Levosimendan Comes of Age: 20 Years of Clinical Use

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This year marks the 20th anniversary of levosimendan in clinical use. To commemorate this milestone, the *Journal of Cardiovascular Pharmacology* and *Cardiac Failure Review* are jointly publishing a general review and opinion paper, which is authored by 51 prominent experts from 23 European countries, entitled *Levosimendan efficacy and safety: 20 years of SIMDAX in clinical use*. Levosimendan was introduced for the short-term treatment of acutely decompensated severe chronic heart failure. It is approved for situations where conventional therapy is inadequate and is one of the few new entries in the past 20 years in a problematic area of heart failure management. Its efficacy and safety have been documented by real-world evidence and data from randomized controlled trials involving more than 9000 patients. More than 200 clinical trials have evaluated levosimendan in various therapeutic settings, including perioperative and advanced heart failure, and a plethora of meta-analyses[1] have shown a consistent trend toward efficacy and safety; in particular, the increase in mortality often identified with adrenergic/catecholaminergic inotropes, such as dobutamine, has not been observed with levosimendan.

Nearly, 1500 publications in PubMed over the past 3 decades attest to the impact that levosimendan has had in the clinic and the laboratory (Fig. 1). The *Journal of Cardiovascular Pharmacology* has published no fewer than 47 reports on this drug, from its early characterization as a class III inotrope.[2,3] At the other end of the timescale is the very recent contribution by Al-Chalabi et al[4] outlining the case for levosimendan in the management of amyotrophic lateral sclerosis (ALS). In between, there has been a long road of clinical evolution and development, paving the way to the clinical use of levosimendan in more than 60 countries and territories but not yet in the United States.

The physiological actions of levosimendan are pleiotropic (Fig. 2). Levosimendan was developed as an agent that increases cardiac contractility by calcium sensitization of troponin C.[5,6] However, it also functions as an inodilator by causing vasodilation through the activation of ATP-sensitive potassium (K_{ATP}) channels in vascular smooth muscle cells of various vascular beds simultaneous with its effect on cardiac inotropy. Hence, and unlike adrenergic drugs, levosimendan can augment cardiac output without a commensurate increase in workload or oxygen requirements of the heart. It is now known as well that levosimendan may also offer cardioprotection by opening mitochondrial and sarcolemmal K_{ATP} channels in cardiac myocytes.

As a drug that exerts its inotropic effect at the level of the sarcomere, levosimendan would seem to qualify as a "myotrope" according to a recently proposed scheme.[7] In actual fact, however, that classification characterized levosimendan as a "calcitrope", that is to say an agent that increases contractility by increasing the intracellular calcium levels of cardiac myocytes. Such agents generally have unfavorable long-term consequences in heart failure arising from increased cardiac oxygen demands. This classification of levosimendan was predicated on its inhibition of certain isoforms of phosphodiesterase. Moreover, this action was considered responsible for reports of an adverse or neutral effect of levosimendan on mortality in certain heart failure trials. However, as noted above, levosimendan-mediated inotropy is achieved without detriment to myocardial oxygen demand or energy efficiency,[8] and as discussed in the anniversary review and opinion paper, phosphodiesterase specificity

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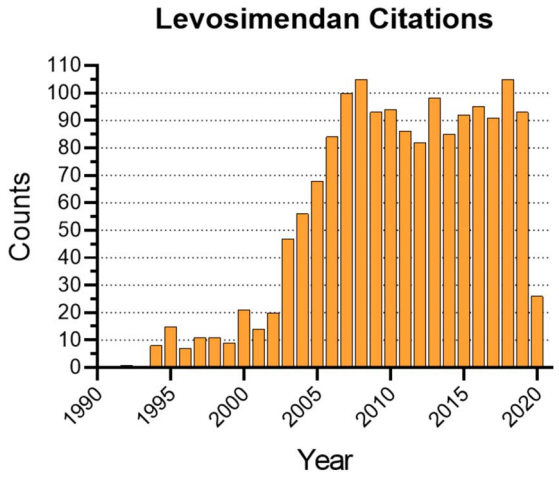

FIGURE 1. Citations of levosimendan in the scientific literature. PubMed was searched for the term "levosimendan" on April 24, 2020.

and dosage considerations would seem to discount this possibility as a material contributing factor to the in vivo effects of levosimendan administered at advised therapeutic doses.[9] Those findings speak rather to the complexity of heart failure and to the possibility that studies designed in a state of imperfect knowledge of how best to identify and capture relevant clinical outcomes may have frustrated investigations into the impact of levosimendan on mortality. The fact that in the GALACTIC trial short-term use of conventional and long-established vasodilators was no more efficacious at influencing longer-term mortality as several novel agents points toward fundamental obstacles underlying the lack of success that has attended the development of new drug therapies for acute heart failure in recent decades.[10] Viewed in that light, the absence of a robust general indication of a deleterious effect on long-term survival benefit differentiates levosimendan[1] significantly from established adrenergic inotropes and from various newer candidate therapies. Affirmative trends in nonfatal clinical outcomes are also relevant to a fully nuanced appraisal of levosimendan in heart failure management.[11]

As described in the accompanying 20-year review, levosimendan has long since evolved beyond the confines of its original indication of acute heart failure in adults and has demonstrated encouraging effects in various conditions where inotropy may be appropriate, including Takotsubo cardiomyopathy, cardiogenic and septic shock, and right ventricular failure; expansion into pediatric cardiovascular medicine is being explored and assessment of its potential in the management of pulmonary hypertension in heart failure patients with preserved ejection fraction is being advanced (www.ClinicalTrials.gov Identifier: NCT03541603). Levosimendan is also being evaluated in an array of situations that lie outside cardiovascular medicine, including ALS and ICU-acquired weakness of the respiratory muscles.

The breadth of these applications may be regarded as the fruit of the original research from which levosimendan emerged; time and expertise invested in gaining detailed understanding of this drug's pharmacology and effects on cellular processes, combined with a coherent commercial strategy that promotes dialog and collaboration, has provided a foundation from which the ingenuity of clinical researchers has been able to range widely. As a result, levosimendan reaches its 20th birthday firmly established in the day-to-day repertoire of the clinical arena where it was first introduced but also still as an asset in the development of new treatment principles both in heart failure management

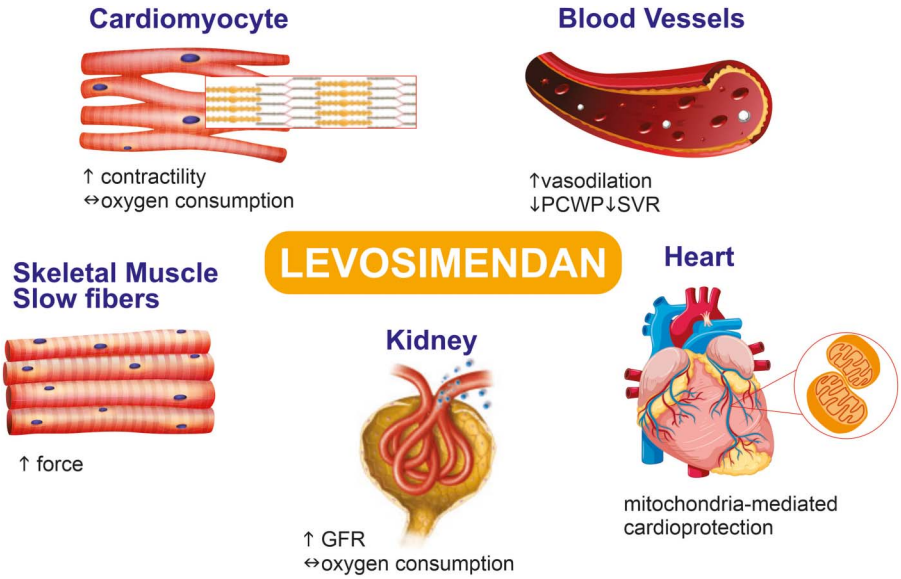

FIGURE 2. An overview of the pleiotropic actions of levosimendan. Levosimendan acts as an inotrope by enhancing the calcium sensitivity of troponin C in heart muscle, thereby increasing the force of contraction and ensuring an enhancement in cardiac output without a commensurate increase in oxygen requirements of the heart. A similar action may occur in the slow skeletal muscle fibers, for instance in the diaphragm, that would be of help in weaning from ventilation or delaying the need for ventilation in patients with ALS. By opening K_{ATP} channels in the vascular smooth muscle cells of certain vessels, levosimendan causes vasodilation and a reduction of system vascular resistance (SVR), seen also as a decrease of pulmonary capillary wedge pressure (PCWP), and ensuring an enhancement in cardiac output on top of its inotropic actions. A similar action on mitochondrial and sarcolemmal K_{ATP} channels in cardiac myocytes is linked to cardioprotection. Finally, the uneven vasodilation achieved by levosimendan on afferent versus efferent glomerular arterioles increases the glomerular filtration rate (GFR) without increasing renal oxygen demand.

and in a range of other situations. This continuing relevance and versatility should be a source of satisfaction to all those involved in the origin and development of this agent.

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