ESC HEART FAILURE
ESC Heart Failure 2021; **8**: 4454–4464
Published online 30 October 2021 in Wiley Online Library (wileyonlinelibrary.com) **DOI:** 10.1002/ehf2.13669

REVIEW

Levosimendan-induced venodilation is mediated by opening of potassium channels

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Abstract

Unique vascular responses adhere to the cardiovascular efficacy of the inodilator levosimendan. In particular, selective venodilation appears to explain its clinical benefit during pulmonary hypertension complicated by heart failure with preserved ejection fraction. Vasodilators increase vessel diameter in various parts of the vascular system to different degrees and thereby influence blood pressure, its distribution, and organ perfusion depending on their mechanisms of action. Levosimendan and its long-lived active metabolite OR-1896 mobilize a set of vasodilatory mechanisms, that is, the opening of the ATP-sensitive K^+ channels and other K^+ channels on top of a highly selective inhibition of the phosphodiesterase III enzyme. A vessel-specific combination of the above vasodilator mechanisms—in concert with cardiac effects and cardiovascular reflex regulations—illustrates the pharmacological profile of levosimendan in various cardiovascular disorders. While levosimendan has been known to be an inotrope, its properties as an activator of ATP-sensitive K^+ channels have gone largely ignored with respect to clinical applications. Here, we provide a summary of what is known about the ATP-sensitive K^+ channel properties in preclinical studies and now for the first time, its ATP-sensitive K^+ channel properties in a clinical trial.

Keywords Pulmonary hypertension; Heart failure with preserved ejection fraction; Therapy; Venodilation; Pharmacology; Levosimendan

Received: 27 August 2021; Accepted: 27 September 2021
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Introduction

Tissue-specific and vessel-specific differences in the availability of drug-responsive vasodilating mechanisms explain distinct pharmacological responses upon vasodilator administrations. Vasodilation affects peripheral and central circulation, target organ function, and clinical outcomes in a way specific for the employed drug and its concentration. The above factors set the basis for the applicability of different vasoactive agents in cardiovascular diseases.

Levosimendan is an inodilator used to restore haemodynamic balance in acute cardiac care. After extensive studies, the emerging consensus is that the vasodilatory properties of levosimendan are due to ATP-sensitive K^+ (K(ATP)) channel activation.[1–3] In general, K^+ outflux (upon K^+ channel activation/opening) shifts vascular smooth muscle cell membrane potential to more negative values (i.e. hyperpolarization) with a consequent vasodilatation because of Ca^{2+} channel closure.[4] Nonetheless, due to its complex pharmacodynamic and pharmacokinetic profile, levosimendan-induced vasodilation requires additional consideration and, in particular, when its region-specific vasodilatory properties are evaluated throughout the cardiovascular system.

Marked reductions in pulmonary capillary wedge pressure (PCWP) and improvements in pulmonary circulation have been recognized long ago as hallmarks of levosimendan during intravenous administrations in acute and advanced heart failure (HF).[5] Moreover, results of preclinical investigations suggested that levosimendan might reduce right ventricular afterload by relaxing pulmonary arteries and alleviate pulmonary oedema by pulmonary venodilation.[6,7] The safety and efficacy of a repeated weekly intravenous infusion of

levosimendan formulation has been recently tested in patients with stable pulmonary hypertension (PH) and heart failure with preserved ejection fraction (HFpEF), where initial data also implicated favourable vascular and clinical responses. Interestingly, reductions of PCWP and central venous pressure (CVP) were demonstrated in the absence of systemic or pulmonary arterial vasodilation, or changes in cardiac index.[8] Accordingly, selective venodilation leading to the redistribution of stressed blood volume (SBV) to the splanchnic venous reservoir has been proposed to explain these findings.[9]

Here, we provide an overview on the pharmacological mechanisms that can form the basis of the pulmonary-selective and veno-selective effect of levosimendan and evaluate the related pharmacologic, physiologic, and clinical implications.

The complex mechanism of levosimendan-induced vasodilation

Levosimendan-induced K(ATP) channel activation was first reported in rat mesenteric arterial myocytes and ventricular cardiomyocytes on the basis of whole-cell and single channel patch-clamp experiments under *in vitro* conditions.[10,11] These findings were subsequently corroborated in *ex vivo* and *in vivo* experiments in the coronary circulation of isolated guinea pig hearts, in isolated small mesenteric arteries of the rat, in the renal circulation of mice, and in human internal thoracic arteries.[12–15] Interestingly, in porcine endothelium denuded epicardial coronary arteries and in human umbilical arteries, the vasodilator effects of levosimendan were associated with the combined activation of voltage-gated K^+ channels (K_V channels) and large conductance Ca^{2+}-activated K^+ channels (BK_{Ca} channels).[16,17] Moreover, in human internal thoracic arteries levosimendan-evoked relaxations were explained by the simultaneous activation of K(ATP) and BK_{Ca} channels.[18] Of note, results of levosimendan administrations in human internal thoracic arteries implicated sex-specific differences, whereby the vasodilatory effects of levosimendan were more pronounced in male participants than in female participants.[19]

Results of parallel preclinical studies using porcine coronary arteries extended the above observations towards additional effector mechanisms and suggested the involvement of intracellular cyclic adenosine monophosphate (cAMP) accumulation in the framework of β-adrenergic signalling.[20] An increase in cAMP concentration would activate the protein kinase A enzyme to phosphorylate and inhibit the myosin light chain kinase enzyme thereby leading to vasorelaxation. The involvement of cAMP in the levosimendan-evoked vascular responses, and at relatively high drug concentrations in particular, is not surprising in view of its highly selective inhibitory effect on the phosphodiesterase (PDE) III isozyme (i.e. without PDE IV inhibition at low levosimendan concentrations).[21]

Interestingly, in an *in vitro* experimental study on porcine coronary endothelial cells an additional, nitric oxide-(NO) dependent vasodilating mechanism (with the potential involvement of the cyclic guanosine monophosphate (cGMP)—protein kinase G—myosin light chain kinase enzyme axis) has been also suggested for levosimendan.[22] Moreover, an interaction between K(ATP) channel activations and NO signalling in reducing cell death has also been implicated upon intracoronary levosimendan administrations in pigs.[23]

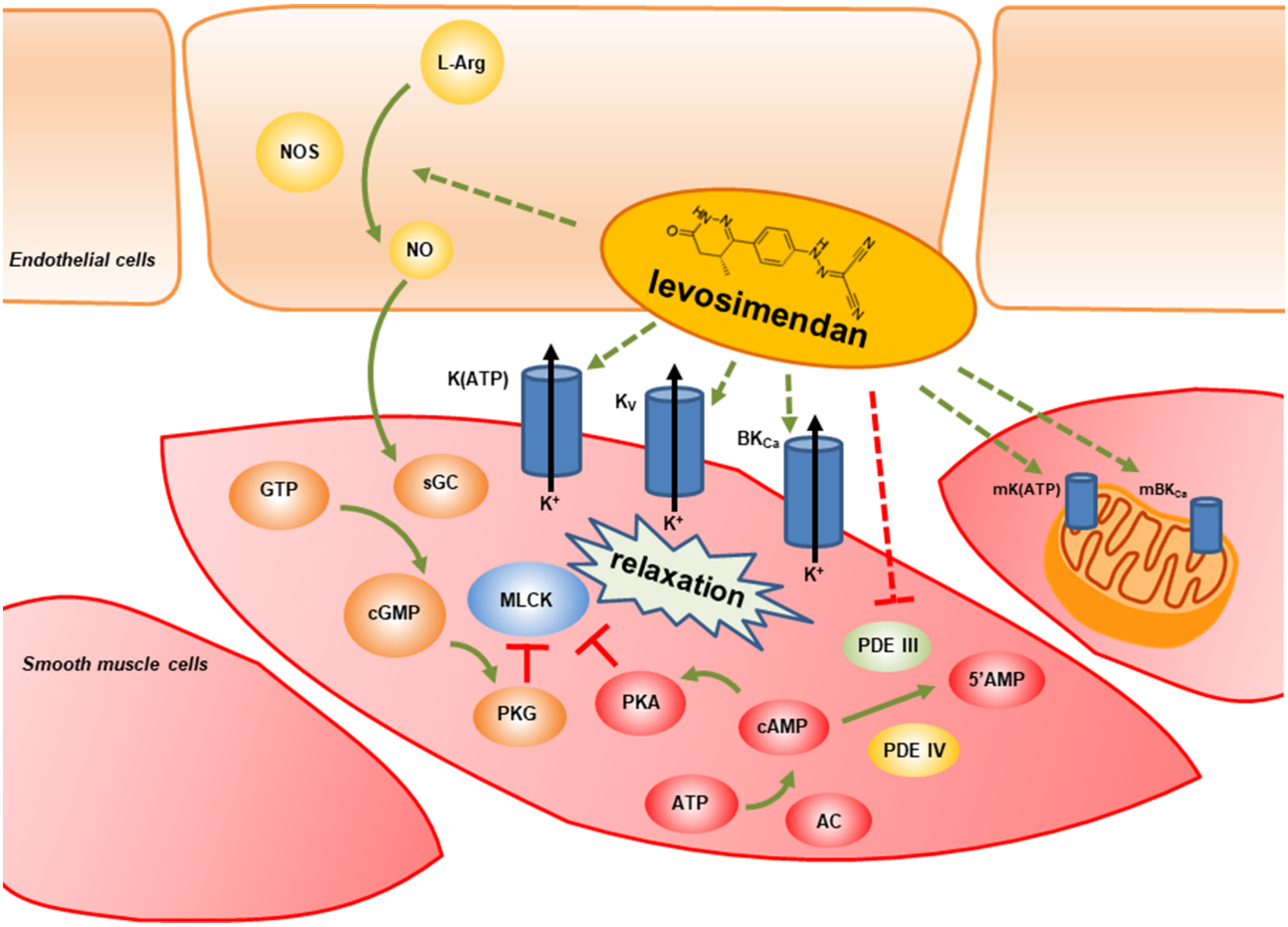
K^+ channel openings were also linked to the vasodilating effects of OR-1896, the long-acting metabolite of

Table 1 Levosimendan- (LS) and OR-1896- (OR) induced vasodilating mechanisms

Effector	Drug	Vascular bed (species)	Reference
K(ATP)	LS	Mesenteric artery (rat)	Yokosihiki *et al*.[10]
	LS	Coronary circulation (guinea pig)	Kaheinen *et al*.[13]
	LS	Renal circulation (mice)	Zager *et al*.[15]
	LS	Internal thoracic artery (human)	Yildiz, Seyrek, *et al*.[12]
	OR	Skeletal muscle arteriole (rat)	Erdei *et al*.[24]
	LS/OR	Resistance arteriole (rat)	Gödény *et al*.[25]
	LS	Portal vein (human)	Pataricza, Höhn, *et al*.[26]
K_V + BK_{Ca}	LS	Coronary artery (pig)	Pataricza, Krassói, *et al*.[16]
	LS	Umbilical cord artery (human)	Yildiz, Nacitarhan, *et al*.[17]
BK_{Ca}	OR	Coronary arteriole (rat)	Erdei *et al*.[24]
K(ATP) + BK_{Ca}	LS	Internal thoracic artery (human)	Usta *et al*.[18]
	LS	Saphenous vein (human)	Höhn *et al*.[27]
cAMP	LS	Coronary artery (pig)	Gruhn *et al*.[20]
K(ATP) + cAMP + cGMP	LS	Pulmonary circulation (cat)	De Witt *et al*.[28]
		Pulmonary artery (guinea pig)	Rieg, Rossaint, *et al*.[6]
K(ATP) + BK_{Ca} + cAMP + cGMP	LS	Pulmonary vein (guinea pig)	Rieg, Rossaint, *et al*.[6]
K(ATP) + K_V + cAMP + cGMP	LS	Pulmonary circulation (human)	Rieg, Suleiman, *et al*.[7]
NO	LS	Coronary endothelial cells (pig)	Grossini *et al*.[22]

BK_{Ca}, large conductance Ca^{2+}-activated K^+ channels; cAMP, cyclic adenosine monophosphate; cGMP, cyclic guanosine monophosphate; K(ATP), ATP-sensitive K^+ channel; K_V channels, voltage-gated K^+ channels; NO, nitric oxide.

Figure 1 Schematic illustration of levosimendan-induced putative vasodilating mechanisms. Levosimendan is capable to mobilize a set of vasodilatory mechanisms. Stimulatory and inhibitory effects are illustrated by green and red arrows, respectively. Effects of levosimendan are highlighted by dashed arrows. 5′AMP: 5′ adenosine monophosphate; AC, adenylate cyclase; ATP, adenosine triphosphate; cAMP, cyclic adenosine monophosphate; cGMP, cylic guanosine monophosphate; GTP, guanosine triphosphate; L-Arg: L-arginine; MLCK, myosin light chain kinase; NO, nitric oxide; NOS, nitric oxide synthase; PDE III, phosphodiesterase III; PDE IV, phosphodiesterase IV; PKA: protein kinase A; PKG, protein kinase G; sGC, soluble guanylate cyclase. See the text for further abbreviations and details.



levosimendan. OR-1896-elicited vasodilation largely depended on BK_{Ca} channel activations in isolated coronary microvessels, and K(ATP) channel activation in skeletal muscle arterioles of the rat.[24] In an *in vivo* follow-up investigation on real resistance arterioles (that are pertinent to the regulation of microcirculation), levosimendan and OR-1896-induced dilation were similarly effective and were both dominated by K(ATP) channel activation.[25]

The involvement of K(ATP) channel activations were also demonstrated with levosimendan administrations in isolated human portal vein preparations.[26] In human saphenous vein preparations, levosimendan-evoked vasodilation was explained by the combined K(ATP) and BK_{Ca} channel activation.[27]

Taken together, results of preclinical investigations (using sulfonylureas and other types of K^+ channel blockers) pointed to the involvement of more than a single mechanism for the explanation of levosimendan-induced vasodilation in several vascular beds (*Table 1*). Accordingly, activation of K(ATP) channels and other types of K^+ channels together with a variable degree of PDE inhibition can all be involved in this effect depending on the characteristics of the vascular bed and the nature of the experimental conditions (e.g. levosimendan dose) (*Figure 1*).

The mechanism of levosimendan-induced vasodilation in the pulmonary circulation

The involvement of K(ATP) channel activation in levosimendan-induced pulmonary vasodilation was clearly demonstrated under sophisticated experimental conditions

DOI: 10.1002/ehf2.13669

in cats *in vivo*.[28] Moreover, in precision-cut lung slices from guinea pigs, complex signalling pathways were associated with levosimendan-evoked vascular smooth muscle relaxation. While in pulmonary arteries, the involvement of K(ATP) channel activation and cAMP/cGMP-dependent processes were stressed, in pulmonary veins, additional roles for K_V and BK_{Ca} channel activation was postulated.[6] Subsequent investigations confirmed and extended these observations for the human lung whereby levosimendan-induced vascular smooth muscle relaxation was explained by a combination of K(ATP) and K_V channel activation, as well as by increased intracellular cAMP and cGMP.[7] Interestingly, levosimendan also attenuated the vascular remodelling process in a rat model of pulmonary hypertension suggestive for K(ATP) channel-dependent long-term anti-proliferative and anti-inflammatory effects.[29]

The role of mitochondrial K(ATP) channels in the levosimendan-evoked cardiovascular effects

In addition to the effects on vascular smooth muscle cells, levosimendan was also shown to open mitochondrial K(ATP) channels (mK(ATP) channels) in cardiomyocytes,[30–32] which has been associated—in both *ex vivo* and *in vivo* models—with pharmacological pre-conditioning[33,34] and post-conditioning.[33,35] Interestingly, activation of another mitochondrial K^+ channel, the mitochondrial BK_{Ca} channel (mBK_{Ca} channel), has been also demonstrated during levosimendan-evoked cardiac pre-conditioning and post-conditioning in rats.[36,37]

Overall, the cardiovascular significance of K(ATP) and/or mK(ATP) (and possibly other K^+) channel activations has been supported by repeated observations related to levosimendan-evoked clinical benefits.[38,39] For example, K(ATP) channel activation was a prerequisite for improved survival following cardiopulmonary resuscitation in levosimendan-treated rats following ventricular fibrillation.[40] In line with preclinical studies of these kinds, pharmacological pre-treatment with levosimendan significantly improved outcomes in patients undergoing coronary artery bypass graft surgery.[41] Of note, the administration of sulfonylureas did not attenuate the haemodynamic or other effects of levosimendan under clinical conditions suggestive for the significance of the several times higher concentrations of sulfonylureas used in experimental settings than in clinical conditions.[42] It is also a matter of importance that levosimendan shares its K(ATP) channel agonist property with the anti-angina medication nicorandil.[43] Nicorandil, however, has a pronounced negative inotropic effect while levosimendan—in line with its unique dual inodilator mechanism - is a positive inotrope.[44]

Importantly, the sum of levosimendan-evoked effects on cardiac mitochondria, cardiomyocytes and coronary circulation preserves the overall energy balance of cardiac function, which has not been shown for any other inodilator.[45]

Levosimendan-evoked K(ATP) channel activation beyond the cardiovascular system

Levosimendan-induced K(ATP) channel activation in combination with BK_{Ca} channel activation has been identified in tracheal ring preparations of guinea pigs.[46] Importantly, levosimendan prevented bronchoconstriction via K(ATP) channel activation in rabbits *in vivo*, which can be of importance for patients with decreased cardiorespiratory reserve.[47] Additionally, lung tissue integrity was protected in a rat model of pulmonary ischaemia and reperfusion through mitigated levels of apoptosis by levosimendan-evoked post-conditioning.[48]

Levosimendan also induced relaxation of human myometrial strip preparations via K(ATP) channel activation.[49] Moreover, the anticonvulsant effects of levosimendan (and thus its influence on the central nervous system) has also been associated with K(ATP) channel activation.[50]

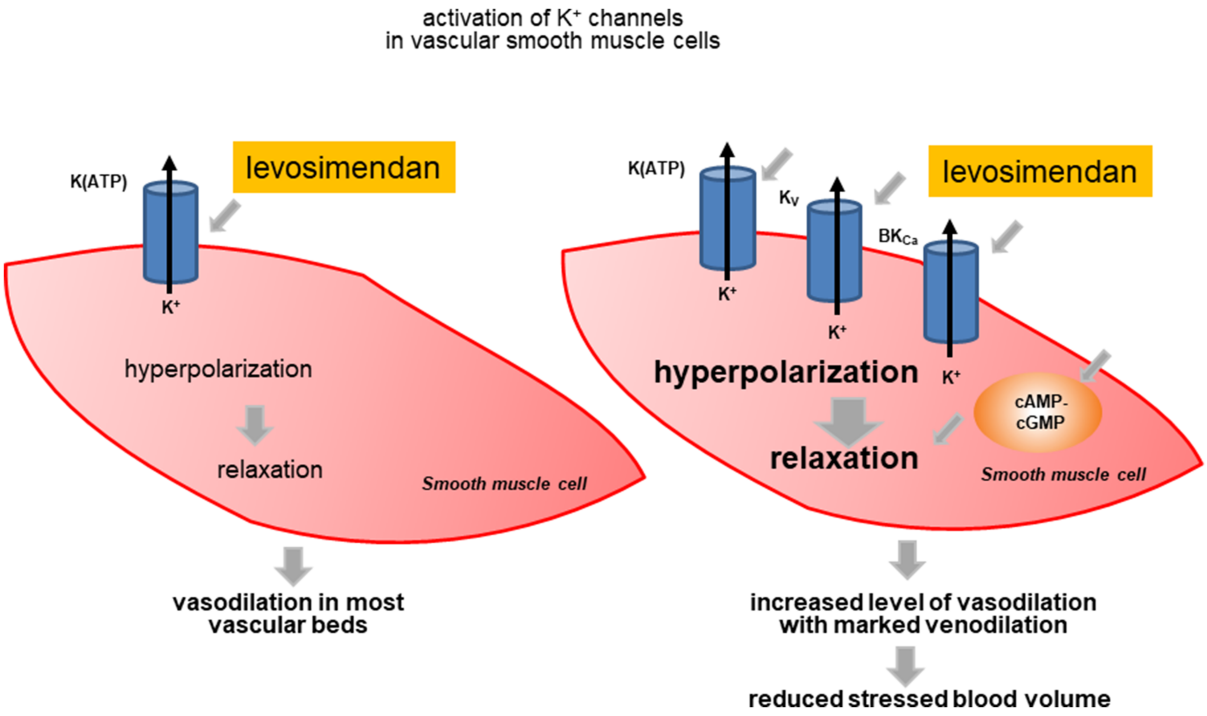
An effect of levosimendan on liver mitochondria has been documented,[30] which—in association with the levosimendan-induced increase in liver blood flood[51]—could explain the protective effect elicited by the drug against liver ischaemia–reperfusion.[52] Similar observations in a pig model, where the protective effects of levosimendan against ischaemia/reperfusion injury on kidney function were demonstrated, support the activation of mK(ATP) channels in organ-protective effects.[53]

Characteristics of levosimendan-induced vasodilation in view of other vasodilators

Results detailed above illustrate a complex mechanism of action for levosimendan-induced vasodilation that involve the activation of sarcolemmal and mitochondrial K^+ channels and the modulation of cyclic nucleotide levels in cardiovascular and other tissues. Here, we postulate that the combination of these effector mechanisms, together with its other cardiovascular effects, form the foundation for the unique organ-selective and veno-selective characteristics of levosimendan that cannot be reproduced by single drug-target interactions (*Figure 2*).

Indeed, in porcine coronary vascular smooth muscle cells, levosimendan-evoked vasodilation was paralleled by an

Figure 2 Hypothetical explanation for increased tissue sensitivity of levosimendan-evoked vasodilation with marked venodilation. An increased level of levosimendan-induced vasodilation can relate to more than a single vasodilator effector mechanism.



apparent Ca^{2+}-desensitization (thus giving space for K^+ channel activation), an effect that was not seen upon the administration of milrinone, a PDE III inhibitor.[54] Likewise, in contrast to levosimendan, dobutamine (a β-mimetic) evoked frequent arrhythmias and suggested distinct effects on $[Ca^{2+}]_i$ in a model of ischaemia and reperfusion of Langendorff-perfused guinea pig hearts.[55] Moreover, while the concentration dependencies of levosimendan and OR-1896 on systemic cardiovascular haemodynamic responses (e.g. blood pressure, pulse pressure, rate-pressure product, cardiac output, & peripheral resistance) were similar, they were different from those evoked by dobutamine or milrinone in rats *in vivo*.[56]

In a canine model, Pagel *et al*.[51] showed that levosimendan and milrinone cause different alterations in regional tissue perfusion while producing similar systemic haemodynamic effects. Importantly, levosimendan decreased vascular resistance in the renal and splanchnic circulation while milrinone increased it. Moreover, in that model, milrinone did not reduce pressure work index (an estimate of myocardial-oxygen consumption) in contrast to levosimendan.[57] In a dog model, Schwarte *et al*.[58] showed that levosimendan was superior to milrinone and dobutamine in selectively increasing microvascular gastric mucosal oxygenation.

In an experimental study conducted in instrumented cats, levosimendan was significantly more potent in decreasing lobar pulmonary arterial pressure than either of the type III or IV PDE inhibitors, or the K(ATP) channel agonist pinacidil.[28]

In summary, cardiovascular responses following levosimendan administration are distinguishable from those evoked by activators of the β-adrenergic system and consequently from sole intracellular cyclic nucleotide changes (*Table 2*).

Levosimendan in pulmonary hypertension from heart failure with preserved ejection fraction

Recent investigations into the mechanisms of elevated PCWP in HF have drawn attention to increased SBV as playing an important role.[9] Total blood volume of the body is divided into two functional compartments: SBV and unstressed blood volume (UBV). UBV is the amount of blood required to fill the vascular system just to the point wall stress and mean circulatory filling pressure start to rise; SBV is the blood volume about UBV. Thus, TBP = SBV + UBV (*Figure 3*). The splanchnic circulation constitutes the body's largest reservoir of UBV, predominantly in the veins, which can be recruited rapidly to the SBV pool. Importantly, the splanchnic reservoir is responsive to changes in sympathetic tone due to the large concentration of adrenergic receptors in the walls of venous

DOI: 10.1002/ehf2.13669

Table 2 Cardiovascular profiles of levosimendan (LS) and other inodilators in comparative studies

Drug	Examined parameter	Effect	Preparation (species)	Ref.
LS	$[Ca^{2+}]_i$-force relationship	Desensitization	Coronary arteries (pig)	Bowman *et al*.[54]
Milrinone	"	No desensitization		
LS	Post-ischaemic arrhythmia	None	Isolated hearts (guinea pig)	Du Toit *et al*.[55]
Dobutamine	"	Frequent		
LS/OR-1896	Mean arterial pressure	Decrease (high potential)	Instrumented animals (rats)	Segreti *et al*.[56]
	Pulse pressure	Decrease (high potential)		
	Rate-pressure product	Decrease (low potential)		
	Cardiac output (LS)	Increase (high potential)		
	Peripheral resistance	Decrease (high potential)		
Milrinone	Mean arterial pressure	Decrease (low potential)		
	Pulse pressure	Decrease (low potential)		
	Rate-pressure product	Decrease (low potential)		
	Cardiac output	Small increase (low potential)		
	Peripheral resistance	Decrease (low potential)		
Dobutamine	Blood pressure	No effect		
	Pulse pressure	Increase		
	Rate-pressure product	Increase (high potential)		
	Cardiac output	No effect		
	Peripheral resistance	No effect		
LS	Pulmonary lobar pressure decrease	High potency	Instrumented animals (cats)	De Witt *et al*.[28]
Siguazodan	"	Low potency		
Rolipram	"	Low potency		
Pinacidil	"	Low potency		
LS	Regional distribution of cardiac output	LS-specific combination at comparable systemic effects	Anaesthetized animals (dogs)	Pagel *et al*.[51,57]
	Renal vascular resistance	Decrease		
	Splanchnic vascular resistance	Decrease		
	Pressure work index	Decrease		
Milrinone	Regional distribution of cardiac output	Milrinone-specific combination at comparable systemic effects		
	Renal vascular resistance	Increase		
	Splanchnic vascular resistance	Increase		
	Pressure work index no effect			
Pimobendan	Regional distribution of cardiac output	Pimobendan-specific combination at comparable systemic effects		
	Renal vascular resistance	Increase		
	Splanchnic vascular resistance	Increase		
	Pressure work index	No effect		
LS	Oxygenation of gastric mucosa	Selective increase	Anaesthetized animals (dogs)	Schwarte *et al*.[58]
Milrinone	"	No effect		
Dobutamine	"	Non-selective increase		

Milrinone, pimobendan, and siguazodan are inhibitors of the PDE III enzyme, rolipram is an inhibitor of the PDE IV enzyme, and pinacidil is an activator of K(ATP) channels.

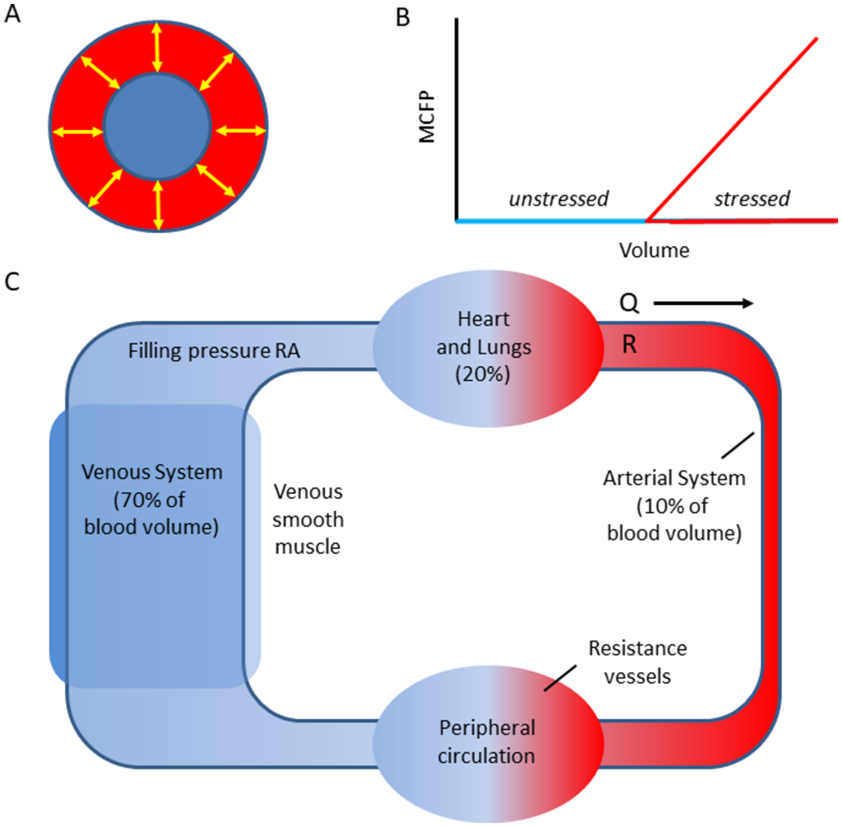
vessel that regulate their smooth muscle tone and thus the capacity of the venous system. SBV plays a critical role in determining venous pressure[61] and is an adaptive mechanism that regulates systemic and pulmonary venous pressures during exercise, times of stress, and in response to haemorrhage. Chronic increases in SBV become maladaptive from the sustained elevated activity of the sympathetic nervous system that occurs in HF and in pulmonary hypertension.

The importance of SBV in HF was recently validated by experiments in patients with chronic HF and elevated PCWP. A percutaneous splanchnic ganglion nerve block that temporarily dilated the splanchnic veins was shown to markedly lower CVP and PCWP at rest and during exercise with a reduction in estimated SBV.[62] The splanchnic veins have also been shown to dilate in response to K(ATP) activators.[26]

The Hemodynamic Evaluation of Levosimendan in Patients With PH-HFpEF (HELP) trial was a mechanistic trial designed to understand the mechanisms behind a potential benefit of levosimendan in patients with PH-HFpEF.[8] PH-HFpEF was chosen as the disease to study because of the following[63]: (1) it is a progressive and fatal disease with no effective treatment and a high unmet medical need; (2) it has become increasingly common in pulmonary hypertension specialty clinics; (3) a chronic elevation in PCWP at rest which worsens with exercise has been identified as an important target to achieve clinical benefit; and (4) the inotropic properties of

DOI: 10.1002/ehf2.13669

Figure 3 Stressed and unstressed vascular volume. The volume inside a vessel at near zero transmural pressure is termed 'unstressed volume' (blue). It fills the system without exerting tension in the vessel wall. The blood volume that creates positive transmural pressure via the elastic recoil of the vessel wall is termed 'stressed volume' (red). Mean circulatory filling pressure (MCFP) is a function of stressed volume and vascular compliance; compliance is the slope of the pressure–volume curve above the unstressed volume. (A) Cross section of a blood vessel. (B) The relationship between blood volume and MCFP. (C) The venous system contains approximately 70% of the blood volume. The splanchnic vascular bed serves as a reservoir and will adjust the amount of venous return based on signalling from the autonomic nervous system. In chronic HF, the increased sympathetic tone associated with activation of the renin–angiotensin–aldosterone system will also activate the splanchnic circulation to increase venous return, referred to SBV. This will increase the CVP and the pulmonary capillary wedge pressure. Q, cardiac output; R, systemic vascular resistance; RA: right atrium. Panels (A) and (B) freely adapted from Grübler *et al.*[59] Panel (C) is freely adapted from Noel-Morgan and Muir.[60]



levosimendan could prove helpful in patients with coexistent right HF.[64]

Levosimendan has demonstrated to be consistently effective in lowering PCWP in a broad spectrum of acute HF trials.[65] The classical teaching was that the fall in PCWP was attributed to its inotropic effect which would, theoretically, increase LV ejection and thereby result in greater 'emptying' of the pulmonary venous system; potential concomitant lusitropic effects have also been postulated to improve relaxation to enhance diastolic filling. However, the haemodynamic studies of levosimendan in HF patients show a rapid and marked reduction in PCWP before meaningful increases in cardiac output occur, which raised questions about a different mechanism of action.[66]

The HELP trial had two phases. Phase 1 was an open-label lead-in where patients would undergo a rest and exercise right heart catheterization to set a baseline haemodynamic profile of the PH-HFpEF. The patients then received a 24 h intravenous infusion of levosimendan and returned to the lab the following day for a repeat haemodynamic study. Those patients who demonstrated a $>$4 mmHg reduction in exercise PCWP were characterized as levosimendan *responders* and were enrolled into Phase 2, which was a 6 week outpatient, randomized, placebo-controlled, blinded study design. Phase 1 allowed the evaluation of the mechanism of action of levosimendan with patients serving as their own control. It showed significant reductions in PCWP and CVP at rest and exercise with no change in cardiac output, supporting effects on both venous pressure independent of any inotropic property of levosimendan, which were similar to the effect of splanchnic ganglion blockade. Phase 2 tested the durability of weekly levosimendan infusions over 6 weeks, followed by an end-of-study right heart catheterization at rest and exercise. The 24 h haemodynamic changes persisted

over the 6 weeks, but importantly were associated with a significant increase in exercise capacity. An analysis of the data supports that the mechanism of action to be a reduction in SBV, with no evidence for an inotropic effect.[67] This is consistent with the vasodilator effects of levosimendan as a K(ATP) channel activator on the splanchnic bed.[26]

There are also considerable data that support the down-regulation of K^+ channels as one of the fundamental processes that underlies the development of pulmonary hypertensive vascular disease.[68] Whether a long-term reduction in pulmonary arterial pressure due to the K(ATP) channel activation from levosimendan is also possible in these patients is unknown, but needs to be studied to see if this additional property of levosimendan could reverse the underlying pulmonary vascular disease.

Conclusions

Preclinical investigations with various vascular (arterial and venous) and non-vascular preparations identified K^+ channel (most frequently K(ATP) channel) activation as a mediator of the levosimendan-mediated smooth muscle relaxing effects. The pharmacological profile of levosimendan and of its long-acting metabolite, OR-1896, is very similar in this respect. Methodological and tissue-specific characteristics may explain part of the discrepancies among the observed combinations of additional effector mechanisms (including K_V and BK_{Ca} channels, cAMP and NO—cGMP). Of note, the expression levels of K^+ channel subtypes depend on the type of vascular bed and cardiovascular diseases.[69] Intuitively, the number of levosimendan-mobilized targets may correlate with the tissue sensitivity for vasodilation (e.g. in the pulmonary circulation and in peripheral veins) and can form the basis of its favourable haemodynamic profile with low-dose levosimendan administrations (*Figure 2*).

Undoubtedly, levosimendan affects a host of vasodilatory mechanisms and its smooth muscle relaxing effects extend beyond the cardiovascular system. The vasodilation is exerted in many vascular beds: in arteries and veins and in the peripheral and central circulations. Levosimendan mobilizes vasodilating mechanisms in combinations allowing for a differential and region-specific regulation in vascular beds and for the promotion of venodilation in the absence of systemic effects on the cardiovascular system as a whole at relatively low levosimendan concentrations. This feature differentiates this drug from other vasodilators or inodilators.

Conflicts of interest

S.R. is Chief Medical Officer at Tenax Therapeutics. P.P. is full time employee at Orion Pharma. Z.P. and D.B. have nothing to declare.

Funding

This work was supported by project TKP2020-IKA-04 and TKP2020-NKA-04 from the National Research, Development and Innovation Fund of Hungary, under the 2020–4.1.1-TKP2020 funding scheme. This work was also supported by the GINOP-2.3.2-15-2016-00043 project. The project is co-financed by the European Union and the European Regional Development Fund. The research group of Z.P. is supported by the Hungarian Academy of Sciences.

Compliance with ethical standards

Ethics approval and consent to participate

The submitted work is original and has not been published elsewhere in any form or language.

Consent for publication

All listed authors have approved the manuscript before submission, including the names and order of authors.

Research involving human participants and/or animals

This review paper does not report on original data. Nevertheless, this review paper refers to the results of a completed clinical trial [Hemodynamic Evaluation of Levosimendan in Patients With PH-HFpEF (HELP); NCT03541603] published elsewhere (JACC Heart Fail. 2021 May;9(5):360-370. https://doi.org/10.1016/j.jchf.2021.01.015.).

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