LEVOSIMENDAN IN THE PEDIATRIC PATIENT

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The mechanisms of inotropes

The purpose of inotropic interventions in heart failure is to increase the muscular contractile force of the myocardium. Current approaches to increasing contractility are accomplished primarily through increasing the influx of calcium or maintaining higher calcium levels in the cytosol of cardiac myocytes during an action potential. Much of the mechanistic data in this realm is based on animal models. Contraction occurs in several ways. First, catecholamines increase contractile force largely via the β-adrenoceptor-adenylyl cyclase system. Through protein kinase A, the β-adrenoceptor system phosphorylates L-type calcium channels to increase calcium influx and ryanodine receptors to increase sarcoplasmic reticulum calcium release, resulting in activation of actomyosin cross-bridges. Phosphorylation of phospholamban accelerates accumulation of calcium. In addition, relaxation is supported by phosphorylation of troponin I due to reduced calcium sensitivity of troponin C (positive lusitropy). Length-dependent activation of cross-bridges — the so-called 'Frank – Starling mechanism' — plays a role along with contraction frequency-dependent activation of contractile force, where increasing heart rate causes more calcium to enter the cardiomyocyte for release during the next contraction. At the cross-bridge level, cyclic adenosine monophosphate (cAMP)-mediated increase in contractility reduces the attachment time of the individual cross-bridge. As a result, this cAMP-mediated inotropy increases the rate of force development and rate of relaxation, potentially at the expense of 'energetic efficiency'.
The impact of these molecular changes occurs at the level of the smallest force-producing unit, the actomyosin cross-bridge. During a cross-bridge cycle, the myosin head attaches to actin, rotates to

produce force, and maintains during the ‘on-time’. This effect is dependent upon the availability of high energy phosphates that are hydrolysed during this process. Thereafter, the cross-bridge detaches again to enter its non-force-producing state for the duration of the ‘off-time’. The contractile force depends on the number of cross-bridges attached per unit of time. These cross-bridges are activated by calcium binding to troponin C with the subsequent conformational changes of tropomyosin and troponin I to facilitate actomyosin interaction. The muscle relaxes when calcium is pumped back into the sarcoplasmic reticulum by the sarcoplasmic reticulum calcium pump (SERCA) and transported outside the cell by the sodium–calcium exchanger, a process that is also dependent on cellular metabolism. On the level of the actomyosin cross-bridge, inotropy relies largely on: (i) the amount of calcium available to bind to troponin C, (ii) the calcium affinity of troponin C, and (iii) the duration of the force-producing state with availability of high energy phosphates.

Inotropic therapy and Levosimendan

Decompensated heart failure can affect infants and children with primary myocardial disease secondary to myocarditis or idiopathic dilated cardio-myopathy, after systemic sepsis, and, perhaps most commonly, after surgery for congenital heart disease. The intensive care management of severe cardiac failure in children is aimed at improving myocardial performance and modifying loading conditions, using pharmacologic agents and nonpharmacologic therapies including ventilation. Catecholamines are often useful in the short term but may have unwanted chronotropic effects and can increase myocardial oxygen consumption. Tachyphylaxis, desensitization of beta-adrenergic pathways in patients with chronic heart failure, and concomitant use of beta-blockers may further limit the efficacy of catecholamines in those

patients who are in greatest need of effective inotropic therapy. Thus, agents with alternative modes of action may be particularly appealing for these children.

Levosimendan (Levo) is a calcium-sensitizer that exerts inotropic actions by binding to cardiac troponin C and increasing the sensitivity of the contractile apparatus to calcium. Levo also produces coronary and peripheral vasodilation by opening the mitochondrial adenosine triphosphate-dependent potassium channels of vascular smooth muscle.

Experience with Levo in the pediatric setting

From January 2018 to June 2019 in our Cardiac Intensive Care Unit, levo was administered 232 times to 64 patients who received an average (standard deviation) number of 3.6 (5.2) runs of the drug at a dose of 0.1 mcg/kg/min. According to admission records, these patients were predominantly non-surgical medical (132 times, 57%) and surgical (emergent procedures in 47 cases -20%- and 55 elective procedures -23%-). These patients were 1,500 (2,161) days old. Differently, levosimendan was not administered to the remaining 557 patients corresponding to a total of 949 admissions. Unsurprisingly, the admission diagnoses were different in this subgroup and included 610 elective surgery patients (64%), 272 medical patients (27%) and 45 emergent surgeries (5%), with 4% of patients without classification. Age of this group was 2,100 (3,063) days old.

In order to more granularly observe the hemodynamic effects of this drug on post-operative low cardiac output syndrome, a recent randomized controlled trial was conducted at our Institution in neonates undergoing risk-adjusted classification for congenital heart surgery (RACHS) 3 and 4 procedures who were randomized to receive either a 72 h continuous infusion of 0.1 mcg/kg/min levosimendan or standard post-CPB inotropes infusion. Sixty-three patients (32 cases and 31 controls) were recruited. There were no differences between groups regarding demographic and

baseline clinical data. No side effects were observed. There were no significant differences in mortality (1 vs. 3 patients, p = 0.35), length of mechanical ventilation (5.9 ± 5 vs. 6.9 ± 8 days, p = 0.54), and pediatric cardiac intensive care unit (PCICU) stay (11 ± 8 vs. 14 ± 14 days, p = 0.26). The incidence of Low cardiac output syndrome showed a clear trend to improvement because it occurred in 37 % of levosimendan patients and in 61 % of controls (p = 0.059, OR 0.38, 95 % CI 0.14–1.0). Postoperative heart rate was significantly decreased in the levo group, with a significant difference at 6 (p = 0.008), 12 (p = 0.037), and 24 postoperative hours (p = 0.046). Lactate levels also showed a signiciant improvement in the levosimendan group, with a significant difference at PCICU admission (p = 0.015) and after 6 h (p = 0.048). Inotropic score was significantly lower in the levosimendan group at PCICU admission, after 6 h and after 12 h, (p <0.0001). According to multivariate analysis, a lower lactate level 6 h after PCICU admission was independently associated with levosimendan administration after correction for CPB time and the need for deep hypothermic circulatory arrest. In our experience, levosimendan infused in high risk cardiac-surgery patients was well tolerated with a potential benefit of levosimendan on postoperative hemodynamic and metabolic parameters.

A recent meta-analysis on 5 randomized controlled trials concluded that “the current level of evidence is insufficient to judge whether prophylactic levosimendan prevents low cardiac output syndrome and mortality in pediatric patients undergoing surgery for congenital heart disease”. However, the current level of evidence is insufficient to judge whether prophylactic levosimendan prevents low cardiac output syndrome and mortality in paediatric patients undergoing surgery for congenital heart disease. So far, no significant differences have been detected between levosimendan and standard inotrope treatments in this setting. Published literature presents serious risk of bias (performance and detection bias due to unblinded setting of two RCTs), serious

risk of inconsistency, and serious to very serious risk of imprecision (small number of included patients, low event rates).

Furthermore, the utilization of the drug in patients with cardiac failure should not necessarily be prophylactic in order to prevent post-operative LCOS, which is strictly related to the effects of surgery and/or cardiopulmonary bypass.

Experience in specific populations

Benefit from inotropes might only be restricted to sub-phenotypes of heart failure

Heart failure is not a singular disease. Rather, it is a syndrome that likely comprises several diseases with unique underlying mechanisms and trajectories. Moreover, classification systems based on a century old assessment of functional status (NYHA class), or LVEF cut-points are fundamentally dissociated from both mechanistic and clinical actuality. Whereas trials of neurohormonal blockade have succeeded despite these constraints, we might now need to identify specific subgroups of the syndrome that respond favorably to inotropes, in a manner analogous to cardiac resynchronization therapy. Thus far, all clinical trials of positive inotropes in heart failure have been anchored in broad measures of disease, leading to overly simplified and often inaccurate assumptions about how these therapies might help patients. The significant drawbacks of this approach were demonstrated in a post-hoc analysis of the OPTIME-CHF trial that showed a substantial impact of heart failure aetiology (ischaemic vs. non-ischaemic) on clinical outcomes with milrinone, with harm seen in patients with ischaemic disease. In a manner analogous to how a therapy would not be tested generically for lung cancer or anaemia, we would be well served by testing future inotropes in a sub-population of the syndrome (e.g. non-ischaemic dilated cardiomyopathy) that might benefit from the therapy. While there is a dearth of relevant data to approve therapies based on subtypes of heart failure, one population that may benefit are

those with advanced, chronic heart failure and low out- put. Alternatively, inotropes with potentially anti-remodelling properties, such as omecamtiv mecarbil, could potentially be used at an earlier stage.

Levosimendan effects on energetics of univentricular hearts after palliation

We recently studied vebntricular arterial coupling (VAC) in a small subgroup of neonates with univentricular heart after palliation with the Norwood or the hybrid procedure. This specific population resulted in "uncoupled" conditions (VAC>1), that highlighted the clinical state better than other hypoperfusion indexes (e.g. absolute CI values, lactates, base excess): the higher was the pre-infusion VAC, the better appeared the improvement achieved by this drug. The administration of levosimendan in these children was peculiar and rather rdelayed. The median post-operative time of levosimendan administration to our sample was 14 days and all patients had closed sternum. Above all, in none of the described cases significant hemodynamic instability was present nor the issue of pulmonary overflow was suspected. All patients showed some form of uncoupling between the single ventricle and the arterial circulation (e.g. VAC>1) that was present both in patients with low CI (e.g. below 1.5 ml/min/m2) and in those with apparently normal CI (e.g. above 2.5 L/min/m2). This is a specifically important aspect in univentricular anatomies. In particular, as showed by our findings, relatively high arertial elastance (Ea) and low ventricular elastance (EMAX) values were present in these patients. This is likely due to the poor contractile efficiency of neonatal myocardium coupled with the high impedance of neo-aortas (pressure overload) and the volume overload that is present in univentricular hearts (even when Qp/Qs is balanced). Interestingly, VAC modifications seemed not to be related to the type of palliation (hybrid procedure vs Norwood stage I) and as a matter of fact, literature has not expressed clear advantages of one technique vs the other. It is likely that, in terms of ventricular

energetics, both aortic arch reconstruction with shunt and ductal stenting with pulmonary banding imply high ventricular afterload and increased Ea values. In the midterm, the EMAX level needed to couple such condition has to be relatively high and may progressively deteriorate: in our opinion, this is exactly the clinical condition we decided to manage with levosimendan. According to our results, the improvement in VAC depended on Ea reduction but, to a greater extent, to EMAX increase. Interestingly, not all patients responded to the therapy in the same way and, apparently, younger patients showed a lower response to levosimendan than older ones. This is potentially due to the immaturity of neonatal hearts that, among other features, feature a poor control of intra cytosolic calcium concentration from an underdeveloped sarcoplasmic reticulum with contractile dependence on free cytosolic Calcium fluxes and immature mitochondria, irregularly scattered between few and relatively disorganized sarcomeres, leading to a lower effect of calcium sensitizers drug (or, potentially, to the requirement of higher dosages). Also interesting is the finding that cardiac mechanical efficiency (CME), the ratio of stoke work (SW) over pressure-volume area (PVA), increased, whereas PVA (the sum of SW to potential energy -PE) did not show significant modifications: this might be due to the fact that SW increased at the expenses of PE. In other words, levosimendan recruited “potential” contractility of these hearts by increasing their efficiency. Unsurprisingly, indexes of diastolic function (i.e. central venous pressure, end diastolic volume, diastolic elastance) were not significantly affected by levosimendan therapy, even if the significant decrease of heart rate, that might be secondary to improvement of systolic function, certainly contributed to prolong diastolic ventricular filling times.

Conclusions

Heart failure in children is typically observed in cardiomyopathies and post cardiac surgery patients. Levosimendan has been studied in multiple settings and unequivocal data is not currently available regarding its efficacy in the pediatric setting. The main benefits of the drug are related to the potential of acting in a non-catecholamine-like fashion, being a calcium sensitizer. This may imply its administration together or in place of more commonly infused drugs (e.g. adrenalin, milrinone). Also, its potent vasodilation effect can be theoretically useful in patients with "uncoupled" VAC. All published experiences, furthermore, confirm its safety profile at all pediatric ages. At our institution levosimendan is frequently administered to patients below 5 years of age and typically admitted with a "medical" diagnosis. However, in a randomized trial on elective neonates undergoing high risk surgery, levosimendan showed to improve perfusion indexes and reduce inotropic score with an evident tendency to reduce the occurrence of post-operative low cardiac output. Furthermore, interestingly, levosimendan reduced heart rate of treated patients, implying an improved systolic function and the optimization of diastolic times. Future studies should better clarify the optimal timing and subgroup population at which this drug may display its most beneficial effects, possibly coupled with direct cardiac output measurements.

SUGGESTED READINGS

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