Pharmacological Heart Failure Therapy in Children: Focus on Inotropic Support

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Contents

Abstract

Pediatric heart failure is a clinical syndrome, which needs to be distinctly defined and the pathophysiological consequences considered. Pharmacological treatment depends on the disease- and age-specific myocardial characteristics. Acute and chronic low cardiac output is the result of an inadequate heart rate (rhythm), myocardial contractility, preload and afterload, and also ventriculo-ventricular interaction, synchrony, atrio-ventricular and ventricular-arterial coupling. The treatment of choice is curing the cause of heart failure, if possible.

Acute HF therapy is still based to the use of catecholamines and inodilators. The cornerstone of chronic HF treatment consists of blocking the endogenous, neurohumoral axis, in particular the adrenergic and renin-angiotensin-aldosterone system.

Before neprilysin inhibitors are used in young children, their potential side-effect for inducing Alzheimer disease needs to be clarified. The focus of the current review is put on the differential use of the inotropic drugs as epinephrine, norepinephrine, dopamine and dobutamine, and also the inodilators milrinone and levosimendan. Considering effects and side-effects of any cardiac stimulating

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© Springer Nature Switzerland AG 2019
Handbook of Experimental Pharmacology, https://doi.org/10.1007/164_2019_267

treatment strategy, co-medication with ß-blockers, angiotensin converting inhibitors (ACEIs), angiotensin blockers (ARBs) and mineralocorticoid receptor antagonists (MRAs) is not a contradiction, but a senseful measure, even still during the acute inotropic treatment.

Missing sophisticated clinical trials using accurate entry criteria and clinically relevant endpoints, there is especially in cardiovascular diagnosis and treatment of young children a compromise of evidence-based versus pathophysiology-based procedures. But based on the pharmacological and pathophysiological knowledge a hypothesis-driven individualized treatment is already currently possible and therefore indicated.

Keywords
Children · Heart failure · Inotrops · Pharmacology

1 Definition and Pathophysiology of Heart Failure

Pediatric heart failure (HF) is defined as a clinical syndrome (Kirk et al. 2014; Braunwald 2013). Cardiac output (CO) and systemic blood flow (SBF) are acute or chronically reduced, whether at rest or only during exercise. Therefore, HF is also characterized by a general mismatch of blood supply and demand independent whether caused by ventricular dysfunction, pressure or volume overload, or arrhythmias. From the pathophysiological point of view, low CO might be caused by the sum of all components but even any single component of either inadequate heart rate (rhythm), myocardial contractility, preload and afterload or loss of ventriculo-ventricular interaction, synchronized contractility, or atrioventricular and ventricular-arterial coupling.

Neurohumoral and molecular abnormalities are related to the severity of HF and independent if caused by pump or over-circulation failure. Over-circulation can also be related to a normal or even hypercontractile myocardium. Causes of pump failing might be associated with congenital or acquired diseases. Therefore, the treatment of choice of any heart failure is correction of the cause of the disease, whenever such is possible.

2 Pharmacological Therapy of Pediatric Heart Failure (PHF)

Medical HF therapy of adult patients with chronic heart failure led to a significant improvement in survival (Braunwald 2013). While acute HF therapy is still related to the use of catecholamines and inodilators, the cornerstone of chronic HF treatment consists of blocking the endogenous, neurohumoral axis, in particular the adrenergic and renin-angiotensin-aldosterone system (Yancy et al. 2017). Since decades, ß-blockers (BB), angiotensin-converting enzyme inhibitors (ACEIs), angiotensin II receptor blockers (ARBs), and mineralocorticoid receptor antagonists (MRAs) are successfully used in adults with a safe, but highly effective, treatment profile (Yancy et al. 2017). Meanwhile, novel agents, which combined blocking of neprilysin

enzyme and angiotensin receptors (sacubitril, Entresto®), are approved for HF therapy in adults (McMurray et al. 2014). However, that does not mean neprilysin enzyme inhibitors have to be used in children; at first, there is not a need for utilizing inhibitors of the enzyme neprilysin as long as the current available anti-congestive cardiovascular drugs are not fully exhausted in terms of the drug-specific pharmacological profile and tailored to the disease. Furthermore, the theoretical side effects of neprilysin inhibitors inducing Alzheimer disease need fully be excluded. Neprilysin is an important cerebral transmitter for avoiding plaque formation (Yasojima et al. 2001; Farris et al. 2007; El-Amouri et al. 2008). Nevertheless, considering the success story in treating adult HF, the question arises: what did run wrong over the last decades treating pediatric patients with HF? Especially, considering patients with a high cardiac regeneration potential, which inverse correlates to the patient's age (Mollovaa et al. 2013). Still today, the pediatric heart failure therapy is based on the triple *D* strategy (Kreidberg et al. 1963; Engle et al. 1978; Digitalis Investigation Group (DIG) 1997; Rodriguez et al. 2008; Kantor et al. 2013), *d*iuretics, *d*igoxin, and *d*iet (fluid restriction). Diuretics are used as first-line heart failure drugs, oftentimes independent on their need and the pathophysiological condition with any signs of systemic or pulmonary vein congestion, only based on the diagnosis "heart failure," neglecting that HF is a "syndrome" in consequence of multiple possible diseases (Schranz and Voelkel 2016). The MR-antagonist spironolactone is usually utilized by pediatricians as a diuretic drug, instead of a low dosage with a significant impact on myocardial fibrosis as it could demonstrated in adults (Pitt et al. 1999) and even in children (Masutani et al. 2013).

Digoxin is though recommended but in modern pediatric guidelines remarked with a questionable effectiveness (Kantor et al. 2013). ACEIs and BB are recommended for functional class I and II but still less used (Kantor et al. 2013; Masutani et al. 2013), not to mention their use, tailored on the specific pediatric disease (Rodriguez et al. 2008; Schranz and Voelkel 2016). Still in 2006, only 5% of pediatric HF patients received BB in the USA (Towbin et al. 2006), since then there is only a slight tendency for increasing utilization (Frobel et al. 2009). Additionally, there is not only a low pediatric experience treating chronic heart failure with BB but further without any differential use regarding the specific drug profiles in consideration of the cause of HF (Masarone et al. 2017). It might be a crucial reason that "negative" results of the few studies labeled as evidence-based because of its double-blind, randomized, placebo-controlled multicenter study design led to the worldwide opinion of pediatricians and also pediatric cardiologists that ß-blockers are questionable for treating infants and children with HF (Kantor et al. 2013; Shaddy et al. 2007; Pasquali Sara et al. 2008; Rossano and Shaddy 2014). These results of "evidence-based" studies had a dramatic impact on the current chronic therapy of HF in children. Considering the lack of "evidence-based" studies, the chance arises that pediatric heart failure therapy will become earlier individualized by pharmacological and pathophysiological knowledge in context of the molecular specifics of pediatric cardiovascular diseases (Noori and Seri 2015).

3 Acute Heart Failure Therapy

Regarding HF caused by myocardial dysfunction, the goal of acute medical therapy consists of life-saving measures to transfer the acute dysfunctional heart back to normal or chronic livable condition. In affluent countries, patients with irreversible myocardial injuries are bridged for heart transplantation (HTx) in part with utilizing an assist device (Towbin et al. 2006); young children with left-sided dilated cardiomyopathy (DCM) and preserved right ventricular function are also back to a functional regeneration (Schranz et al. 2013, 2018).

4 Inotropic Drugs

4.1 Considerations Before Utilizing Inotropic Drugs

4.1.1 Receptor: Physiological Aspects

Adrenergic receptors (ARs) are involved in the regulation of cardiovascular, bronchial, and gastrointestinal smooth muscle tone. In principle, three AR types are differentiated, alpha-, beta (ß)-, and dopaminergic receptors; endogenous AR agonists are available as sympathetic transmitter and neurohumoral agents (Lefkowitz and Caron 1985).

Alpha-1 (a,b,c)-adrenergic and alpha-2 (a,b,c) receptors are differentiated (Han et al. 1987); alpha-1 agonists cause phosphatidylinositol-dependent cellular calcium influx; postsynaptic alpha-1 AR stimulation leads to vasoconstriction, positive-inotropic, and negative-chronotropic myocardial effects. Presynaptic alpha-2 AR stimulation counteracts via adenyl cyclase pathway the alpha-1 AR activation; one important effect is the inhibition of norepinephrine release from the synaptic vesicles. The central alpha-2 stimulation inhibits via reflex circuit within the locus coeruleus and leads to peripheral vasodilation and heart rate decrease. Stimulation of postsynaptic alpha-2 AR is associated with an arteriolar vasoconstriction (Brodde 1991). The main ARs of the heart are ß1- and ß2-receptors (Bristow 1989); the role of also cloned ß3-ARs concerning its sinoatrial effects is still not fully understood (Emorine et al. 1989).

Non-failing adult hearts have ß1/ß2 ratio of almost 80 to 20, respectively (Brodde 1991; Bristow 1989). The affinity of ß2-AR to the adenylate cyclase (AC) seems to be higher; both ß-ARs transmit positive-inotropic and positive-chronotropic activity. A failing adult heart is characterized by almost unchanged ß2-AR density, contrary to downregulated ß1-receptors; the resulting ratio changes to a ratio of almost 60 to 40, respectively. Additionally, AR subsensitivity due to uncoupling of ß-AR is described (Brodde 1991). More recently published studies analyzing harvested hearts of adult and pediatric patients with dilative cardiomyopathy (DCM) confirmed the known AR pathophysiology of failing adult hearts but also demonstrate differences to pediatric DCM patients. Pediatric DCM patients showed both ß1- and ß2-AR downregulation (Miyamoto et al. 2014). Considering the pathways of ß1- and ß2-ARs, coupling to intracellular signaling responsible for contractility and

remodeling are different and even though more complex. Chronic ß1-receptor stimulation might be associated with cardiotoxic properties (apoptosis, necrosis), whereas the ß2-receptor stimulation seems to be "cardioprotective" (Bristow 1989; Miyamoto et al. 2014; Lakatta 1993; Xiao et al. 2004; Bernstein et al. 2011). Hence, therapeutic strategies were developed in advanced heart failure patients by blocking selectively the ß1-AR combined with simultaneous ß2-AR stimulation (Navaratnarajah et al. 2014). Patients with myocarditis and DCM (Narula et al. 1996; Collucci 1998) but also children after cardiopulmonary bypass with cardiac arrest seem to have endogenous, norepinephrine-related myocardial injury by excessive ß1-stimulation recognizable by ß1-selective desensitization followed by AR downregulation (Schranz et al. 1993). The mechanism of AR desensitization is caused by AR phosphorylation by a protein kinase and ß-adreno-kinase (Bristow 1989). Regarding coronary vessels, alpha-receptors dominate epicardial coronary vessels, whereas ß-receptors preferring endocardial coronaries (Young et al. 1990). Activation of alpha-receptors led to vasoconstriction. Therefore, newborns with hypoplastic left heart syndrome with an associated small (1–2 mm) ascending aorta are jeopardized by vasoconstriction and consecutive additional ischemic arrest if resuscitated by too high dosages of epi- or norepinephrine. Coronaries and the peripheral vessel system react on ß-AR, in particular of ß2-stimulation with vasodilation as well as the bronchial and gastrointestinal smooth muscle system. Nephrogenic renin release is in particular related to ß1-AR stimulation (Atlas 2007).

4.1.2 Neonatal Myocardial Aspects

Inotropic treatment needs to be reflected in context of the physiologic less compliant myocardium of neonates and in particular premature babies (Teitel et al. 2008; Borg et al. 1984; Jonker et al. 1985; Sperelakis and Pappano 1983). Contrary to highly compliant adult hearts, there is a quite lower ratio of contractile elements to the nutritive interstitial tissue (Teitel et al. 2008; Borg et al. 1984; Sperelakis and Pappano 1983; Li et al. 1996). Only severely injured neonatal hearts (i.e., myocarditis, congenital DCM) might be effectively treated by inotropic agents (Norris et al. 2008) but only in terms of an acute HF treatment. Inotropes are clinically best indicated, when the heart rate does not or increase only slightly during or despite continuous infusion of catecholamines (Norris et al. 2008). Additionally, neonates have an imbalanced cardiac autonomous innervation with vagal preference (Borg et al. 1984), one reason for hypoxia-induced bradycardia or even a systolic reaction of infants compared to tachycardic reactions or ventricular fibrillation as usually seen in adult patients. Despite less matured sympathetic innervation, the cardiac ß-receptors are already fully developed (Atlas 2007; Jonker et al. 1985). Further, the myocardial calcium-dependent contraction as well as relaxation differs between children and adults (Sperelakis and Pappano 1983; Li et al. 1996). Contraction is dependent on the binding of calcium to the myofilaments. But calcium is also important to regulate cardiomyocyte growth, differentiation, and development as well as gene expression (Sperelakis and Pappano 1983). Cardiac myocytes contract by a rapid elevation of calcium of the cytoplasmatic calcium concentration. Adult myocytes open L-type calcium channels during action potential triggering release of

sarcoplasmic stored calcium via ryanodine receptors leading to an approximate tenfold increase of free cytosolic calcium concentrations (Sperelakis and Pappano 1983; Li et al. 1996). Cardiac contraction in premature and term neonates depends mainly on a transmembrane myocardial calcium influx and calcium removal from the cells via Na^{+}/Ca^{2+}exchanger (NCX) receptors. Further, the function of the sarcoplasmatic reticulum is inversely developed to the age (Teitel et al. 2008; Jonker et al. 1985). Considering the physiological conditions of the neonatal heart, calcium is in principle a strong and effective inotropic substance; low calcium levels (< 0.9 mmol/l ionized calcium) have to be avoided in any, especially young, dysfunctional hearts. Further, inotropic properties of digoxin based on NCX blocking properties are also inversely related to the patient's age (Schranz 1993; Louch et al. 2015). However, the less compliant neonatal myocardium and especially of premature hearts contradicts oftentimes an effective use of digoxin as an inotropic drug, but not as a negative chronotropic agent.

4.2 Digoxin

It can be assumed that digoxin is still the most commonly used oral inotropic drug treating pediatric HF in the world. Digoxin is traditionally used despite its very narrow therapeutic range and the lack of trial evidence (Schranz 1993; Louch et al. 2015). In adults, digoxin improved quality of life, but not the survival rate (Seguchi et al. 1999). Digoxin is mostly unsuitable for acute HF treatment especially in the setting of renal failure and acute myocarditis and in combination of amiodarone or even carvedilol, all favoring digoxin toxicity (Digitalis Investigation Group 1997; Ratnapalan et al. 2003); in any case, electrolyte imbalances (low serum levels of potassium and magnesium) should be corrected before therapy with digoxin is started.

For chronic HF therapy, digoxin might be indicated as a fourth-line drug in patients with a pure systolic dysfunctional heart, when ß-blocker, ACEI, and mineralocorticoid inhibitors are already applied, but the heart is still beating too fast and the patient's age is young (Schranz and Voelkel 2016; Hussey and Weintraub 2016). Digoxin should be avoided in HF with a restrictive cardiac physiology and because of its vasoconstrictive properties in patients with a need for a low systemic vascular resistance. The observation of some beneficial effects of digoxin in HLHS during the interstage after Norwood surgery (Oster et al. 2016) might be related to its heart rate-reducing effects and consecutive increased diastolic time interval, which might be related to an improved diastolic inflow counteracting probably a digoxin-dependent increase of systemic vascular resistance.

Targeting digoxin serum concentrations from 0.5 to 0.9 ng/ml is achievable by a maintenance dosage of 10 µg/kg/day.

4.3 Characterization of Catecholamines, PDE-III-Inhibitors and Calcium Sensitizers

Epinephrine and its biosynthetic precursor norepinephrine are endogenous catecholamines. Epinephrine with its ß1-, ß2-, and alpha-adrenoreceptor (AR) stimulation and norepinephrine with ß1- and alpha-AR agonistic properties are worldwide still the most utilized catecholamines (Furchgott 1959). Epinephrine is the drug of choice to resuscitate pediatric patients suffering cardiac arrest; the dose efficacy correlates inversely to the patient's age (Clutter et al. 1980). The hemodynamic effectiveness of epinephrine correlates to its serum concentrations (Shavit et al. 1989). The basal level in adults ranged between 24 and 74 pg/ml. Serum levels between 75 and 125 pg/ml increase the heart rate (ß-stimulation). The diastolic blood pressure might decrease via ß2-stimulation with serum levels of 150–200 pg/ml. Higher serum levels cause vasoconstriction by dominant alpha-receptor stimulation. Depending on the utilized (resuscitation) dosages, coronary and cerebral perfusion pressure should be re-established by vasoconstriction with consecutive increase of systemic vascular resistance (Rs); contractility and heart rate can additionally improve in lower dosages, when myocardial perfusion pressure is re-established and adequate. Contrary to other catecholamines (dobutamine, dopamine), epinephrine has the advantage of a remaining effectiveness also during acidosis. Epinephrine is like isoprenaline a "full AR agonist"; its high affinity to the ß1- and ß2-ARs guarantees effective action also during a dobutamine refractory cardiovascular state (Barber and Wyckoff 2006). The value of the myocardial alpha-receptor stimulation during acute and in particular young patients with decompensated cardiovascular shock is still not fully understood. However, alpha-mimetic stimulation might be inversely preserved to the patient's age; it seems that neonatal myocytes react more pronounced to alpha-AR stimulation compared to adult hearts as well as the troponin C-calcium affinity (Mullett et al. 1992). Considering pharmacological and pathophysiological conditions, the main indication for treating patients with epinephrine is a combined risk of reduced myocardial contractility with endangered coronary perfusion pressure. Epinephrine is usually used by continuous infusion in a wide range of dosages of 0.001–0.01 – 0.1–1 – (5) µg/kg/min depending on the therapeutic aims. The drug is in particular suitable, when the patient's cardiovascular condition is changing in short time intervals. Low dosages, in children even in a dosage of 0.01–0.3 µg/kg/min, outweigh ß-mimetic effects. Regarding special myocardial conditions with a high risk of endogenous induced (norepinephrine release) myocardial apoptosis and necrosis like in infants with DCM, there is a need and not a contradiction utilizing a ß1-receptor blocker (oral bisoprolol or intravenously landiolol, metoprolol or esmolol) together with continuously infused epinephrine (Recla et al. 2013). Highly specific ß1-receptor blockers favor myocardial contractility via ß2-agonistic effects, avoiding further myocardial injury by additional exogenous ß1-stimulation, and do allow alpha-mimetic stimulation, if needed (Wyckoff et al. 2015). Apart from cardiovascular shock, inappropriate epinephrine application needs always, almost continuously excluded; oxygen debt, inadequate vasoconstriction (intravascular volume deficit), disturbance of

microcirculation are well-known side effects. Epinephrine stimulates even the renal renin release and activity via renal ß1-receptor stimulation as well as by vasoconstriction, if not counteracted by an improved cardiac output and consecutive renal blood flow. Positive effects of epinephrine on the respiratory tract might even be attractive (side effects) in cardiovascular-compromised patients. Beneficial effects of epinephrine in low dosage of 0.001 µg/kg/min mediated by ß(2)-receptors are expected in particular to treat young children and infants by its bronchodilative properties and inhibitory effects on mast cell degranulation. Metabolic effects of applied epinephrine correspond to endogenous stress reactions as gluconeogenesis and insulin resistance but also to low potassium serum level related to proarrhythmic effects (ß2-mediated). Alkaline medium inactivates epinephrine; hence combined application with bicarbonate has to be avoided.

Norepinephrine serum levels correlate with the severity of heart failure (Ross et al. 1987). Considering an *age-dependent changes in the beta-adrenoceptor–G protein(s)–adenylyl cyclase system* (Brodde et al. 1995), norepinephrine acts as a positive inotrope as the precursor of epinephrine and as neurotransmitter via ß1- and perhaps alpha-AR mimetic properties. The alpha-mimetic effects constrict veins and arteries; ß2-mimetic effects are not applicable. Norepinephrine continuously infused in a low dosage of 0.01 µg/kg/min stimulates preferentially ß1-receptors; slightly higher dosages of 0.05–0.1 µg/kg/min have mixed ß1- and alpha-mimetic effects; in high dosages, above 0.1 (−5) µg/kg/min, alpha-receptor-related effects are dominant. The main indication of norepinephrine is restoring or maintaining an adequate coronary or myocardial perfusion pressure. The norepinephrine dosage is used by its effects; therefore, therapy counteracting measures as intravascular volume depletion have to be excluded avoiding inadequate high norepinephrine dosages with consecutive myocardial apoptosis followed by necrosis. Volume-resistant cardiovascular conditions with loss of peripheral precapillary vascular tone (sepsis, anaphylactic reaction, post-cardiopulmonary bypass) indicate the use of norepinephrine. Intravascular volume depletion excluded, norepinephrine infusion in relative low dosages of 0.05–0.1 (max0.3) µg/kg/min is highly effective with less side-effects in particular, as on renal and pulmonary vascular system; considering the ratio of effects and side effects, norepinephrine is almost always to prefer dopamine in high (alpha-mimetic) dosage. Side effects of dopamine are tachycardia, pulmonary vasoconstriction, high myocardial oxygen consumption as well as TRH and prolactin inhibiting effects. The option to add dopamine in low dosages (2 µg/kg/min) remains open. An important indication of norepinephrine is "right" heart failure associated with high right ventricular end-diastolic pressures (RVEDP), independent if caused by cardiac or pulmonary diseases. Low myocardial perfusion pressure (difference of systemic diastolic blood pressure and RVEDP or right atrial pressure (RAP)/coronary sinus pressure) needs often be treated by continuous norepinephrine infusion but even by immediate bolus injection in acute cardiovascular-compromised conditions. Myocardia performance is related to the adequacy of coronary perfusion; therefore, an additional ß1-blockade to avoid ß1-related

tachycardia is not a contraindication but a highly effective measure (myocardial necrosis, diastolic time!). Clinical conditions with no chance to reduce pulmonary vascular resistance (Rp) can be effectively treated by increasing systemic vascular resistance (Rs) (Vlahakes et al. 1981).

Dopamine, a precursor of norepinephrine, acts as an endogenous peripheral and central neurotransmitter. Dopamine is a partial AR agonist by dose-dependent stimulation of ß1-, ß2-, alpha-, and dopaminergic (DA) receptors (Lokhandwala and Barrett 1982; Seri 1995; Barrington et al. 1995; Noori and Seri 2012; Liet et al. 2002); opposite to other catecholamines, dopamine's activity is almost 50% related to norepinephrine release from vesicles of sympathetic nerve endings (DA-2 receptor stimulation). Therefore, the inotropic effect of dopamine is limited in newborns and heart-transplanted patients with an imbalanced sympathetic and vagal nerve system and in chronic heart failure with myocardial norepinephrine depletion. Beyond any additional questionable indications for dopamine treating acute pediatric heart failure, the norepinephrine release by dopamine might especially be problematic in patients with myocarditis and dilated cardiomyopathy; apoptosis and necrosis are already induced in the highest degree of ß1-stimulation in consequence of myocardial norepinephrine release. Norepinephrine-related ß1-desensitization is already observed after cardiopulmonary bypass surgery with cardiac arrest (Schranz et al. 1993), which further underlines a problematic use of dopamine as a postsurgical inotropic drug; in addition to its toxicity profile, dopamine specific side effects like low T3 syndrome have to be considered particularly in treating premature patients rarely with a real need for inotropic support. Dopamine is usually used by continuous infusion in variable dosages, in neonates by a dose response based on the patient effect (Dempsey and Barrington 2007); further, the clearance of dopamine is dependent on gestational age and severity of the disease (Seri et al. 1993; Padbury et al. 1987). Low dosages in a range of 1–2 (4) μg/kg/min stimulate preferentially DA-1 and DA-2 receptors with vasodilative effects on renal, mesenteric, and cerebral vessels. Improved renal perfusion and sodium reabsorptive effects at proximal renal tubules induce saluretic effects; DA receptors at the zona glomerulosa of the adrenal cortex inhibit aldosterone release. The dopamine-related inhibition of TSH (low T3 syndrome) and prolactin (immune-modulating) might be forcing infection diseases (Noori et al. 2003). Dopamine dosages of 5–10 μg/kg/min lead to dominated ß-AR-related effects but, as already mentioned, by releasing stored norepinephrine. Contrary to norepinephrine, dopamine acts unpredictable in high alpha-mimetic dosages of 10 μg/kg/min. Dopamine constricts the venous, pulmonary, as well as systemic vascular system mostly associated with a non-opportune tachycardia or even tachyarrhythmia. Animal studies have shown that norepinephrine has a 20 times higher systemic vs pulmonary vasoconstrictive effect (Schindler et al. 2004); therefore, norepinephrine can be used more effective with less side effects than dopamine treating hypotension in context of a pulmonary hypertension.

In summary, the relative uncritical use of dopamine treating in particular premature and term neonates should be considered in terms of effect and possible side effects including currently unknown neurological consequences; a historical

familiarity should not play a role utilizing dopamine especially on neonatal intensive care.

Dobutamine is a synthetically prepared catecholamine with preferential ß1- and ß2-agonistic properties (Sonnenblick et al. 1979). Dobutamine is utilized as a racemic mixture of (+) and (−) isomers. The isomeric mixture is responsible for ß-AR activity but concerning the alpha-receptors with its neutralizing effects. The inotropic activity of dobutamine is preferentially based on stimulation of ß1-AR. Following its synthetic manufacturing in the 1970s, it was even immediately used treating pediatric myocardial diseases (Driscoll et al. 1979; Schranz et al. 1982). The inotropic effect of dobutamine can clinically best monitored by the patient's heart rate response. Dobutamine has been shown to increase cardiac output, by its augmenting effects on stroke volume and/or increase of heart rate. In case of a preferential increase of the cardiac stroke volume, the heart rate remains stable, decreases, or does only slightly increase. Therefore, an inappropriate use of dobutamine is reciprocated by an inadequate increase of the heart rate; only patients with a sinus bradycardia (i.e., patients after heart transplantation, sick sinus syndrome) might benefit from the heart rate increasing ß1- and ß2-effects. Considering the ß-AD agonist dobutamine, systemic and pulmonary vascular resistance (opposite to dopamine) decrease when intravascular volume depletion is excluded and inadequate increase of the heart rate (diastolic filling time) is avoided. In context of a possible mismatch of myocardial oxygen supply and consumption and its ß-adrenergic stimulating effects, tachycardia and tachyarrhythmias need to be permanently considered, as long as dobutamine is used, in particular, if inadequately used or overdosed in relation to the myocardial disease (Roeleveld and de Klerk 2018; Ergenekon et al. 2017). Since phosphodiesterase type III inhibitors are preferentially used in pediatric heart failure patients, dobutamine, even in combination with continuous infusion of low-dose nitroglycerine, is more and more less indicated and applied. Dobutamine is usually utilized in dosages of (2.5) 5–(10) µg/kg/min, which leads to dominated ß-AR-related effects. Dobutamine in high dosage above 10 µg/kg/min is mostly not convincing in relation to positive (inotropic) and negative (chronotropic, antiarrhythmic) effects (HR, myocardial consumption). In cardiogenic shock with associated metabolic acidosis, the partial ß-AR agonist dobutamine is not further indicated, but instead epinephrine is preferentially used.

Milrinone is currently the most used phosphodiesterase type III inhibitor (PDE III inhibitor) treating children with HF (Ferrer-Barba et al. 2016). The bipyridine derivative amrinone and imidazole derivative enoximone were the first PDE III inhibitors used also in children (Dage et al. 1987; Schranz et al. 1989; Allen-Webb et al. 1994). PDE III inhibitors are characterized by blocking the isoenzyme IIIc of phosphodiesterases localized predominantly in heart muscle and vascular smooth muscle cells. The delayed breakdown of cAMP influences also the intracellular calcium homeostasis with an increase of slow calcium influx of the myocardial cells and augmented storage of releasable calcium from the sarcoplasmatic reticulum. The mechanism is related to an increase of contractility. The cAMP increase of the smooth muscle cells improves the calcium efflux and led consecutively to

smooth muscle relaxation (Barton et al. 1996). Regarding the positive-inotropic and vasodilative properties, PDE III inhibitors are grouped into inodilators. The inodilative effect of PDE III inhibitors was evidenced by adult and pediatric patients (Hoffman et al. 2003). However, compared to shorter and stronger acting milrinone, they were affected with too many side effects which include handling problems (central line occlusion) and less control considering a too long half-life but even thrombocytopenic reaction in particular related to the use of amrinone. Proarrhythmic potentials have been seen by the use of all PDE III inhibitors, but heart failure symptoms improve in pediatric patients without an increased incidence of sudden death which have been seen in adult patients treated with PDE III inhibitors (Burkhardt et al. 2015). Considering the receptor and adenylate cyclase-mediated cAMP increase, ß-receptor agonist and PDE III inhibitors have additive, and maybe synergistic, effects. Therefore, low cAMP levels in heart failure seem not to be related to increased PDE activity, but more likely to decrease adenylate cyclase activity associated with downregulation and desensitization of the ß-adrenergic receptor in HF. Important age-related differences in phosphodiesterase activity and effects of chronic PDE III inhibition were observed in idiopathic dilated cardiomyopathy patients (Nakano et al. 2015). Tachyphylaxis or tolerance is described with chronic PDE III inhibitors in adults. Chronic therapy with the PDE III inhibitor milrinone in children led to elevated cAMP and higher downstream phospholamban phosphorylation contributing to sustained hemodynamic benefits in pediatric DCM patients. In contrast, higher total PDE and PDE III activities in adult DCM patients during PDE III inhibitor treatment may perpetuate lower myocardial cAMP and phospholamban phosphorylation levels, limiting the potential benefits of PDE III inhibitors in adults. Therefore, milrinone is effectively used to prevent or treat low cardiac output syndrome (LCOS) in children undergoing heart surgery. It is used for stabilization decompensating heart failure as associated with dilated cardiomyopathy (Nakano et al. 2017; Curley et al. 2017) and even in heart failure with a single ventricle physiology (Curley et al. 2017). The substance is used for bridging to transplant, but even to recovery (Schranz and Voelkel 2016).

Milrinone is used in continuous infusion in dosages ranging between 0.3 and 1 μg/kg/min.

Levosimendan is a further inodilator (Rognoni et al. 2011); it exerts inotropic and vasodilating effects based on myocardial calcium-sensitizing properties opening up vascular ATP-dependent potassium channels. The pharmacological profile of levosimendan makes this drug very attractive in myocardial HF of neonates and infants considering their endogenous myocardial calcium handling (Veldman et al. 2006). Less proarrhythmic and reversal effects of toxic dosages of ß-blockers expand the indication of the use of levosimendan; postoperative low cardiac output or intermittent treatment in infants and young children with DCM even as an accompanying drug are currently the most indicated pediatric cardiovascular conditions (Angadi et al. 2013). Levosimendan is mostly applied in a continuous infusion of 24 h in a dosage of 0.1 or 0.2 μg/kg/min with or without a loading dose for 10–15 min.

Like PDE III inhibitors, hypotension can mostly be avoided if the treated patients have no intravascular volume depletion as very often is observed by overtreatment of diuretics or other reasons of volume loss.

4.3.1 Conclusion

Pharmacological support of the failing pediatric heart remains a challenging task. The first therapeutic goal is resuscitating or maintaining cardiac output, which is vital for sufficient end-organ perfusion. The second aim, however, should be cardiac restoration and regeneration; accepting a chronic heart failure or organ replacement should be the last exit. The regenerative potentials are enormous, the younger the patient is. However, the unique biochemical and structure properties of the neonatal non-failing and especially failing heart do not necessarily allow to extrapolate results of adult's studies to young children. Already the mismatch of noncontractile tissue mass to the contractile myocardium, the differences in intracellular myocardial calcium handling but in particular varieties of receptor physiologies between a failing adult and pediatric heart need to be considered for an adequate cardiac therapy. Missing evidence-based data treating pediatric HF should not be led to therapeutic nihilism; it needs a differentiated, hypothesis-driven therapeutic strategy based on the pharmacological drug profile, pathophysiological condition, and the molecular features. In this context, the pediatric HF is characterized by a lower beta adrenergic agents responsiveness and a heart rate dependent cardiac output; both, limiting the ability to increase stroke volume, favor therefore the use of inodilators of the Ca++-senitizer and PDE-III-inhibitor family. Regenerative strategies with mobilizing endogenous potentials to exogenous supported by exogenous stem cell therapy and gene therapy offer perspectives for future restoration of the failing neonatal and young patients' hearts.

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