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Inotropes and Inodilators for Acute Heart Failure: Sarcomere Active Drugs in Focus

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Abstract: Acute heart failure (AHF) emerges as a major and growing epidemiological concern with high morbidity and mortality rates. Current therapies in patients with acute heart failure rely on different strategies. Patients with hypotension, hypoperfusion, or shock require inotropic support, whereas diuretics and vasodilators are recommended in patients with systemic or pulmonary congestion. Traditionally inotropic agents, referred to as Ca^{2+} mobilizers load the cardiomyocyte with Ca^{2+} and thereby increase oxygen consumption and risk for arrhythmias. These limitations of traditional inotropes may be avoided by sarcomere targeted agents. Direct activation of the cardiac sarcomere may be achieved by either sensitizing the cardiac myofilaments to Ca^{2+} or activating directly the cardiac myosin. In this review, we focus on sarcomere targeted inotropic agents, emphasizing their mechanisms of action and overview the most relevant clinical considerations.

Key Words: acute heart failure syndrome, Ca^{2+} mobilizer, sarcomere targeted agent, levosimendan, omecamtiv mecarbil

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INTRODUCTION

Heart failure (HF) is a complex pathophysiological syndrome involving acute and chronic phenomena. Acute heart failure (AHF) relates to the rapid decline in cardiac pump function requiring urgent medical care. More than 1 million hospitalizations occur annually in the United States because of AHF, and hence it emerges as a major and growing public health burden over the past 2 decades.[1] In addition to its high incidence, AHF is also associated with high mortality rates; the estimated risk of death was reported around 3%–4% in the hospital and approximately 10% after discharge within 60–90 days.[2]

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AHF may arise as a de novo entity in a previously asymptomatic patient or as an acute exacerbation of previously diagnosed chronic HF. According to the current ESC guidelines, AHF is referred in this review as a complex clinical syndrome including the following conditions: worsening or decompensated chronic HF, pulmonary edema, hypertensive acute HF, cardiogenic shock, HF related to acute coronary syndromes, and isolated right-sided HF.[3]

Current pharmacological therapies should respect the distinct clinical and pathophysiological entities of the AHF syndromes. Accordingly, in those patients with hypotension, hypoperfusion, or shock, intravenous inotropic support should be considered to maintain the peripheral perfusion by increasing the cardiac output (CO) and the blood pressure, whereas intravenous diuretics and vasodilators are recommended in patients with pulmonary and/or systemic venous congestion, as well as with signs of elevated filling pressures and vascular volume redistribution.[4]

Unfortunately, not a single conventional treatment strategy proved convincingly effective in reducing HF symptoms and improving short- and long-term mortality rates.[4] Moreover, several HF drugs were shown to increase mortality and morbidity over placebo.[5] For this reason, newly developed cardiovascular agents were designed to have different mechanisms of action from those of traditional drugs. In this review, we will focus on recently developed cardiovascular medications and will put specific emphasis on potential drug interactions with the cardiac sarcomere.

PATHOPHYSIOLOGY OF AHF SYNDROME

Briefly, the pathophysiology of AHF relies on a complex interaction between the weakened cardiac performance and increased systemic vascular resistance (SVR). A novel paradigm suggests that episodes of AHF can be classified as either an acute vascular or cardiac failure.[6] Decline in the cardiac performance by diverse pathological processes (eg, myocardial ischemia and arrhythmia) results in a forward and backward failure, manifesting as low peripheral perfusion with renal impairment and fluid accumulation with severe pulmonary congestion. The vascular pathway is related to the increased SVR and arterial stiffness leading to elevations in the left ventricular end-diastolic pressure. Hence, increased LV filling pressure contributes to pulmonary congestion with concomitant signs of AHF.[7] Although one or another pathway dominates in certain clinical cases, the combination of the above pathologic pathways results in the initiation of AHF by promoting a vicious circle.

ROLE OF INOTROPIC AGENTS IN THE THERAPY OF AHF SYNDROMES

The core of the problem in acute and chronic HF relates to impaired cardiac performance, and hence cardiovascular drugs supporting the pump function (ie, positive inotropic agents) of the failing human heart appeared for a long time as an optimal therapeutic approach. Inotropic agents can be classified by their mechanisms of actions, and the majority of cardiotonic drugs currently in clinical use can be referred to as *calcium (Ca^{2+}) mobilizers* acting by increasing the amplitude of the intracellular Ca^{2+} transient. Over the years, an alternative approach received increasingly more and more attention to support the failing human heart by *targeting the cardiac sarcomere*. This strategy is attractive because it promises to evoke positive inotropy without changes in the Ca^{2+} homeostasis.[8]

Mechanism of Action and Clinical Implications for Ca^{2+} Mobilizers

Ca^{2+} mobilizer inotropic agents load the cardiomyocytes with Ca^{2+} to improve cardiac contractility. Hence, this inotropic intervention can be complicated by deleterious effects limiting its applicability in long-term therapies for patients with AHF syndrome.[9] This is because cardiomyocyte Ca^{2+} loading is associated with enhanced myocardial oxygen (O_2) consumption, increased heart rate (HR), and greater risk of arrhythmias contributing to the higher morbidity and mortality rates.[10]

Ca^{2+} mobilizer agents interfere with various mechanisms of the cardiac excitation–contraction coupling.[11] Cardiac glycosides (eg, digitalis alkaloids) were the first inotropic drugs administered for the therapy of HF. Digoxin was shown to increase Ca^{2+} influx into the cytoplasm by interfering the sarcolemmal sodium–calcium exchange process because of its inhibitory action on the sodium–potassium ATPase (Na^+-K^+ ATPase).[12] Although digoxin reduced the rate of hospitalization because of worsening of HF, long-term mortality rates seemed to be unchanged, and hence clinical data do not confirm a clear benefit on mortality for digoxin treatment.[13,14]

The β-adrenergic agonists and inhibitors of the phosphodiesterase III (PDE III) isoenzyme may also evoke a positive inotropic effect by interfering with cyclic adenosine monophosphate (cAMP)–dependent phosphorylation processes. Dobutamine, a selective β-adrenergic agonist, increase the intracellular Ca^{2+} level through activating this signaling pathway leading to protein kinase A activation. Continuous intravenous dobutamine administration was shown to be associated with increased 6-month mortality rate according to the FIRST trial.[15] Nevertheless, low-dose intravenous dopamine infusion and dobutamine administration result in renal vasodilatation due to β_2-adrenergic receptor activation.[16] Dobutamine is also suspected to decrease renal sympathetic activity contributing to a beneficial effect on the renal function.[17] Because worsening of renal function is associated with a poor prognosis, renal vasodilatation might be favorable in patients hospitalized for AHF syndrome.[18] PDE III inhibitors (eg, milrinone and enoximone) enhance contractility in cardiac myocytes and relaxation in the vascular smooth muscle cells by reducing the rate of cAMP breakdown. Intravenous milrinone administration had no beneficial effect on the intermediate-term clinical outcome when compared with that of placebo in acute exacerbation of chronic HF.[19] Moreover, oral milrinone therapy resulted in increase of morbidity and mortality rates in those of patients with decompensated HF.[5]

Simultaneous modulation of the sarcoplasmic reticulum ATPase 2a (SERCA-2a) and Na^+-K^+ ATPase activity may also provide a cardiotonic effect. Accordingly, istaroxime was proposed for the treatment of AHF through Na^+-K^+ ATP-ase inhibition similarly to that of cardiac glycosides and simultaneous enhancement in sarcoplasmic reticulum (SR) Ca^{2+} uptake by increasing the activity of the SERCA2a.[20] These changes in the Ca^{2+} handling would then promote myocardial contraction and relaxation and evoking thereby a positive ino-lusitropic effect.[20] Some clinical data confirmed the beneficial cardiovascular effects of istaroxime because patients with AHF were reported with increased ventricular filling and systolic blood pressure as well as with decreased wedge pressure values after istaroxime treatment.[21] Nevertheless, cardiovascular drugs promoting Ca^{2+} cycling through the SR [eg, istaroxime and nitroxyl (HNO) donors] might be also referred to as SR Ca^{2+} cycling enhancers to emphasize their mechanism of action involving simultaneous increase in the rate of Ca^{2+} release and re-uptake in contrast to the traditionally inotropes.

Activators of the cardiac ryanodin receptor 2 (eg, HNO donor CXL-1020) promote Ca^{2+} release from the SR and thereby it also exerts an inotropic effect.[22] Further investigations are required to see how this effect can be exploited in the clinical arena (Table 1).

SARCOMERE TARGETED AGENTS: A NOVEL THERAPEUTIC APPROACH FOR AHF SYNDROME

Several different terms and concepts have been associated with cardiac sarcomere targeted agents, that is, Ca^{2+} sensitization of contractile filaments, direct cardiac myosin activation, and cardiovascular drugs with added myofilamental effects (eg, SR-33805 and HNO donors).

Theoretically, clinical use of sarcomere targeted drugs would avoid the disadvantages of Ca^{2+} mobilizers in the therapy of AHF syndrome.[11] This is because pharmacological modification of the cardiac sarcomere is not expected to interfere with the intracellular Ca^{2+} homeostasis at all or not to the same degree, hence their clinical application should not be associated either with increased risk of arrhythmias or cell injury.[23] Furthermore, sarcomere activating inotropes exert their cardiotonic effects presumably without considerable changes in myocardial O_2 consumption, and thereby they can improve the efficiency of chemomechanical energy transduction of the contractile protein machinery.[24] Finally, cardiac sarcomere targeted agents can be effective in the diseased myocardium, where cardiac dysfunction is accompanied by diverse pathophysiological conditions (eg, acidosis and ischemia-reperfusion injury).[11]

Historically, the concept of direct sarcomere targeting emerged for over 2 decades, when AR-L 115BS was reported as a potent inotropic agent involving direct activation of the myofilaments through increased affinity of the thin filaments

TABLE 1. Inotropic Mechanisms and Drugs

Inotropic Agents	
Calcium mobilizers	
Na^+-K^+ ATPase inhibitors	digoxin
PDE-inhibitors	enoximone, milrinone, pimobendan
β-adrenegic agonists	adrenaline, dopamine, dobutamine
Sarcoplasmic reticulum Ca^{2+} cycling enhancers	
Na^+-K^+ ATPase inhibitor + SERCA activator	istaroxime
Ryanodine receptor 2 and SERCA activator	CXL-1020
Sarcomere targeted agents	
Ca^{2+} sensitizers	levosimendan, pimobendan
Myosin activator	omecamtive mecarbil
Drugs with added myofilamental effects	SR-33805, CXL-1020

for Ca^{2+}.[25] Unfortunately, the first molecule was shown to have deleterious activities because AR-L 115BS also acts through A1 adenosine receptor antagonism and inhibition of G_i function resulting in a cAMP and consequently Ca^{2+} accumulation.[26] Nevertheless, newly designed drugs with directly sarcomere targeted effects seemed soon due to the emergence of the new concept for improving cardiac performance while avoiding deleterious activities (Box 1).

POTENTIAL USEFULNESS OF CA^{2+} SENSITIZER DRUGS IN AHF SYNDROME

Ca^{2+} sensitization refers to increased contractile force production at a given Ca^{2+} concentration.[8] In fact, force augmentation can be achieved through different molecular mechanisms leading to various modifications in the [Ca^{2+}]–contractile force relationship (Fig. 1). First of all, different kinases and phosphatases have the potential to modulate the phosphorylation status of myofilamental proteins, and hence they offer pharmacological targets for the modulation of the myofilamental response to Ca^{2+}.[27,28] Moreover, certain drugs targeting the interaction between cardiac troponin C (cTnC) and troponin I (cTnI) (eg, levosimendan) were also demonstrated to sensitize the myofilaments to Ca^{2+}, and this effect can thus evoke a leftward shift in the [Ca^{2+}]–contractile force relationship without increases in force production at maximal or minimal Ca^{2+} concentrations.[27,29] Downstream from these regulatory contractile proteins, the actin–myosin interface can serve also as a potential target for Ca^{2+} sensitizing drugs. Using this mechanism, EMD-57033 was shown to evoke prominent Ca^{2+} sensitization; nevertheless, this effect was accompanied by force augmentation not only at saturating Ca^{2+} levels but even at diastolic Ca^{2+} concentrations thereby compromising diastolic relaxation.[27,30,31] Finally, Ca^{2+} sensitization may reflect simply an elevation of the maximal Ca^{2+}-activated force production without changes in the midpoint of [Ca^{2+}]–contractile force relationship.[8,27]

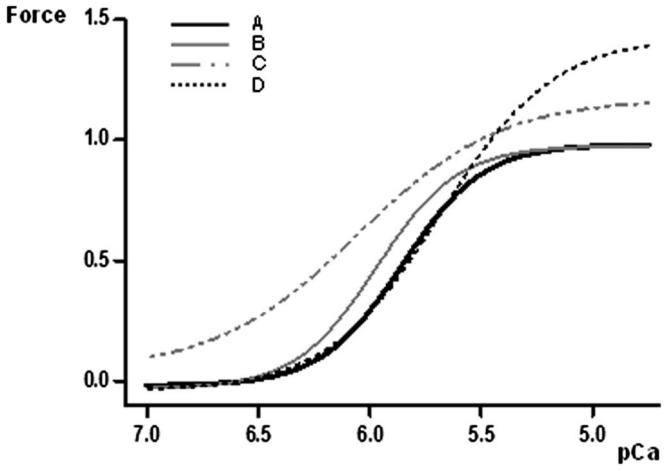

FIGURE 1. Ca^{2+} sensitization refers to increased contractile force production at a given Ca^{2+} concentration. Levosimendan (B) evokes a leftward shift in the [Ca^{2+}]–contractile force relationship without increase in the force production at maximal and minimal Ca^{2+} concentrations (control) (A). Ca^{2+} sensitization can involve force augmentations at diastolic Ca^{2+} concentrations and in the maximal force values (C). Theoretically, Ca^{2+} sensitizers might evoke increases only in the maximal force production (D).

Implications for Sarcomere Targeted Agents

- The application of inotropes can be complicated by deleterious side effects due to an increased Ca^{2+} load for cardiomyocytes
- Sarcomeric proteins are increasingly considered as potential new pharmacological targets to achieve positive inotropy without Ca^{2+} loading of the cardiomyocytes
- Modulation of different contractile proteins convey distinct mechanical responses
- Sarcomere targeted drugs may have additional cardiovascular effects
- Sarcomere activation may result in a favorable clinical outcome in selected patient populations

Levosimendan, the Inodilator Ca^{2+} Sensitizer

Levosimendan [the (−) enantiomer of 4-(1,4,5,6-tetrahydro-4-methyl-6-oxo-3-pyridazinyl)phenylhydrazonopropanedinitrile] is currently the only Ca^{2+}-sensitizer drug suggested for the treatment of the acute HF syndrome by ESC guidelines. The mechanisms of action for levosimendan involves 3 major processes: Ca^{2+} sensitization through a selective binding to the Ca^{2+}-saturated cTnC; opening of ATP-sensitive potassium (K_{ATP}) channels in the vascular smooth muscle cells and those of in the mitochondria (Fig. 2).[32]

Ca^{2+} Sensitizing Effect of Levosimendan

The troponin complex formed by 3 smaller proteins (cTnC, cTnT, and cTnI) is the sarcomeric Ca^{2+} sensitive regulator of skeletal and cardiac muscle contraction. During systole, binding of Ca^{2+} to the regulatory sites of cTnC enhances its interaction with cTnI and results in a dissociation of the

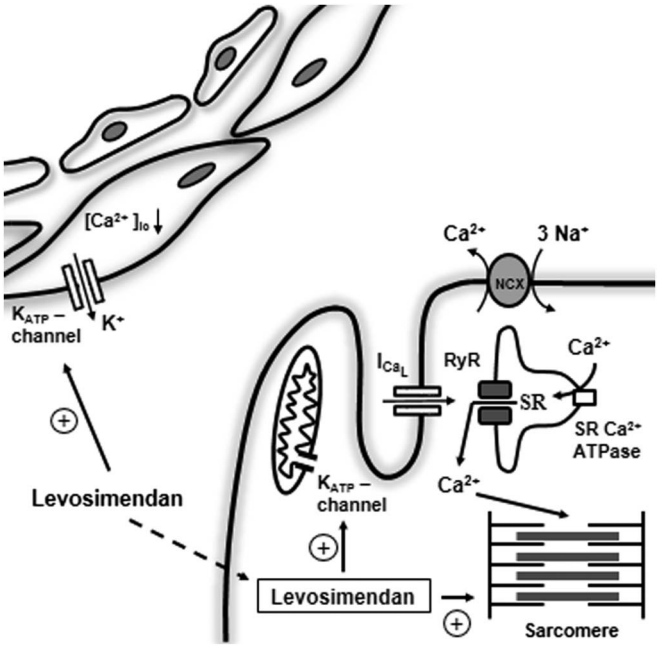

FIGURE 2. Triple mechanism of action of levosimendan. Levosimendan activates ATP-sensitive K^+ (K_{ATP}) channels in vascular smooth muscle cells. The consequent hyperpolarization inhibits inward Ca^{2+} currents resulting in vasorelaxation. Additionally, levosimendan exerts a Ca^{2+} sensitizing effect in cardiomyocytes due to the interaction with cardiac troponin C. Activating of the mitochondrial K_{ATP} in the cardiomyocytes results in short- or long-term cardioprotection. K_{ATP} channel, ATP-sensitive K^+ channel; NCX, sodium-potassium exchanger; I_{CaL}, inward calcium current; SR Ca^{2+} ATPase, Sarcoplasmic reticulum calcium ATPase.

inhibitory domain of cTnI from the actin filaments.[33] Moreover, Ca^{2+}-activated structural changes of cTnC may also evoke conformational alterations of the tropomyosin binding cTnT, promoting the translocation of the troponin–tropomyosin complex away of the actin filaments to uncover the myosin binding sites on actin.[34] All of these changes will contribute to the transition of the actin–troponin–tropomyosin complex from the blocked towards its force-generating open conformation.[33]

Levosimendan interacts specifically with the hydrophobic region of cTnC close to its D/E linker domain on the N-terminal region,[35] where the consequence of levosimendan binding is the stabilization of the open conformation of cTnC–Ca^{2+} complex strengthening its binding to cTnI. In other words, levosimendan increases the affinity of cTnC–Ca^{2+} complex for the cTnI and thus promoting a Ca^{2+} sensitizer effect through a disinhibition mechanism.[36] Levosimendan binds to cTnC in a stereo-selective manner because it was reported to be a more effective Ca^{2+} sensitizer agent than of its dextrorotatory stereoisomer referred as dextrosimendan.[37] Ca^{2+} sensitization with levosimendan offers increased cardiac contractility without changes in the intracellular Ca^{2+} concentration.[38]

Ca^{2+} sensitizer agents may impair myocardial relaxation due to Ca^{2+} sensitization at diastolic Ca^{2+} concentrations.[39] Nevertheless, diastolic function is not impaired by levosimendan treatment because drug binding to the N-terminal region of cTnC is highly Ca^{2+} dependent with a subsequent release from the binding site at diastolic Ca^{2+} levels.[40] Additionally, the magnitude of Ca^{2+} sensitization with levosimendan seems to be less than those of other Ca^{2+} sensitizing agents, which is also favorable for myocardial relaxation.[32] Moreover, positive lusitropic effects were also reported on levosimendan administrations, and not only for the healthy but also for the failing myocardium, as well.[41]

Phosphodiesterase Inhibitory Effect of Levosimendan

Levosimendan was reported to be highly selective enzyme inhibitors for the PDE III isoform in vitro.[42] Nevertheless, its effects on cAMP-dependent intracellular protein phosphorylation have not been supported equivocally.[43,44] Preclinical data suggested that that levosimendan can exert a positive inotropic effect through a Ca^{2+} sensitizing mechanism without modifications in the intracellular cAMP concentrations.[42] Of note, inhibition of the PDE III isoenzyme can be compensated by PDE IV, and hence PDE III inhibition alone might not be sufficient to increase intracellular cAMP concentrations. Accordingly, different isoenzymes of the PDE family (eg, PDE III and IV) are necessary to be blocked simultaneously and for that, higher than therapeutic levosimendan plasma concentrations should be used. The bottom line is that nonselective PDE-inhibitors (eg, milrinone) are expected to evoke more robust elevations in intracellular cAMP levels than selective PDE-inhibitors.[45]

Vasodilating Effect of Levosimendan

Levosimendan possess vasodilator effects, which were previously demonstrated at both of the arterial[46] and venous[47] sides of the vasculature as well as in coronary[48] and pulmonary arteries.[49] The vasodilator property of levosimendan involves the activation of various types of K^+ channels with a consequent hyperpolarization of the vascular smooth muscle cells. This mechanism of action results in a decrease of the intracellular Ca^{2+} concentration, initiating vascular relaxation.[50]

The opening of the glibenclamide-sensitive K_{ATP} channels was first described as an important mediator of levosimendan-induced vasodilatation by using patch clamp technique in rat mesenteric arterial myocytes.[51] Additionally, voltage-gated (K_v) and Ca^{2+}-activated K^+ channels (BK_{Ca}) were demonstrated to be involved in the levosimendan-evoked vasorelaxation, as well.[49] The proportion of the different K^+ channels in the vasodilator responses may rely on the size of the vessel, as it seems that levosimendan may preferentially stimulate K_V and BK_{Ca} channels in large conductance vessels and the K_{ATP} channel in small resistance vessels.[52,53] Moreover, the origin of the vascular beds also determines the vasodilator properties of levosimendan because the vasodilator potential of levosimendan was not identical in the pulmonary and peripheral vasculature.[54]

Organoprotective Effects of Levosimendan

More and more preclinical studies illustrate levosimendan as a potent organoprotective drug, exerting its beneficial effects not only in the myocardial tissue,[55] but also in the

kidney,[56] brain,[57] liver,[58] and in the gastrointestinal tract,[59] as well. Moreover, levosimendan was also reported to prevent sepsis-induced multiorgan damage through its antiproliferative and antiinflammatory actions.[60] Administration of levosimendan results in the downregulation of the NF-κB dependent inflammatory pathway and in the decrease of the excessive nitric oxide (NO) production in an experimental model of septic shock.[61] Leukocyte adhesion, inflammatory cytokine production, and release of reactive O_2 species were also attenuated by levosimendan treatment protecting thereby the failing heart and peripheral organs in septic shock.[62,63]

Cardioprotective properties of levosimendan may be related directly to its beneficial hemodynamic effects through dilating the arterial and venous side of the vascular beds. Consequent decrease in the preload and afterload may contribute to an energetically favorable condition related to the reduction of myocardial O_2 demand.[64] In addition to its advantageous vascular effects, myocardial protection evoked by levosimendan administration is also implied as a consequence of opening mitochondrial K_{ATP} (mK_{ATP}) channels.[65] Accordingly, activation of the mK_{ATP} channels initiates K^+ influx into the mitochondria with a consecutive decrease of the mitochondrial transmembrane potential, which stabilizes that organelle and optimizes the energy production through improving the efficiency of the oxidative metabolism.[65] Inhibitors of mK_{ATP} channels (eg, 5-hydroxy-decanoic acid) can fully abolish the antiischemic effect of levosimendan, suggesting a critical role of mK_{ATP} channels in cardioprotection.[66,67] Additionally, changes in the membrane potential of the mitochondria inhibit the opening of mitochondrial permeability transition pore, which initiates an antiapoptotic pathway through aborting the release of cytochrome c and activation of caspases.[68]

The cardioprotective action of levosimendan also involves the activation of the *reperfusion injury salvage kinase pathway* because its protein kinase B (Akt) and extracellular signal regulated kinase (Erk)-mediated central processes are upregulated either directly or indirectly on levosimendan treatment.[69,70] The above cascades initiate antiproliferative, antiphagocyte, and antiapoptotic effects through phosphorylation-dependent processes contributing to the levosimendan-induced preconditioning and postconditioning.[71]

Furthermore, the cardioprotective effect of levosimendan has been associated with NO-mediated pathways, and accordingly enhanced NO production was reported in coronary endothelial cells and in cardiomyocytes on levosimendan administrations.[72,73] It is currently debated, whether increased NO production is mediated directly through reperfusion injury salvage kinase–dependent signaling pathway or involves initial mitochondrial processes by opening of mK_{ATP} channels. Anyhow, upregulated NO production elicits reduced cell death during ischemia-reperfusion injury because of activating a collection of diverse survival mechanisms.[73–75]

Taken together, the combination of the detailed levosimendan-induced processes may be manifested clinically as short- and long-term myocardial protection.[76]

Clinical Implication for Levosimendan Treatment

Levosimendan is generally well tolerated in patients with AHF syndrome. Common side effects are hypotension and headache due to its vasodilating properties occurring more frequently in case of application with high loading doses. Atrial fibrillation, hypokalemia, and tachycardia are considered as less common side effects.[32]

To answer the question of whether the use of levosimendan might have overall favorable effects during acute and/or decompensated HF, numerous clinical investigations have been performed. The initial optimism driven by the improvement of short- and mid-tem mortality in early clinical trials (LIDO and RUSSLAN) was tempered by the less favorable outcomes of recent studies (SURVIVE and REVIVE).[77] Nevertheless, more recent meta-analyses have reported that administration of levosimendan is associated with a significant reduction of mortality in critically ill patients and in those of undergoing cardiac surgery.[78,79] Possible explanation of this discrepancy may emerge from the heterogeneity in clinical characteristics of the patient populations included in previous clinical studies. Additionally, concomitant vasodilator or diuretic therapy and differences in dosage regimen may serve with the most probable explanation for the partly disappointing results in the SURVIVE and REVIVE studies.

Pimobendan

Pimobendan is a Ca^{2+} sensitizer agent with an added PDE III inhibitory effect. The Ca^{2+} sensitizing and PDE III inhibitor activity of pimobendan are exerted at the same concentration range.[11] Ca^{2+} sensitization through binding to cTnC is decreased in the failing human myocardium when compared with that of nonfailing controls and can be abolished under acidic conditions.[80,81] Ca^{2+} overload due to PDE III inhibition might be a potential source for the observed increased incidence of arrhythmias. Accordingly, pimobendan was reported to decrease the refractoriness of left ventricular (LV) enhancing its susceptibility toward the development of ventricular arrhythmias in a postinfarction dog model.[82] Furthermore, chronic pimobendan administration might trigger mitral valve regurgitation and myocardial hypertrophy in dogs.[83] Nevertheless, pimobendan improved exercise capacity, LV performance, and quality of life in patients with severe congestive heart failure, although the risk for death was slightly increased.[84] There is lacking clinical data, whether pimobendan treatment would be beneficial in patients with AHF syndrome.

TARGETING THE CARDIAC SARCOMERE WITH MYOSIN ACTIVATORS

Targeting the cardiac sarcomere may be achieved by using the so-called cardiac myosin activator agents, as well. The theory behind this direct myosin activation is that selective modulation of the kinetics of cardiac myosin heads would improve cardiac performance while avoiding the adverse effects of traditional inotropic drugs.[85] It is to be mentioned that myosin activation can be also regarded as a Ca^{2+}-sensitizing positive inotropic mechanism that targets the contractile process downstream from the Ca^{2+}–cTnC interaction.[11]

Omecamtiv Mecarbil

The goal of optimization during the development of myofilament targeted myosin activator agents was to find

a stable molecule for short intravenous or oral administration while possessing favorable properties (eg, selectivity for cardiac myosin or no effect on Ca^{2+} handling). Ultimately, the drug candidate CK-1827452 was identified.[86]

Mechanism of Action of Omecamtiv Mecarbil

Omecamtiv mecarbil, previously referred as CK-1827452, exerts a positive inotropy through its selective binding to the S1 domain of the cardiac myosin where the relay helix and converter domain converge at the base of the force-producing lever arm. The mechanism of action evokes a conformational change in the nucleotide-binding domain of the cardiac myosin head contributing to the allosteric activation of its mechanical and enzymatic properties (Fig. 3).[86] Importantly, myosin activation does not occur when fast skeletal and smooth muscle myosin is present instead of the cardiac isoform implying a cardioselective manner of the omecamtiv mecarbil binding.[87,88]

Consistent with the allosteric modulation in the nucleotide-binding domain of the cardiac myosin, omecamtiv mecarbil, accelerates the inorganic phosphate release from the myosin heads, which is the rate-limiting step of the acto-myosin cycle. In other words, omecamtiv mecarbil increases the ATPase rate of the cardiac myosin, accelerating thereby the transition rate from the weakly to the strongly actin-bound conformation. This kind of mechanism of action also suggests that myosin activation may result in an increase of the available force-producing myosin heads in the sarcomere, indicating "more hands pulling on the rope."[87,88] Because application of omecamtiv mecarbil is associated with a decrease in the actin-independent release of P_i without any changes in the Ca^{2+} homeostasis, the myocardial O_2 consumption remains unaltered parallel with its improved efficiency[88] (Box 2).

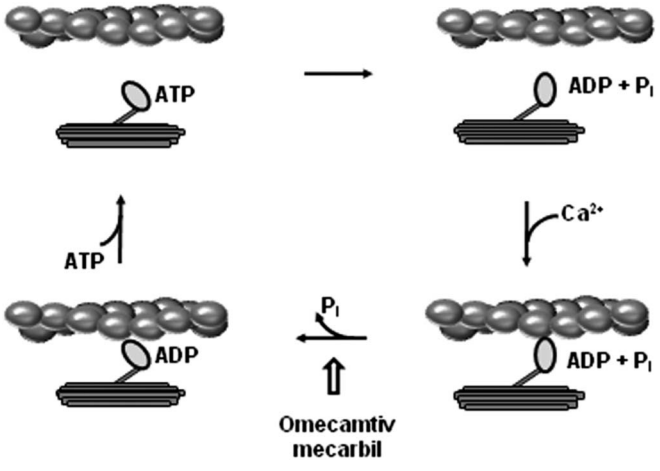

FIGURE 3. Actin–myosin cycling involves coupled biochemical and mechanical events. ATP binding to the myosin heads results in a dissociation from the actin filaments. Then, ATP is hydrolyzed to ADP + P_i. In the presence of Ca^{2+}, the myosin head binds to the actin filament forming a weakly attached conformation. Thereafter, P_i dissociates from the myosin heads resulting in a high affinity cross-bridge accompanied by the force producing power stroke step. Omecamtiv mecarbil interferes with the rate-limiting step of the actin–myosin cycle by accelerating P_i release from the myosin heads. Consequently, omecamtiv mecarbil increases the number of force-generating myosin heads contributing to enhanced cardiac contractility.

Mechanism of Action of Omecamtiv Mecarbil

- Myosin activation through cardioselective binding to myosin heads
- Acceleration of the rate-limiting Pi release step of the actin–myosin cycle
- More hands pulling on the rope

Preclinical Trials

The putative positive inotropic effect of omecamtiv mecarbil was firstly demonstrated by in vitro investigations. Omecamtiv mecarbil significantly increased the fractional shortening in isolated rat cardiomyocytes without any changes in the Ca^{2+} homeostasis measured by the fluorescent Ca^{2+} indicator. Furthermore, myosin activation resulted in an increase not only in the magnitude but also in the duration of contraction.[87]

In an in vivo dog model with pacing-induced systolic HF after myocardial infarction or chronic pressure overload, omecamtiv mecarbil infusion was shown to enhance LV stroke volume, CO, and systolic ejection time in addition to a decrease of HR, total peripheral vascular resistance, and loading pressures. Additionally, myocardial O_2 consumption and the rate of LV pressure development (dP/dT) were not affected by the application of omecamtiv mecarbil when compared with that of traditional inotropes. Interestingly, omecamtiv mecarbil produced greater and more significant increases in the systolic properties of dogs with HF compared with those of control healthy animals.[89]

One should also consider that increase in the systolic ejection time must occur at the expense of diastole, impeding thereby the ventricular and coronary filling. However, because intravenous administration of omecamtiv mecarbil was reported to decrease HR, improvements of systolic emptying should not compromise diastolic function and coronary flow.[90]

Clinical Consideration of Omecamtiv Mecarbil

Because the preclinical data demonstrated beneficial cardiovascular effects of myosin activation,[91] omecamtiv mecarbil was tested in a phase I study to determine the dose-dependent augmentation of the cardiac function and the maximum-tolerated doses and plasma concentration of the drug.[92] In the first-in-men dose-escalating study, omecamtiv mecarbil was reported to enhance the systolic functions of the LV in a dose- and concentration-dependent manner using a dose range of 0.005–1 $mg^{-1} \cdot kg \cdot h^{-1}$. Cardiac myosin activation was not accompanied by impairments in the diastolic functions in those of healthy volunteers. Additionally, the maximum-tolerated dose for omecamtiv mecarbil was 0.5 $mg^{-1} \cdot kg \cdot h^{-1}$ without any dose-related adverse effects.

The dose-limiting toxic effect was myocardial ischemia due to the detailed prolongation of the systolic ejection time.[92]

Subsequently, a double-blind, placebo-controlled, dose-ranging phase II trial was carried out in patients with systolic HF to elucidate the safety and tolerability of omecamtiv mecarbil. This clinical investigation revealed that the cardiovascular effects of the myosin activator were comparable with those of healthy volunteers assessed in the phase I study. The well-tolerated plasma concentration of omecamtiv mecarbil was proved to be within a range of 100–1200 ng/mL. At a higher plasma concentration, some of the patients revealed signs of myocardial ischemia due to the excessive prolongation of the systolic ejection time.[93]

Most recently, a randomized, controlled phase IIb trial (ATOMIC-AHF) was undertaken to evaluate the safety and efficiency of omecamtiv mecarbil in those of hospitalized with AHF. The ATOMIC-AHF revealed that myosin activation did not meet the primary end point of the study because no significant effect on dyspnea was demonstrated. Nevertheless, administration of omecamtiv mecarbil proved to be clinically safe, and the results also suggested a tendency towards reduction of worsening HF.[94–96]

Taken together, omecamtiv mecarbil seems to be a very promising approach for the treatment of systolic HF, although further clinical investigations should be evolved to elucidate whether the theory of myosin activation may be translated into the clinical practice.

CARDIOVASCULAR DRUGS WITH ADDED MYOFILAMENTAL EFFECTS—A FUTURE PERSPECTIVE

In addition to the Ca^{2+} sensitization with levosimendan and myosin activation with omecamtiv mecarbil, other cardiovascular drugs were reported to possess with added myofilamental effects. For example, SR-33805 and CXL-1020 can be also considered as an inotropic agent targeting the cardiac sarcomere.[22,97] Although the beneficial cardiovascular effects of the drugs with added myofilamental effects were demonstrated previously in preclinical investigations, further clinical trials should be performed to determine whether those applications would serve with a future perspective in the therapy of AHF syndrome.

SR-33805 was characterized firstly as a potent L-type Ca^{2+} channel (LTP) inhibitor with a consequent negative inotropic effect in electrically stimulated healthy rabbit preparations.[98] Interestingly, SR-33805 did not affect the Ca^{2+} transient in failing cardiomyocytes suggesting that its effect depends mainly on the membrane potential itself. Because HF is characterized by abnormalities in the excitation–contraction coupling and Ca^{2+} handling, electric remodeling with depolarized membrane potential may explain the decreased capacity of SR-33805 to inhibit LTP in failing myocytes.[99] Moreover, SR-33805 was demonstrated as a potent positive inotropic agent improving the contractility of the failing rat hearts by a Ca^{2+}-sensitizing mechanism relying on 2 different strategies.[100] Direct sensitization of the myofilaments was demonstrated by force measurements in permeabilized myocyte-sized preparations after in vitro SR-33805 treatment.[101] Additionally, SR-33805 targets in vivo the phosphorylation status of Ser23/24 in cTnI by an inhibition of protein kinase A activity, resulting thereby in enhanced responsiveness of the cardiac myofilaments for Ca^{2+}. Another interesting feature of SR-33805 is its beneficial effect on myocardial relaxation.[100]

HNO donor agents were previously shown to have beneficial cardiovascular effects. Accordingly, HNO donated by Angeli's salt exerted a positive inotropic and lusitropic action in dogs with HF induced by chronic LV pacing independently from the β-adrenergic signaling.[102] However, the clinical utility of Angeli's salt remained limited due to its chemical instability. A chemically unrelated agent, CXL-1020, was demonstrated to reduce both of LV and RV filling pressures and SVR similarly to that of Angeli's salt, while increasing CO and stroke volume index in patients with systolic HF.[103] HNO is hypothesized to interact with specific reactive thiol groups present in the contractile machinery promoting thereby the maximal Ca^{2+} activated force production.[104] Accordingly, HNO-mediated disulfide bond formation between critical cysteine residues of cardiac myofilaments enhanced contractile function by increasing myofilamental responsiveness to Ca^{2+}. Those findings indicate thereby a redox-based posttranslational modification in the cardiac sarcomere, providing a potential therapeutic approach for HF.[105] In addition to that of direct myofilamental effects, CXL-1020 is capable of increasing LV contractility by enhancing the Ca^{2+} cycling of the SR, as well.[22] Hence, HNO enhances ryanodin receptor 2 and SERCA2a activity without recruiting extracellular Ca^{2+} through L-type Ca^{2+} channels.[22,106,107]

CONCLUSIONS

Little progress has been made in the therapy of AHF syndrome during the last decades. Previous guidelines emphasized, that clinical application of Ca^{2+} mobilizer inotropes may have beneficial effects by increasing the cardiac contractility at whatever cost. Nevertheless, this hypothesis failed because recent clinical trials proved that impaired clinical outcome does not necessary follow the increased cardiac performance. Limitations of traditional inotropic therapy may be attributed to their mechanisms of action. Ca^{2+} mobilization increasing Ca^{2+} load may worsen ischemia by enhancing myocardial O_2 consumption and increasing the risks for arrhythmias. Sarcomere targeted agents can potentially alleviate these problems. Novel strategies with Ca^{2+} sensitizers with or without additional effects exhibit promising preclinical and clinical results. Nevertheless, further clinical trials will help to decide, whether this hypothesis can be translated into favorable clinical outcome. However, because levosimendan has shown evidence of short-term benefits without adverse long-term events, we think this should be the minimum standard for any future inotropic or inodilator drug developed for the treatment of HF.

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