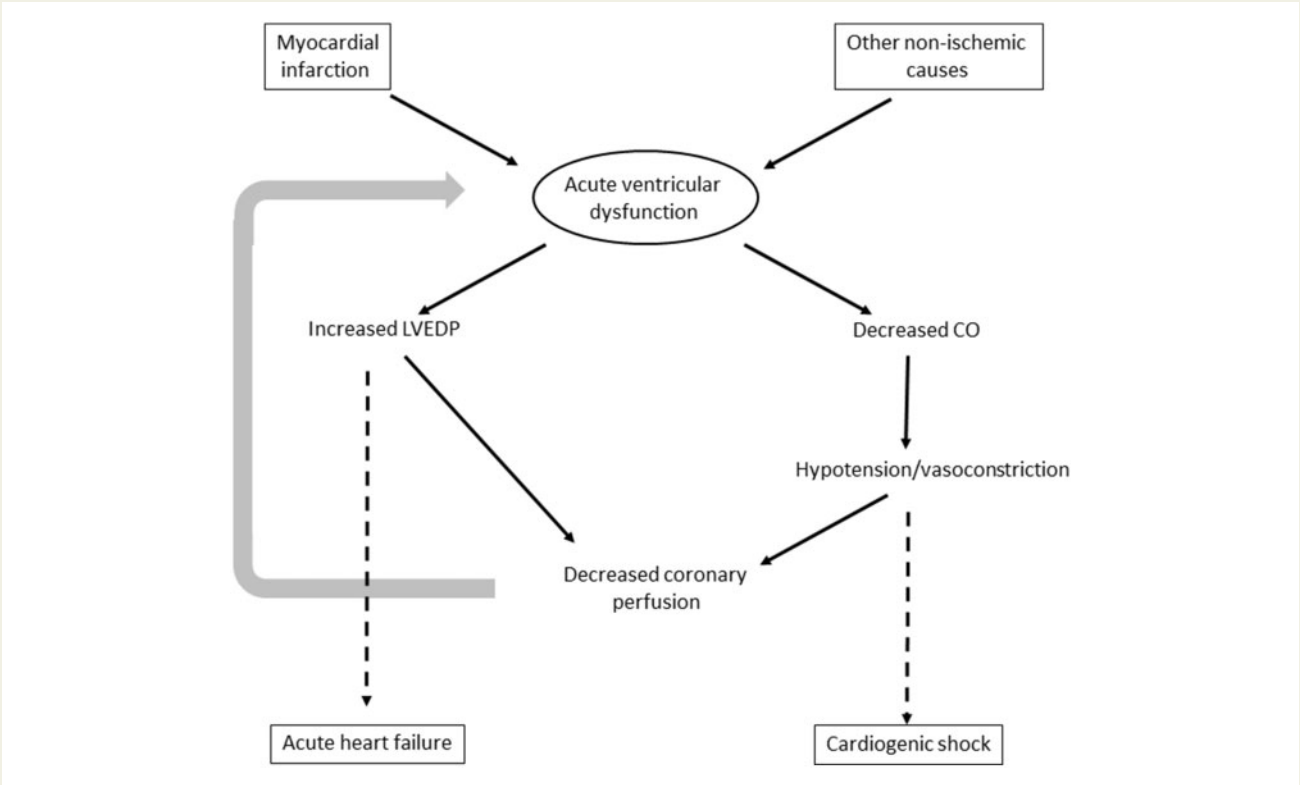

Figure 1 Schematic representation of the cascade of events leading to acute heart failure and cardiogenic shock. CO, cardiac output; LVEDP, left ventricular end-diastolic pressure.

the onset of overt symptoms or its prophylactic use before planned therapeutic procedures might bridge the patient through the critical phase, preventing haemodynamic worsening, and AHF.

While the use of levosimendan has been extensively investigated in clinical studies on overt AHF and cardiogenic shock, its potential use at an earlier stage is not yet defined. Therefore, our goal goes beyond the analysis of the available clinical trial data that have evaluated the effectiveness and safety of levosimendan in manifest AVD. In this review, we will provide the rationale, the existing experimental data, and the emerging clinical experience supporting an early use of levosimendan in patients with AVD or its preventive use in patients with pre-existing ventricular dysfunction undergoing myocardial stress procedures.

Pathophysiology of acute ventricular dysfunction

The key mechanisms involved in both ischaemic and non-ischaemic AVD are ischaemia, necrosis, and stunning.[1,2] Myocardial ischaemia relies on an imbalance between myocardial oxygen consumption and delivery.[4] Determinants of myocardial oxygen consumption are left ventricular mass, myocardial work (depending on heart rate and blood pressure), end-diastolic ventricular filling pressure, and inotropic status.[4] Oxygen supply to the heart is strictly dependent on coronary blood flow, which may be reduced in case of mechanical and/or functional coronary flow impairment, leading to a reduction of aerobic metabolism.[4] Acute ischaemia induces profound metabolic and ionic perturbations in the affected myocardium, and it depresses systolic function. On the one hand, a fall in systolic arterial pressure leads to systemic hypoperfusion, tissue hypoxia, and subsequent end-organ dysfunction.[4] On the other hand, the increase in left ventricular and atrial pressure and pulmonary venous pressure may cause pulmonary oedema and a further reduction of coronary blood flow.[4] These haemodynamic changes depend on the severity and duration of ischaemia, on the presence of coronary collateral flow, on the number of ventricular segments involved, and on the pre-existing cardiac functional reserve.[4]

The recovery of systolic function normally occurs rapidly after transient episodes of ischaemia; however, in case of sustained and severe ischaemia, persistent contractile dysfunction without myocyte necrosis has been observed.[4,5] This phenomenon is named stunned myocardium. Protract and intense sublethal acute ischaemia, as occurs during ACS and in general in all kinds of AVD, causes stunning on restoration of myocardial oxygen delivery, which can spontaneously normalize within days or weeks in the absence of necrosis. Stunned myocardium is considered the main time-dependent mechanism contributing to persistent myocardial dysfunction after an acute primary or secondary non-necrotic ischaemic event.[6] From a clinical point of view, stunned myocardium significantly contributes to AVD, and it may lead to AHF and even to cardiogenic shock. The pathogenesis of sustained myocardial dysfunction in stunning remains incompletely clarified. Generation of oxygen-derived free radicals, inflammation, and transient calcium overload leading to decreased

calcium sensitivity of the myofilaments are believed to be major factors.[7] However, the final mechanism responsible for the contractile depression appears to be a decreased sensitivity of the myofibrils to calcium.[7] Therefore, calcium sensitization might directly improve the function of stunned myocardium.[8]

Mechanisms of action of levosimendan

All inotropic agents currently available in clinical practice share a common feature, i.e. they increase contraction by raising intracellular calcium.[9] Although this is achieved by different mechanisms of action, the improvement in cardiac contraction is paralleled by an increase in myocardial oxygen consumption. Moreover, these drugs may have chronotropic, proarrhythmic, and direct myocyte-toxic effects, and they may induce coronary hypoperfusion, exacerbating oxygen delivery/consumption mismatch.[9] Differently, levosimendan does not raise intracellular calcium level, but it selectively binds to cardiac troponin C, enhancing the myofilament sensitivity to calcium.[3] Therefore, the levosimendan-induced improvement in myocardial contraction is not associated with a significant increase in oxygen consumption. However, although levosimendan is mainly regarded as a calcium sensitizer, it has been shown to cause inotropic effect also through the inhibition of phosphodiesterase-3 (PDE-3).[10,11] This effect may account for some experimental evidence reporting a similar oxygen consumption during infusion of levosimendan and dobutamine[12] or milrinone.[13]

By opening the ATP-sensitive potassium (K_{ATP}) channels in the vasculature, levosimendan also induces vasodilation and increases tissue perfusion in all arterial and venous vascular beds, including coronary arteries.[14] By reducing cardiac afterload, levosimendan may even decrease myocardial oxygen consumption, which, combined with the increase in coronary flow, results in an overall myocardial energy-sparing effect.[15] Notably, this beneficial effect is enhanced in patients treated with beta-blockers,[16] with the two therapeutic strategies having a synergic anti-ischaemic effect. Additional positive effects of levosimendan, which have been demonstrated in animal models and may be particularly useful in patients with AVD, include anti-remodelling, anti-stunning, anti-inflammatory, and anti-apoptotic effects.[3]

The pharmacokinetics of levosimendan is unique and of potential interest in the setting of AVD. The drug has a half-life of about 1.5 h, it reaches peak concentration within 4 h of the start of the infusion without a bolus, and it is rapidly eliminated mainly by kidneys.[17] Levosimendan is excreted into the small intestine and metabolized by intestinal bacteria to OR-1855. This metabolite is further metabolized by acetylation to OR-1896, which represents ~5% of the initial levosimendan dose. This metabolite is pharmacologically as potent as levosimendan itself, and the mechanism of the positive inotropic effect induced by this metabolite is very similar to that of levosimendan, that is calcium sensitization and PDE-3 inhibition.[18] Notably, OR-1896 as a longer half-life than levosimendan.[19] Indeed, the peak concentration of OR-1896 in plasma is observed ~60 h after levosimendan initiation in healthy subjects and 70–80 h in patients with heart failure.[17–19] The slow formation and elimination of OR-1896 account for the persistent haemodynamic effects of levosimendan, lasting for more than 10 days.[20] Therefore, levosimendan is the only current inotropic drug that maintains its effects beyond its infusion time, a feature that may be useful during cardiac function recovery from an acute insult.

Experimental and clinical evidence on levosimendan in acute ventricular dysfunction

Several experimental and clinical reports support the anti-ischaemic, anti-necrotic, and anti-stunning effects of levosimendan in patients with AVD.[21–25] The effects of levosimendan on myocardial oxygen consumption were characterized for the first time in humans in 1997.[21] Consistently with previous experimental reports,[22] Ukkonen *et al.*[21] demonstrated that levosimendan increases stroke volume and cardiac output in healthy subjects without an increase in myocardial oxygen demand. This neutral effect on myocardial energy need was then confirmed in patients with decompensated heart failure.[23] The beneficial effect on the energy balance of the myocardium has been demonstrated also in studies comparing levosimendan with dobutamine and milrinone.[21] Differently from these drugs, increased doses of levosimendan are paralleled by an increase in the inotropic effect,[24] without significant changes in myocardial energy demand. Another mechanism contributing to the overall anti-ischaemic effect derives from experimental evidence demonstrating that both levosimendan and OR-1896 reduce coronary vascular resistance and modulate coronary microcirculation via activation of K_{ATP} channels.[19]

Experimental studies demonstrated that levosimendan infusion, administered before and throughout the coronary occlusion period, limits myocardial infarct size.[26] Du Toit *et al.*[27] demonstrated that levosimendan reduces myocardial infarct size when used either to pre-treat the heart or as a preconditioning or post-conditioning procedure. In this study, the most effective cardioprotection, in terms of infarct size reduction and cardiac output increase, was obtained with levosimendan pre-treatment.[27] Yet, when levosimendan was started after coronary occlusion, it still significantly reduced infarct size, and it led to a better preservation of left ventricular function and to reduced left ventricular remodelling.[28] These beneficial effects are likely due to the opening of K_{ATP} channels, which leads to coronary vasodilation and increase in coronary blood flow, including collateral blood flow.[26] Moreover, through the stimulation of the K_{ATP} channels, levosimendan induces cardiomyocyte preconditioning.[26] Therefore, collateral recruitment, direct coronary vasodilatation, and cardiomyocyte preconditioning are likely the mechanisms involved in the cardioprotective effect of levosimendan.

Anti-stunning effects of levosimendan have been demonstrated in animal studies, where it improved regional contractile function of stunned myocardium after post-ischaemic reperfusion.[29] In the clinical arena, it has been demonstrated that, in ACS patients without AHF undergoing PCI, overall and regional left ventricular function was improved by levosimendan but not by angioplasty itself.[30] Indeed, in this study, levosimendan reduced the number of hypokinetic segments, which indicates an effect of this drug beyond afterload reduction. More recently, a randomized placebo-controlled trial has investigated the possible anti-stunning effects of levosimendan in ST-

elevation acute myocardial infarction (STEMI) patients with AHF treated with primary PCI.[31] Again, a significant improvement in regional contractility was observed with levosimendan and not with placebo 5 days after drug infusion.

At present, no study has firmly established the beneficial impact on infarct size of levosimendan in STEMI patients undergoing primary PCI, a clinical scenario where the anti-ischaemic, anti-necrotic, and anti-stunning effects of the drug might be expressed at most. If the aforementioned experimental observations are relevant to patients, early levosimendan administration will be expected to be beneficial in those with a large area of myocardium at risk. Indeed, a single bolus of levosimendan, given immediately after primary PCI in STEMI patients with left ventricular dysfunction, demonstrated to improve haemodynamics, diastolic function, and coronary flow reserve on the infarct-related artery compared to placebo.[32,33] Similar results are also achievable by intra-aortic balloon pump (IABP). Indeed, in a pilot study on patients with cardiogenic shock complicating acute myocardial infarction, levosimendan resulted in haemodynamic effects comparable to those seen with IABP, in terms of increase in cardiac index and cardiac power index, and reduction in systemic vascular resistances.[34] However, differently from levosimendan, IABP is associated with potential vascular and haemorrhagic complications, and, more importantly, its benefit vanishes when it is removed. Conversely, since experimental and clinical evidence has demonstrated that the recovery of ventricular contractile function after a transient insult may occur within days or weeks,[6,35,36] the persistent pharmacological effect of levosimendan beyond its infusion can bridge the patient to recover from myocardial stunning.[37,38] On these bases, levosimendan may have the requisites to be considered for early support in patients with AVD, in order to limit the ongoing ischaemic process, facilitate functional recovery, and, ultimately, prevent overt AHF and cardiogenic shock. However, it should be kept in mind that the prolonged systemic vasodilation induced by levosimendan may in some cases turn into an unfavourable effect. Indeed, some patients may develop an unexpected hypovolaemia and/or vasoplegia during the subsequent clinical course that may be accentuated by the persistent haemodynamic effect of the drug and make the clinical management of these patients even more complex.

Other potential clinical scenarios

Apical ballooning syndrome

Apical ballooning syndrome (ABS), also known as takotsubo syndrome, is more common among middle-aged women, and it is believed to occur in 1–2% of ACS patients. From a pathophysiological point of view, ABS is an acute cardiomyopathy characterized by AVD unrelated to epicardial coronary artery anatomy and blood flow distribution. Generally, systolic dysfunction affects middle and apical segments of the left ventricle, leading to 'apical ballooning', with relative sparing of the basal areas. Clinical presentation of ABS usually mimics an acute myocardial infarction, but coronary angiogram is normal in most cases. Takotsubo syndrome, as such, is often associated with left ventricular outflow tract obstruction due to the hyperdynamic contraction of the basal segments, impairing cardiac output, and potentially causing cardiogenic shock. Systolic anterior motion of the mitral valve may be associated with mitral regurgitation that further impairs cardiac function. Many stressful or emotional situations or exposure to high doses of sympathomimetic drugs have been identified in patients developing ABS. In particular, evidence supports the active role of catecholamines in the acute phase. This direct myocardial injury, along with the induction of both epicardial and microvascular coronary spasm, determines an increased cardiac workload, favouring the oxygen supply/demand mismatch. In most cases, AVD related to ABS does not require. However, when inotropic support is required, catecholamine infusion, which is the cornerstone in the pharmacological treatment of AVD, may have a negative effect, worsening apical ballooning and/or inducing left ventricular outflow obstruction.[39] Indeed, in a context where catecholamines are the main aetiological factors, their use may worsen the clinical picture by favouring inotropism and coronary vasoconstriction. Against this background, levosimendan may be considered as a suitable pharmacological alternative in AVD due to ABS. A few explorative studies have addressed this issue and demonstrated that levosimendan use is safe and likely efficacious in ABS.[40] However, more robust data are needed to confirm these preliminary findings.

Acute right ventricular dysfunction

Acute right ventricular dysfunction is commonly observed as a result of acute myocardial infarction or pulmonary embolism. By combining pulmonary vascular resistance reduction with increased right ventricular contractility, levosimendan has been shown to improve ventriculo-arterial coupling,[41] an expression of right cardiovascular efficiency. Of note, in animal models of pulmonary-embolism-induced right ventricular failure, levosimendan improved the interplay between cardiac function and pulmonary arterial system more than dobutamine.[41,42] A case report supported the effective use of levosimendan in a patient with life-threatening pulmonary embolism.[43] Levosimendan was also demonstrated to improve right ventricular haemodynamic parameters in patients with isolated and combined right ventricular failure due to ACS complicated by cardiogenic shock.[44] Moreover, the beneficial effect of levosimendan, in terms of reduced right ventricular afterload and improved right ventricular contractility and diastolic function was reported in patients with advanced heart failure[45] and in those with acute respiratory distress syndrome.[46] Based on this very preliminary evidence, it can be suggested that the beneficial effects of levosimendan are also present in acute right ventricular dysfunction. However, more clinical studies are needed before a formal recommendation for levosimendan use in this setting.

Prophylactic use in high-risk patients undergoing cardiac and non-cardiac procedures

Acute ventricular dysfunction may also occur in patients with pre-existing left ventricular dysfunction undergoing a planned procedure associated with myocardial stress. The poor, or absent, myocardial contractile reserve may not allow the patient to tolerate even minor myocardial insults that, in turn, can precipitate a hitherto stable clinical condition. Indeed, a prolonged depression of cardiac contractility and an increase in myocardial oxygen consumption occur after cardiac surgery, due to transient ischaemia during cardioplegia and cardiopulmonary bypass, after PCI, due to periprocedural myocardial

Table 1 Current (recruiting or not recruiting yet) studies focusing on early or preventive use of levosimendan available at ClinicalTrials.gov (updated to 10 October 2019)

	Study no. 1	Study no. 2	Study no. 3	Study no. 4
ClinicalTrials.gov Identifier	NCT03855579	NCT04020263	NCT03699215	NCT03436095
Study start	March 2019	December 2019	October 2018	January 2017
Study type	Interventional	Interventional	Interventional	Observational
Phase	4	3	3	—
Study design	RCT	RCT	RCT	Prospective study
Status	Recruiting	Not yet recruiting	Not yet recruiting	Recruiting
Clinical setting	Off-pump CABG surgery	CS	STEMI without CS	Ventilator weaning
Interventions	Intraoperative levosimendan vs. milrinone	Within 12 h from CS onset levosimendan vs. placebo	CCU arrival levosimendan vs. placebo	Levosimendan + nutrition +rehabilitation
Main outcomes	Intraoperative MAPneed for inotropes	30-day mortality30-day mortality and/or ELS and/or dialysis	Infarct size at CMR	Rate of weaning ventilator
Estimated enrolment (*n*)	60	610	184	90

CABG, coronary artery bypass graft; CCU, coronary care unit; CMR, cardiac magnetic resonance; CS, cardiogenic shock; ELS, extracorporeal life support; MAP, mean arterial pressure; RCT, randomized clinical trial; STEMI, ST-elevation acute myocardial infarction.
Study no. 1 = Levosimendan vs. milrinone in off pump CABG surgery.
Study no. 2 = Effect of early use of levosimendan vs. placebo on top of a conventional strategy of inotrope use on a combined morbidity–mortality endpoint in patients with cardiogenic shock.
Study no. 3 = Clinical trial in patients who have suffered a heart attack and who have undergone catheterization treated with levosimendan.
Study no. 4 = The clinical study of bundle measures to improve the success rate of patients with difficult ventilator weaning.

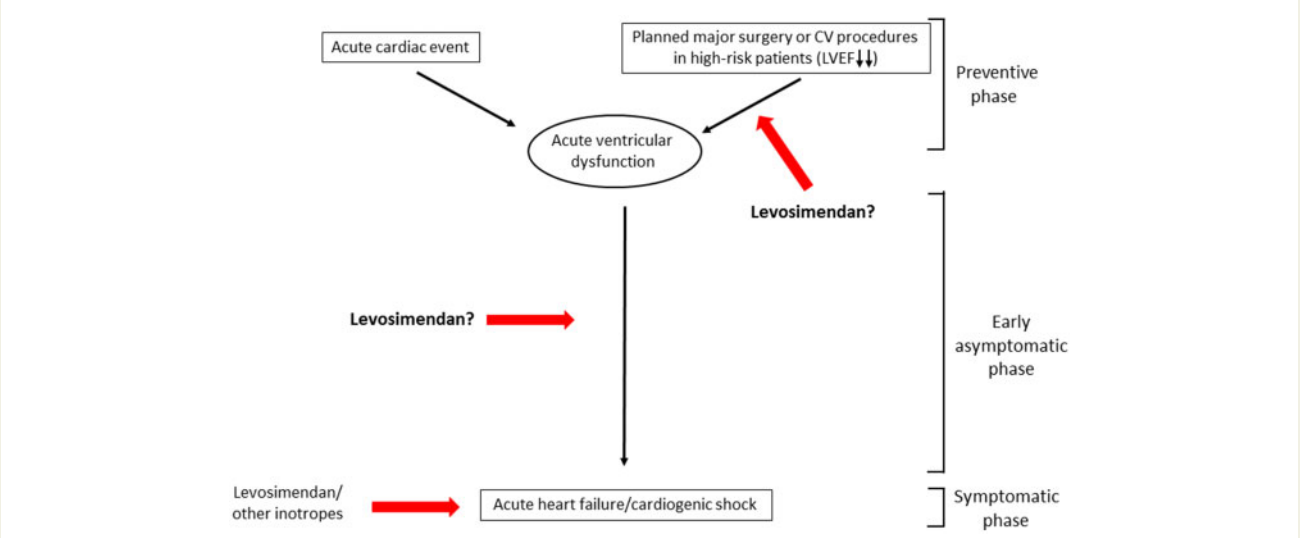

Figure 2 Potential clinical scenarios for levosimendan. CV, cardiovascular; LVEF, left ventricular ejection fraction.

injury, after ablation of ventricular tachycardia, due to the induction of sustained tachyarrhythmias and catheter-induced direct myocardial injury, and in high-risk non-cardiac surgery.[47]

So far, much attention has been focused on the cardiac surgery setting.[48,49] Indeed, preoperative reduced left ventricular function has been recognized as the main risk factor for low cardiac output syndrome after cardiac surgery. The rationale of using levosimendan in the preoperative setting is to achieve the maximal left ventricular ejection fraction (LVEF) improvement before cardiac surgery initiation. Yet, the greatest haemodynamic response to levosimendan occurs within 1–3 days of starting infusion.[20] Recently, two randomized multicentre studies were published on the preoperative use of levosimendan in patients with low LVEF undergoing cardiac surgery.[50,51] In contrast to the preceding smaller trials, which produced

a promising image of levosimendan in the preoperative setting, these latest two studies failed to find a levosimendan-related benefit. However, in both cases, the study design might have influenced the results. Indeed, in one study, levosimendan infusion was started 30 min before surgery,[50] while in the other it was started after anaesthetic induction,[51] allowing a very short time between levosimendan infusion beginning and surgery. Therefore, in these trials, the pharmacological effect was possibly reached after the first post-operative day, so that the investigated strategy cannot be considered as a truly preventive one.

Weaning from mechanical circulatory and/or respiratory support

Other potential clinical scenarios for levosimendan include its use in weaning from temporary left ventricular mechanical support devices, like IABP, Impella, and veno-arterial extracorporeal membrane oxygenation (VA-ECMO). The phase of weaning from these mechanical devices may fail in many cases, due to the increasing workload imposed to the ventricles during the progressive reduction in circulatory support. Thus, most patients require inotropic drugs to support myocardial contractile function during and after weaning, in the attempt to further recover cardiac function. The limited clinical evidence currently available suggests that levosimendan offers some important advantages over other inotropes for this vulnerable period, in terms of less myocardial oxygen consumption and prolonged haemodynamic effect. Although this levosimendan-based strategy has been preliminarily reported by some groups,[52,53] this practice needs to be investigated in the future, as the use of VA-ECMO will likely increase in the setting of AVD.

In addition, weaning from mechanical ventilation may be particularly challenging in patients with cardiac dysfunction, in whom the sudden increase in left ventricular diastolic pressure and the concomitant sympathetic hyperactivation due to the withdrawal of sedation may be poorly tolerated and may cause acute pulmonary oedema and respiratory weaning failure. In a prospective observational study including patients with reduced LVEF and difficult weaning from mechanical ventilation, levosimendan improved cardiac contractility and resulted in an increased likelihood of successful liberation from mechanical respiratory support.[54]

Future perspectives

Despite the promising evidence derived from experimental and clinical studies, the impact on outcome of an early or preventive use of levosimendan should be confirmed in large-scale randomized clinical trials. However, information on ClinicalTrials.gov (updated to October 2019) shows that only few studies focusing on this specific use of levosimendan are currently ongoing (*Table 1*). Nevertheless, their results might shed a light on the clinical characteristics of patients who may benefit from such a therapeutic approach, the most appropriate timing of drug administration, and its potential impact on hard clinical endpoints.

Conclusions

Due to its haemodynamic and anti-ischaemic effects and to its pharmacodynamics properties, the use of levosimendan appears to be a possible strategy in a number of cardiovascular diseases. Its prophylactic administration may be beneficial in selected high-risk patients or in clinical conditions where classical inotropes have no reason to be used (*Figure 2*). Considering the increasing experimental and clinical evidence, it can be suggested that, in patients with AVD, as well as in those with pre-existing ventricular impairment undergoing acute cardiac stress procedures, levosimendan may be considered for the prevention of overt AHF and cardiogenic shock.

Conflict of interest: none declared.

References

1. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JG, Coats AJ, Falk V, González-Juanatey JR, Harjola VP, Jankowska EA, Jessup M, Linde C, Nihoyannopoulos P, Parissis JT, Pieske B, Riley JP, Rosano GM, Ruilope LM, Ruschitzka F, Rutten FH, van der Meer P; Authors/Task Force Members; Document Reviewers. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC)Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur Heart J* 2016;**37**:2129–2200.
2. Nieminen MS, Brutsaert D, Dickstein K, Drexler H, Follath F, Harjola VP, Hochadel M, Komajda M, Lassus J, Lopez-Sendon JL, Ponikowski P, Tavazzi L; EuroHeart Survey Investigators, Heart Failure Association, European Society of Cardiology. EuroHeart Failure Survey II (EHFS II): a survey on hospitalized acute heart failure patients: description of population. *Eur Heart J* 2006;**27**:2725–2736.
3. Nieminen MS, Buerke M, Cohen-Solál A, Costa S, Édes I, Erlikh A, Franco F, Gibson C, Gorjup V, Guarracino F, Gustafsson F, Harjola VP, Husebye T, Karason K, Katsytadze I, Kaul S, Kivikko M, Marenzi G, Masip J, Matskeplishvili S, Mebazaa A, Møller JE, Nessler J, Nessler B, Ntalianis A, Oliva F, Pichler-Cetin E, Pöder P, Recio-Mayoral A, Rex S, Rokyta R, Strasser RH, Zima E, Pollesello P. The role of levosimendan in acute heart failure complicating acute coronary syndrome: a review and expert consensus opinion. *Int J Cardiol* 2016;**218**:150–157.
4. Crossman DC. The pathophysiology of myocardial ischaemia. *Heart* 2004;**90**:576–580.
5. Kloner RA, Jennings RB. Consequences of brief ischemia: stunning, preconditioning, and their clinical implications: part 2. *Circulation* 2001;**104**:3158–3167.
6. Matsuzaki M, Gallagher KP, Kemper WS, White F, Ross J. Sustained regional dysfunction produced by prolonged coronary stenosis: gradual recovery after reperfusion. *Circulation* 1983;**68**:170–182.
7. Bolli R, Marbán E. Molecular and cellular mechanisms of myocardial stunning. *Physiol Rev* 1999;**79**:609–634.
8. Soei LK, Sassen LM, Fan DS, van Veen T, Krams R, Verdouw PD. Myofibrillar Ca^{2+} sensitization predominantly enhances function and mechanical efficiency of stunned myocardium. *Circulation* 1994;**90**:959–969.
9. Francis GS, Bartos JA, Adatya S. Inotropes. *J Am Coll Cardiol* 2014;**63**:2069–2078.
10. Orstavik O, Ata SH, Riise J, Dahl CP, Andersen GØ, Levy FO, Skomedal T, Osnes JB, Qvigstad E. Inhibition of phosphodiesterase-3 by levosimendan is sufficient to account for its inotropic effect in failing human heart. *Br J Pharmacol* 2014;**171**:5169–5181.
11. Endoh M. Does levosimendan act as a Ca^{2+} sensitizer or PDE3 inhibitor?: Commentary on Orstavik et al., Br J Pharmacol 171: 5169-5181. *Br J Pharmacol* 2015;**172**:4594–4596.
12. MüLler S, How O-J, Jakobsen Ø, Hermansen SE, Røsner A, Stenberg TA, Myrmel T. Oxygen-wasting effect of inotropy: is there a need for a new evaluation? An experimental large-animal study using dobutamine and levosimendan. *Circ Heart Fail* 2010;**3**:277–285.
13. Axelsson B, Johansson G, Abrahamsson P, Gupta A, Tydén H, Wouters P, Haney M. Milrinone and levosimendan during porcine myocardial ischemia – no effects on calcium overload and metabolism. *Acta Anaesthesiol Scand* 2013;**57**:719–728.
14. Yokoshiki H, Katsube Y, Sunagawa M, Sperelakis N. Levosimendan, a novel Ca^{2+} sensitizer, activates the glibenclamide-sensitive K^+ channel in rat arterial myocytes. *Eur J Pharmacol* 1997;**333**:249–259.
15. Kaheinen P, Pollesello P, Levijoki J, Haikala H. Effects of levosimendan and milrinone on oxygen consumption in isolated guinea-pig heart. *J Cardiovasc Pharmacol* 2004;**43**:555–561.

16. Follath F, Cleland JG, Just H, Papp JG, Scholz H, Peuhkurinen K, Harjola VP, Mitrovic V, Abdalla M, Sandell EP, Lehtonen L; Steering Committee and Investigators of the Levosimendan Infusion versus Dobutamine (LIDO) Study. Efficacy and safety of intravenous levosimendan compared with dobutamine in severe low-output heart failure (the LIDO study): a randomised double-blind trial. *Lancet* 2002;**360**:196–202.
17. Antila S, Kivikko M, Lehtonen L, Eha J, Heikkila A, Pohjanjousi P, Pentikainen PJ. Pharmacokinetics of levosimendan and its circulating metabolites in patients with heart failure after an extended continuous infusion of levosimendan. *Br J Clin Pharmacol* 2004;**57**:412–415.
18. Ørstavik Ø, Manfra O, Andressen KW, Andersen GØ, Skomedal T, Osnes JB, Levy FO, Krobert KA. The inotropic effect of the active metabolite of levosimendan, OR-1896, is mediated through inhibition of PDE3 in rat ventricular myocardium. *PLoS One* 2015;**10**:e0115547.
19. Takahashi R, Talukder MA, Endoh M. Inotropic effects of OR-1896, an active metabolite of levosimendan, on canine ventricular myocardium. *Eur J Pharmacol* 2000;**400**:103–112.
20. Lilleberg J, Laine M, Palkama T, Kivikko M, Pohjanjousi P, Kupari M. Duration of the haemodynamic action of a 24-h infusion of levosimendan in patients with congestive heart failure. *Eur J Heart Fail* 2007;**9**:75–82.
21. Ukkonen H, Saraste M, Akkila J, Knuuti MJ, Lehikoinen P, Någren K, Lehtonen L, Voipio-Pulkki LM. Myocardial efficiency during calcium sensitization with levosimendan: a noninvasive study with positron emission tomography and echocardiography in healthy volunteers. *Clin Pharmacol Ther* 1997;**61**:596–607.
22. Edes I, Kiss E, Kitada Y, Powers FM, Papp JG, Kranias EG, Solaro RJ. Effects of Levosimendan, a cardiotonic agent targeted to troponin C, on cardiac function and on phosphorylation and Ca^{2+} sensitivity of cardiac myofibrils and sarcoplasmic reticulum in guinea pig heart. *Circ Res* 1995;**77**:107–113.
23. Ukkonen H, Saraste M, Akkila J, Knuuti J, Karanko M, Iida H, Lehikoinen P, Någren K, Lehtonen L, Voipio-Pulkki LM. Myocardial efficiency during levosimendan infusion in congestive heart failure. *Clin Pharmacol Ther* 2000;**68**:522–531.
24. Sato S, Talukder MA, Sugawara H, Sawada H, Endoh M. Effects of levosimendan on myocardial contractility and Ca^{2+} transients in aequorin-loaded right-ventricular papillary muscles and indo-1-loaded single ventricular cardiomyocytes of the rabbit. *J Mol Cell Cardiol* 1998;**30**:1115–1128.
25. Erdei N, Papp Z, Pollesello P, Edes I, Bagi Z. The levosimendan metabolite OR-1896 elicits vasodilation by activating the K(ATP) and BK(Ca) channels in rat isolated arterioles. *Br J Pharmacol* 2006;**148**:696–702.
26. Kersten JR, Montgomery MW, Pagel PS, Warltier DC. Levosimendan, a new positive inotropic drug, decreases myocardial infarct size via activation of K(ATP) channels. *Anesth Analg* 2000;**90**:5–11.
27. Du Toit EF, Genis A, Opie LH, Pollesello P, Lochner A. A role for the RISK pathway and K(ATP) channels in pre- and post-conditioning induced by levosimendan in the isolated guinea pig heart. *Br J Pharmacol* 2008;**154**:41–50.
28. Tarkia M, Stark C, Haavisto M, Kentala R, Vähäsilta T, Savunen T, Strandberg M, Saunavaara V, Tolvanen T, Teräs M, Pietilä M, Nyman L, Duvall E, Saukko P, Levijoki J, Roivainen A, Saraste A, Knuuti J. Effect of levosimendan therapy on myocardial infarct size and left ventricular function after acute coronary occlusion. *Heart* 2016;**102**:465–471.
29. Jamali IN, Kersten JR, Pagel PS, Hettrick DA, Warltier DC. Intracoronary levosimendan enhances contractile function of stunned myocardium. *Anesth Analg* 1997;**85**:23–29.
30. Sonntag S, Sundberg S, Lehtonen LA, Kleber FX. The calcium sensitizer levosimendan improves the function of stunned myocardium after percutaneous transluminal coronary angioplasty in acute myocardial ischemia. *J Am Coll Cardiol* 2004;**43**:2177–2182.
31. Husebye T, Eritsland J, Müller C, Sandvik L, Arnesen H, Seljeflot I, Mangschau A, Bjørnerheim R, Andersen GØ. Levosimendan in acute heart failure following primary percutaneous coronary intervention-treated acute ST-elevation myocardial infarction. Results from the LEAF trial: a randomized, placebo-controlled study. *Eur J Heart Fail* 2013;**15**:565–572.
32. De Luca L, Proietti P, Celotto A, Bucciarelli-Ducci C, Benedetti G, Di Roma A, Sardella G, Genuini I, Fedele F. Levosimendan improves hemodynamics and coronary flow reserve after percutaneous coronary intervention in patients with acute myocardial infarction and left ventricular dysfunction. *Am Heart J* 2005;**150**:563–568.
33. De Luca L, Sardella G, Proietti P, Battagliese A, Benedetti G, Di Roma A, Fedele F. Effects of levosimendan on left ventricular diastolic function after primary angioplasty for acute anterior myocardial infarction: a Doppler echocardiographic study. *J Am Soc Echocardiogr* 2006;**19**:172–177.
34. Christoph A, Prondzinsky R, Russ M, Janusch M, Schlitt A, Lemm H, Reith S, Werdan K, Buerke M. Early and sustained haemodynamic improvement with levosimendan compared to intraaortic balloon counterpulsation (IABP) in cardiogenic shock complicating acute myocardial infarction. *Acute Card Care* 2008;**10**:49–57.
35. Campodonico J, Mapelli M, Spadafora E, Ghilardi S, Agostoni P, Banfi C, Sciomer S. Surfactant proteins changes after acute hemodynamic improvement in patients with advanced chronic heart failure treated with Levosimendan. *Respir Physiol Neurobiol* 2018;**252-253**:47–51.
36. Mushtaq S, Andreini D, Farina S, Salvioni E, Pontone G, Sciomer S, Volpato V, Agostoni P. Levosimendan improves exercise performance in patients with advanced chronic heart failure. *ESC Heart Fail* 2015;**2**:133–141.
37. Fang M, Cao H, Wang Z. Levosimendan in patients with cardiogenic shock complicating myocardial infarction: a meta-analysis. *Med Intensiva* 2018;**42**:409–415.
38. Maharaj R, Metaxa V. Levosimendan and mortality after coronary revascularisation: a meta-analysis of randomised controlled trials. *Crit Care* 2011;**15**:R140.
39. Arias AM, Oberti PF, Pizarro R, Falconi ML, de Arenaza DP, Zeffiro S, Cagide AM. Dobutamine precipitated Takotsubo cardiomyopathy mimicking acute myocardial infarction: a multimodality image approach. *Circulation* 2011;**124**:e312–e315.
40. Santoro F, Ieva R, Ferraretti A, Ienco V, Carpagnano G, Lodispoto M, Di Biase L, Di Biase M, Brunetti ND. Safety and feasibility of levosimendan administration in takotsubo cardiomyopathy: a case series. *Cardiovasc Ther* 2013;**31**:e133–137.
41. Guarracino F, Cariello C, Danella A, Doroni L, Lapolla F, Stefani M, Baldassarri R, Vullo C. Effect of levosimendan on ventriculo-arterial coupling in patients with ischemic cardiomyopathy. *Acta Anaesthesiol Scand* 2007;**51**:1217–1224.
42. Kerbaul F, Rondelet B, Demester JP, Fesler P, Huez S, Naeije R, Brimioulle S. Effects of levosimendan versus dobutamine on pressure load-induced right ventricular failure. *Crit Care Med* 2006;**34**:2814–2819.
43. Powell BP, Simes D. Levosimendan in acute pulmonary embolism. *Anaesth Intensive Care* 2007;**35**:771–772.
44. Russ MA, Prondzinsky R, Carter JM, Schlitt A, Ebelt H, Schmidt H, Lemm H, Heinroth K, Soeffker G, Winkler M, Werdan K, Buerke M. Right ventricular function in myocardial infarction complicated by cardiogenic shock: improvement with levosimendan. *Crit Care Med* 2009;**37**:3017–3023.
45. Parissis JT, Paraskevaidis I, Bistola V, Farmakis D, Panou F, Kourea K, Nikolaou M, Filippatos G, Kremastinos D. Effects of levosimendan on right ventricular function in patients with advanced heart failure. *Am J Cardiol* 2006;**98**:1489–1492.
46. Morelli A, Teboul JL, Maggiore SM, Vieillard-Baron A, Rocco M, Conti G, De Gaetano A, Picchini U, Orecchioni A, Carbone I, Tritapepe L, Pietropaoli P, Westphal M. Effects of levosimendan on right ventricular afterload in patients with acute respiratory distress syndrome: a pilot study. *Crit Care Med* 2006;**34**:2287–2293.
47. Katsaragakis S, Kapralou A, Drimousis P, Markogiannakis H, Larentzakis A, Kofinas G, Misthos P, Filis K, Theodorou D. Prophylactic preoperative levosimendan administration in heart failure patients undergoing elective non-cardiac surgery: a preliminary report. *Hellenic J Cardiol* 2009;**50**:185–192.
48. Wang W, Zhou X, Liao X, Liu B, Yu H. The efficacy and safety of prophylactic use of levosimendan on patients undergoing coronary artery bypass graft: a systematic review and meta-analysis. *J Anesth* 2019;**33**:543–550.
49. Zhu J, Zhang Y, Chen L, He Y, Qing X. Levosimendan in patients with low cardiac output syndrome undergoing cardiac surgery: a systematic review and meta-analysis. *Anaesth Crit Care Pain Med* 2019;**38**:243–249.
50. Mehta RH, Leimberger JD, van Diepen S, Meza J, Wang A, Jankowich R, Harrison RW, Hay D, Fremes S, Duncan A, Soltesz EG, Luber J, Park S, Argenziano M, Murphy E, Marcel R, Kalavrouziotis D, Nagpal D, Bozinovski J, Toller W, Heringlake M, Goodman SG, Levy JH, Harrington RA, Anstrom KJ, Alexander JH; LEVO-CTS Investigators. Levosimendan in patients with left ventricular dysfunction undergoing cardiac surgery. *N Engl J Med* 2017;**376**:2032–2042.
51. Cholley B, Caruba T, Grosjean S, Amour J, Ouattara A, Villacorta J, Miguet B, Guinet P, Lévy F, Squara P, Aït Hamou N, Carillon A, Boyer J, Boughenou M-F, Rosier S, Robin E, Radutoiu M, Durand M, Guidon C, Desebbe O, Charles-Nelson A, Menasché P, Rozec B, Girard C, Fellahi J-L, Pirracchio R, Chatellier G. Effect of levosimendan on low cardiac output syndrome in patients with low ejection fraction undergoing coronary artery bypass grafting with cardiopulmonary bypass: the LICORN randomized clinical trial. *JAMA* 2017;**318**:548–556.
52. Jacky A, Rudiger A, Krüger B, Wilhelm MJ, Paal S, Seifert B, Spahn DR, Bettex D. Comparison of levosimendan and milrinone for ECLS weaning in patients after cardiac surgery—a retrospective before-and-after study. *J Cardiothorac Vasc Anesth* 2018;**322**:2112–2119.
53. Vally S, Ferdynus C, Persichini R, Bouchet B, Braunberger E, Lo Pinto H, Martinet O, Vandroux D, Aujoulat T, Allyn J, Allou N. Impact of levosimendan on weaning from peripheral venoarterial extracorporeal membrane oxygenation in intensive care unit. *Ann Intensive Care* 2019;**9**:24–32.
54. Kaltsi I, Angelopoulos E, Tzanis G, Sideris A, Tyrovolas K, Kokkoris S, Gratziou C, Nanas S, Routsi C. Contribution of levosimendan in weaning from mechanical ventilation in patients with left ventricular dysfunction: a pilot study. *Crit Care Res Pract* 2019;**24**:7169492.