Heart failure (pediatrics)/therapy

When drawing up a treatment plan, it is important to know the cause and pathophysiological type of heart failure. The basic goal of drug therapy is to reduce preload and afterload, increase cardiac contractility (inotropic) and improve tissue oxygen supply.

General precautions

Improving ventilation *in children with congestion or pulmonary edema is achieved by* raising the upper half of the body *to 45° (this reduces venous return and promotes pooling of blood in the peripheral veins). Humidified and tempered O_2* (oxygen therapy) is given to all critically ill patients with acute heart failure, the application of "UPV with positive overpressure" will reduce the alveolar component of pulmonary edema, reduces preload and afterload. Careful treatment with oxygen is required in cyanotic defects for the possible induction of PDA closure and in defects with a large left-to-right shunt, as a decrease in pulmonary vascular resistance leads to an increase in the L–P shunt.

Maintenance of **normothermia**, adequate **analgosedation**, ev. by myorelaxation during UPV, we reduce O_2 consumption. In case of dyspnoea or tachypnea, we prefer parenteral nutrition due to the risk of aspiration. In cardiomyopathies with a proven defect in carnitine, we administer L-carnitine.

Especially in the smallest children, heart failure is a condition with a high energy demand. It is necessary to ensure an *increase in energy intake*, either parenterally or enterally (nasogastric, nasojejunal tube, possibly gastrostomy).

Drug affecting venous return (preload)

Administering preload-reducing medications (diuretics and venodilators) in heart failure with reduced contractility will improve cardiac performance by reducing ventricular size and reducing wall tension. Venodilators cause "pooling" of blood in the periphery, reducing both right- and left-sided diastolic volumes. Myocardial tension gradually decreases and its perfusion improves during diastole. First of all, we reduce preload by restricting fluids and administering diuretics.

Diuretic

Diuretics relieve symptoms of pulmonary congestion and peripheral edema. We most often use ***furosemide*** in a dose of 0.5–2 mg/kg i.v. as a bolus, usually 3x daily or continuously up to a maximum total dose of 10 mg/kg/day. Much smaller doses, approx. 0.5–1 mg/kg, often lead to good diuresis. We therefore always titrate the dosage according to diuresis values. By directly acting on the loop of Henle, it causes the excretion of ions Na^+, K^+, Cl^- and body water. It has a quick and short-term effect. For long-term diuretic treatment, when there is a risk of hypokalemia, ***spironolactone*** is indicated in a dose of 1–3 mg/kg/day divided into 3 doses. Spironolactone is a competitive aldosterone inhibitor acting on the distal renal tubule. It has a very weak diuretic effect by itself, but potentiates the effect of other diuretics. It partially antagonizes the loss of potassium ions. In combination with ACE inhibitors or potassium supplementation, it causes hyperkalemia.

The administration of diuretics and venodilators has adverse effects in patients with reduced myocardial contractility, but with a deficit in circulating volume or insufficient chamber filling!

Farm affecting afterload

Inadequate, "overshot" vasoconstriction changes the initially compensatory mechanism into a disadvantageous increase in afterload, which ultimately worsens myocardial performance. The afterload-reducing drug will reduce myocardial workload, improve cardiac output and peripheral perfusion. Arterial relaxation increases ejection fraction, increases stroke volume, and decreases left ventricular end-systolic volume.

Pharmacological representatives are vasodilators, e.g. *hydralazine*, which is not used much anymore. On the contrary, we use drugs that simultaneously reduce afterload and preload - ***ACE inhibitors*** and ***nitroglycerin*** , in severe cases then *sodium nitroprusside*.

A farm affecting preload and afterload

The common denominator for this group of drugs is the reduction of peripheral vascular resistance. They have a combined effect on veins and arteries. It should be emphasized that high peripheral vascular resistance is a common symptom during shock states in children. We are talking about the fact that hypodynamic (low flow) shock is typical for children. Affecting the resistance and capacity of the systemic vascular bed has an effect on cardiac performance. An increase in peripheral vascular resistance with unchanged preload and contractility reduces cardiac output. The use of vasodilators and other drugs with a relaxing effect on the smooth muscle of peripheral vessels can modify cardiac performance in heart failure. Peripheral vascular vasodilatation reduces myocardial afterload. By increasing the capacity of the systemic flow, the preload of the myocardium also decreases and the filling volume of the heart decreases. However, the reduction of peripheral resistance carries the risk of severe hypotensionze, which in the case of subclinical or unrecognized hypovolemia can lead to a life-threatening

condition. Simultaneously with the reduction of SVR, the regulatory mechanisms of fluid redistribution are disrupted. When using vasodilator therapy, it is advisable to monitor filling and systemic pressures. Medicines that reduce high SVRI include sodium nitroprusside, nitroglycerin and ACE inhibitors, and to a lesser extent dehydrobenzperidol or chlorpromazine.

Sodium nitroprusside

Nitroprusside is a fast-acting peripheral vasodilator. It has a direct vasodilating effect on arterioles and veins. It primarily reduces afterload and thus increases cardiac output. The result is reduced filling of the left ventricle, relief of pulmonary congestion, reduction of volume and pressure in the left ventricle, better emptying of the left ventricle in systole, reduced oxygen consumption by the myocardium. Its effect is tied to its immediate administration, i.e. after stopping the infusion, the effect is immediately lost. When using it, invasive blood pressure monitoring is absolutely necessary. Prolonged administration may lead to an increase in the serum level of cyanides - their control is necessary. In case of intoxication, disorders of consciousness, MAC appear. The recommended dose is 0.5–10 μg/kg/min., the dose is titrated according to the effect. As a rule, we start with a low dose and depending on the effect, we increase the doses by approx. 0.5 g/kg/min. after 10 minutes. Nitroprusside can be combined with dopamine or dobutamine because they have a synergistic effect on increasing cardiac output. Due to its drastic effect, which can also be associated with serious complications, we only use nitroprusside in the most severe cases.

Nitroglycerin

Venodilators are indicated for elevated EDP. The main representative is nitroglycerin. It has a direct venodilating effect, it dilates the smooth muscle of the vascular wall, predominantly systemic veins and coronary arteries. In low doses, it leads to venodilatation and a reduction in preload. High doses cause more pronounced vasodilation in the pulmonary basin (cave! – congestion), dilation of arterioles and reduction of afterload. Pharmacological effects depend mainly on the state of the intravascular volume, less on the dose (hypovolemia increases the risk of hypotension). Usual doses are 0.25–5–(10) μg/kg/min. continuously i. v.

ACE inhibitors

ACE-inhibitors lead to vasodilation and reduction of aldosterone secretion. The result is increased sodium excretion, which leads to a decrease in systemic peripheral resistance, a decrease in EDP and an increase in cardiac output. Another positive effect is the ability to remodel the hypertrophic myocardium of the ventricles. A representative is, for example, enalapril, p. o doses. 0.15–0.5 mg/kg/d in 1–2 doses, for i. v. treatment 5–10 μg/kg/dose 1–3 times within 24 hours

Glycosides

The role of digoxin in acute critical conditions has always been limited by a narrow therapeutic range, slow onset of action, and potentially life-threatening side effects. Glycosides have a positive inotropic effect, which is accompanied by a negative chronotropic and dromotropic effect. Glycosides inhibit Na/K-ATPase, leading to an increase in intracellular calcium, which increases myocardial inotropic force. Hyperkalemia reduces the binding of digoxin to ATPase, hypokalemia has the opposite effect and can increase its toxicity. The most used agent is digoxin. Its advantages include the possibility of p. o. administration and also the fact that, unlike other inotropics, it inhibits sympathoadrenal stimulation. Its biggest disadvantage is the narrow therapeutic index and therefore the necessity of monitoring serum concentrations. Digoxin affects the repolarization phase and thus has a proarrhythmogenic effect (prolongs the PR interval). Other disadvantages include stimulation of the vagus nerve, it does not favorably affect the tissue extraction of oxygen from hemoglobin. Administration of digoxin in infants and toddlers with a heart rate < 100/min is clearly risky. The indication is mainly heart failure with significant tachycardia, improvement of systolic function in children without structural heart defects and some types of SVT. The toxic effects of digoxin can present themselves as tachydysrhythmias, ventricular extrasystoles, ventricular tachycardia and ventricular fibrillation. In case of acute intoxication, sinus bradycardia or AV block appears. (See Heart Rhythm Disorders)

In patients with congestive heart failure, the administration of digoxin leads to a decrease in heart rate, an improvement in contractility and a decrease in compensatory sympathomimetic activity. In addition to increasing contractility, glycosides slow conduction in the AV node, increasing vagotonia. This property is used in the treatment of some SVT, atrial flutter and atrial fibrillation.

Today, saturation doses have already been withdrawn, we administer 0.01 mg/kg/day i.v. divided into 2-3 doses. We check the levels 6 hours after the last application, the norm is 1–2 ng/ml. Digoxin toxicity is increased by hypokalemia and hypomagnesemia. We must never administer calcium at the same time as digoxin!

Digoxin increases contractility, slows conduction in the AV node, and increases vagotonia. Digoxin toxicity is increased by hypokalemia and hypomagnesemia. We must never simultaneously digoxinem to give calcium! We must not give digoxin to children who have SF < 100/min !

Inoconstrictive and inodilating treatment

The basic goal of the administration of these substances is to increase tissue perfusion and maintain perfusion gradients, however, a prerequisite for their effect is sufficient filling of the vascular bed. The administration of inodilating substances in a hypovolemic patient can cause serious complications due to hypotension or

tachyarrhythmias. On the other hand, administration of inoconstrictive substances is not effective in normal doses. Vasopressors should be titrated according to perfusion pressure or systemic vascular resistance so that diuresis and physiologic creatinine clearance are optimal.

We also ensure normal reactivity of the myocardium and vascular system by maintaining normal acid-base ratios and levels of electrolytes, especially potassium, magnesium and calcium. Inoconstrictors or inodilators are usually administered with a linear dispenser. When dealing with circulatory complications in critically ill patients, we use one or two substances, exceptionally a larger number. The effect on individual receptors is in some cases dose-dependent (e.g. dopamine, adrenaline) and their introduction into the systemic circulation should be completely separated from other substances. We preferably use multi-way central venous catheters for this purpose. Catecholamine solutions must be protected from light and we require intra-arterial BP measurement when they are administered. Administration into peripheral veins causes early reactive inflammation. Only dobutamine can be administered into the peripheral canal.

From a clinical point of view, it is possible to divide the group of cardiotropic (inotropic) substances into inoconstrictive substances (noradrenaline, adrenaline, dopamine) and inodilating substances (dopexamine, dobutamine, isopreterenol). Phosphodiesterase III (PDE III) blockers are a specific group of inotropic substances.

Calculation of dose for infusion:

- drug dosage in tenths or hundredths of micrograms/kg/min. – e.g. noradrenaline, isoprenaline, adrenaline
  - i 0.3 mg/kg in 50 ml solution → 1 ml/hour. = 0.1 µg/kg/min.;
  - (dosage in the range of 0.5-5 ml/hour);
- drug dosage in "whole" µg/kg/min. – e.g. dopamine, dobutamine;
  - i 30 mg/kg in 50 ml solution → 1 ml/hour. = 10 µg/kg/min.;
  - (dosage in the range of 0.2–2 ml/hour).

For diluting catecholamines, 1/1 FR is most suitable, on the contrary, alkaline solutions are contraindicated.

Mechanism of action

Adrenergic receptors are represented by 8 gene subtypes, but from a practical point of view we distinguish alpha-1, alpha-2, beta-1, beta-2 and D-1 and D-2 receptors.

- Beta-1 and beta-2 receptors are located in the muscle of the ventricular myocardium and the muscle of the atria. In addition, beta-2 receptors are located on the presynaptic endings of sympathetic nerves and stimulate the release of neurotransmitters. In vascular smooth muscle, activation of beta-2 receptors leads to vasodilatation (through the mechanism of smooth muscle relaxation).
- Beta-1 stimulation of the myocardium not only increases inotropy (strength of contraction), but also chronotropy (increased heart rate), dromotropic (increased conduction speed) and bathmotropy (increased excitability) to varying degrees.
- Alpha receptors are mainly found in the smooth muscle of blood vessels, where they cause vasoconstriction. However, alpha-1 receptors are also found in the muscle of the myocardium. However, their irritation does not affect the heart rate.
- Alpha receptors were originally differentiated with respect to their location on nerve endings. The postsynaptic receptor was designated as alpha-1 and the presynaptic receptor as alpha-2. Stimulation of the alpha-1 receptor leads to smooth muscle contraction, while stimulation of the alpha-2 receptor inhibits the release of noradrenaline from presynaptic granules, thus promoting vasodilation.
- Dopaminergic receptors are divided like others into postsynaptic DA-1 and presynaptic DA-2. DA-1 receptors are located in the smooth muscle of renal, splanchnic, coronary and cerebral vessels. Their activation leads to vasodilation. A-2 receptors inhibit the release of noradrenaline from sympathetic endings.

The mechanism of action of phosphodiesterase blockers is based on the fact that normally cAMP is inactivated by phosphodiesterase, which causes its conversion to AMP. Inhibition of phosphodiesterase increases cAMP concentration and enhances beta receptor-mediated activity.

Receptor function disorders

As part of the receptor disorder, the mechanism of reducing the sensitivity of receptors is best described on the principle of agonist-mediated desensitization. Within seconds to minutes after agonist binding to the receptor, uncoupling may occur due to receptor phosphorylation (phosphorylation involves multiple mechanisms). In addition to agonist-mediated desensitization, there are other factors involved in down-regulation: endotoxin, TNF, congestive heart failure. Another mechanism of down-regulation of receptors is their sequestration inside target cells and their subsequent degradation.

Inoconstrictors

Adrenaline

- Adrenaline is produced in the medulla of the adrenal glands from noradrenaline. Adrenaline is a potent, directly acting α-1, β-1 and β-2 receptor agonist.
- Adrenaline vat low concentrations it first affects β-1-receptors. It potentiates the activity of the SA node, increases the heart rate, has a positive inotropic effect. Unfortunately, the increased consumption of oxygen by the myocardium is a disproportionate increase in inotropy and thus decreases myocardial performance. High doses of adrenaline or its use in patients with myocarditis or infarction can lead to the development of

severe atrial and ventricular dysrhythmias.
- Stimulation of β-2 receptors helps vasodilation, decreases SVRI and lowers diastolic blood pressure. A decrease in SVRI increases the direct chronotropic effect of adrenaline. Higher doses of adrenaline already stimulate α-1 receptors, there is an increase in SVRI and, at the same time, pulmonary vascular resistance.
- During stress, when a large amount of adrenaline is flushed out, receptors can be desensitized very quickly, even before the administration of exogenous adrenaline begins.
- Adrenaline is intended for the treatment of shock in connection with myocardial dysfunction, especially in patients after successful cardiopulmonary resuscitation or after a hypoxic-ischemic insult. In septic patients where there was no improvement in the condition after volume expansion, continuous infusion of adrenaline may be beneficial. Adrenaline is most useful in conditions with hypotension, low CI and high SVRI (cold shock = low flow). In low doses 0.005-0.1 μg/kg/min. SVRI decreases slightly, while heart rate, blood pressure and cardiac output increase. In medium doses of 0.1–1.0 μg/kg/min. α-1 adrenergic activity begins to predominate, but the further increase in CO balances the still preserved vasodilation (induced by the activation of β-2 receptors), which leads to a decrease in diastolic pressure. In very high doses (> 1–2 μg/kg/min.), vasoconstriction by activation of α-1 receptors prevails, organ perfusion may already be reduced, afterload increases and myocardial function may decrease. The perfusion of the splanchnic is particularly affected, serum lactate rises.

As part of cardiopulmonary resuscitation, we use α-1 activity, which brings massive vasoconstriction, leads to an increase in SF, BP and vascular resistance. We administer adrenaline in a bolus dose of 0.01 mg/kg. Previously recommended subsequent 10x higher doses (so-called high dose epinephrine) are no longer recommended. We administer the same dose intraosseously, and 0.1 mg/kg intratracheally.

- Adrenaline has a number of side effects. Within the CNS it leads to anxiety, nausea. High doses can cause myocardial ischemia, arrhythmias. Although ventricular tachycardia is rare in childhood, it occurs more often with concomitant myocarditis, hypokalemia, and hypoxemia. Adrenaline also has significant metabolic effects: stimulation of β-2 receptors, which are associated with Na-K-ATPase in muscles, leads to hypokalemia (infusion of 0.1 μg/kg/min. leads to a decrease in potassium by 0.8 mmol /l). β-adrenergic mediated suppression of insulin results in hyperglycemia.
- Adrenaline is degraded by monoamine oxidase or catechol-o-methyl transferase.
- The recommended dosage is 0.005-2.0 μg/kg/min. Adrenaline is stable when diluted to 5% glucose or 1/1 FR.

Noradrenaline

- Noradrenaline is a potent inotropic substance with a direct effect on β-1 and α-1 receptors. It has a powerful vasoconstrictive effect, as α-adrenergic stimulation is not opposed by the β-2 effect. Noradrenaline does not increase the heart rate, as it reflexively reduces the activity of the SA node through the vagus nerve and thus eliminates the expected β-1 chronotropic effect. Noradrenaline also has a powerful inotropic effect. It mainly increases diastolic blood pressure and diuresis. An increase in afterload may increase myocardial oxygen consumption, however, norepinephrine reflexively reduces heart rate and thereby reduces oxygen consumption and improves coronary flow in diastole. It has no β-2 agonist effect. It is one of the most widely used drugs in the treatment of circulatory insufficiency in resuscitation care. It is the vasoconstrictor of first choice today. Noradrenaline improves perfusion in severely hypotensive children with low SVRI and normal or elevated CI. A typical choice is septic or anaphylactic shock. Noradrenaline, like other catecholamines, should be administered only after volume depletion has been completed, ideally in patients where both SVRI and CO/CI can be assessed. In children, noradrenaline is recommended for the high flow form of shock, which is refractory to volume expansion and dopamine.
- On the other hand, norepinephrine can increase blood pressure without improving organ perfusion. Typical cases are low CI, insufficient volume expansion, increase in PCWP. The use of high doses of norepinephrine, which increase pressure but do not improve organ perfusion, may contribute to the development of MODS.
- In general, however, the limitation of upper doses of noradrenaline/adrenaline is the occurrence of adverse effects, i.e. myocardial ischemia, tachycardia and arrhythmias. During extravasation, we quickly infiltrate the affected tissue with phentolamine (5–10 mg in 10 ml 1/1 FR).
- The recommended dosage is 0.01–0.5–1.0 μg/kg/min. The wide range of recommendations is due to the need for titration of continuous noradrenaline administration. Noradrenaline is stable when diluted to 5% glucose.

Dopamine

- Dopamine is a central neurotransmitter, it is also found in the endings of sympathetic nerves and in the medulla of the adrenal glands, where it is a rapidly usable precursor for the formation of noradrenaline. Dopamine affects D1 and D2 receptors (dopa receptors = ɗ-receptors), which are located in the brain and vascular bed of the kidneys, splanchnic and heart. Depending on the dose, it also stimulates α + β receptors, but the affinity for these receptors is lower. Stimulation of D-1 receptors leads to vasodilation, increased perfusion, and can increase the excretion of solutes and water in the kidneys. However, the so-called renal doses of dopamine 2.5–5 μg/kg/min. they are not recommended today because their protective effect on increasing renal perfusion has not been confirmed. By influencing D-2 receptors, dopamine regulates the release of aldosterone and prolactin and also affects the renal clearance of solutes. The fact that newborns and infants show lower sensitivity to dopamine is not definitively confirmed.
- Dopamine is recommended as the drug of first choice in children in septic shock where volume expansion has failed, dopamine is suitable in children with mild myocardial dysfunction and hypotension after cardiopulmonary resuscitation. Severe contractility or vasomotor impairment requires the use of other catecholamines. Children with primary myocardial dysfunction and in the absence of hypotension benefit more from administration of dobutamine or milrinone.
- In a dose below 5 ug/kg/min, the effects by affecting D-1 receptors prevail, in a dose of 5–10 μg/kg/min.

exhibits β-1 adrenergic effects, in doses of 10–15 μg/kg/min. has a mixed α + β effect. Dose increase to > 15 μg/kg/min. leads to stimulation of α-1 receptors.
- In a shock state with hypotension, we start the administration at a rate of 5-10 μg/kg/min, increasing the infusion rate in steps of 2-5 μg/kg/min. We assess the effect of the treatment according to the difference in central and skin temperature, capillary return, diuresis. When doses > 25 μg/kg/min are needed. SVRI (predominance of α-receptor stimulation) increases more significantly than cardiac output. We refer to this condition as dopamine-resistant. Another option is noradrenaline for high flow form (warm shock) or adrenaline for low flow (cold shock).

Disadvantages of dopamine include its proarrhythmogenic effect, tachycardia and increased myocardial oxygen consumption, hypertension. With the exception of bipyridines, all inotropic agents increase myocardial oxygen consumption because they increase myocardial workload. Dopamine and other β-agonists decrease $p(O_2)$ by interfering with alveolar pulmonary vasoconstriction (exacerbation of V/Q imbalance).

- During extravasation, we rapidly infiltrate the affected tissue with phentolamine (5–10 mg in 10 ml 1/1 FR).
- The recommended dosage is 5-20 μg/kg/min. Dopamine is stable when diluted to 5% glucose or 1/1 FR.

Diastolic pressure is most influenced by the tension of the vessel wall: vasodilation leads to a decrease in dTK, vasoconstriction increases dTK!

Inodilators

Dobutamine

- Dobutamine is a synthetic dopamine analogue. It has no dopaminergic activity. It is a potent inodilator with inotropic β-1 and vasodilatory + chronotropic β-2 activity affecting arteriolar and venous channels. Its great advantage is that it does not have its own proarrhythmogenic effect and practically does not have its own toxic effect.
- As part of septic shock, we administer dobutamine if myocardial dysfunction prevails. However, usually the main concern is the regulation of vascular tone, and SVRI-increasing drugs are preferred. In myocardial dysfunction, dobutamine alone or in combination with dopamine increases CO and subsequently blood pressure. However, dobutamine is most often combined with noradrenaline in conditions with myocardial dysfunction associated with a high flow form of shock (sepsis) or ARDS. Dobutamine and noradrenaline are currently the most frequently used combination of vasoactive substances in resuscitation care. In children with myocardial dysfunction, it increases stroke volume and CO, without a significant increase in heart rate. Dobutamine leads to a decrease in SVR and PVR. Indications for the administration of dobutamine in pediatrics are conditions of congestive heart failure with low CI and normal or slightly reduced blood pressure (viral myocarditis, drug-induced cardiomyopathies, myocardial infarctions - M. Kawasaki, abnormal distance of the left coronary artery)
- In myocardial failure, we start with dobutamine and ensure adequate intravascular volume according to CVP values. Simple volume expansion is not appropriate here. Dobutamine is the inodilator of choice today. Dobutamine as a single catecholamine can be administered into a peripheral vein.
- Adverse effects include marked tachycardia, which may increase oxygen consumption and require dose reduction or change to another agent. Rarely, it can cause atrial or ventricular dysrhythmias, especially in patients with myocarditis, electrolyte imbalance or when high doses are administered. Dobutamine, like other inotropic agents, must be administered with caution in patients with left ventricular outflow obstruction (hypertrophic aortic stenosis).
- The recommended dosage is 2-20 μg/kg/min. Children < 1 years may be less responsive to dobutamine or delta doses of dopamine. If doses kby 20 μg/kg/min. do not lead to an improvement in the hemodynamic state, we are considering changing to adrenaline. Dobutamine is stable when diluted to 5% glucose or 1/1 FR.

Dopamine and dobutamine are drugs that increase systolic volume.

Dopexamine

- Dopexamine is a synthetic analogue of dopamine. Its dominant effect is β-2 agonism. It has preserved activity towards the dopa-1 receptor. In the Czech Republic, item no. is not registered.
- The recommended dosage ranges from 0.9-5.0 μg/kg/min.

Isoproterenol

- Isoproterenol is a synthetic catecholamine structurally similar to adrenaline. It is a potent agonist of β-1 and β-2 receptors. It shows extreme chronotropic and bathmotropic activity. In low doses, it has significant vasodilating effects. It has been displaced from clinical use by other, more selective inotropes, as its proarrhythmogenic effects and increased myocardial oxygen consumption are limitations of its use. The previous typical indication for its administration was low cardiac output in patients with pulmonary hypertension in right-sided heart failure at a slow heart rate. It still remains a therapeutic option in conditions with significant bradycardia (AV block II-III degree), where atropine does not work.
- The recommended dosage is 0.01-0.5 μg/kg/min. in conditions of hemodynamic monitoring.

- In children completely refractory to catecholamines, we must rule out unrecognized pathologies: cardiac tamponade, PNO, adrenal insufficiency, hypothyroidism, ongoing blood loss, intra-abdominal injury!

Phosphodiesterase III blockers

- Phosphodiesterase III (PDE III) blockers are divided into bipyridine (amrinone and milrinone) and imidazole (enoximone and pyroximone) preparations. They do not belong to catecholamines, their effect is through selective inhibition of phosphodiesterase III, they do not act on adrenergic receptors or lead to inhibition of Na/K-ATPase. Their effect is similar to dobutamine, i.e. especially the β-2 effect. They increase myocardial contractility, have a vasodilating effect, and improve diastolic function (lusitropic effect). The disadvantage is a whole range of side effects, led by a high proarrhythmogenic effect, the result of which can be systemic hypotension with ventricular tachycardia.
- Indications for amrinone/milrinone in children are normotensive patients with low CI but high SVR despite epinephrine or nitrate infusion. Another indication is low cardiac output in the dilated form of cardiomyopathy when other inotropic support fails.
- Inodilators also solve the problem of down-regulation of β-1 and β-2 receptors, they are also indicated for the toxic effects of nitrates. Conditions with severe heart insufficiency refractory to other treatment or post-operative conditions in cardiac surgery are also indications. When using phosphodiesterase III blockers, most experts recommend continuous infusion to achieve steady state. Because these drugs have a long half-life, their infusion should be stopped at the first signs of tachyarrhythmia, hypotension, or an excessive decrease in SVR, especially if liver or kidney dysfunction occurs at the same time. The hypotensive effects of phosphodiesterase III blockers can be eliminated by replacing co-administered adrenaline with noradrenaline.

Milrinone

- Milrinone is a derivative of amrinone, it has the same mechanism of action and pharmacodynamic profile. However, unlike amrinone, it does not cause thrombocytopenia. Milrinone is indicated in children for nonhyperdynamic septic shock with normal or decreased CI and normal or increased SVRI. Milrinone increases CI, systolic volume, DO2 while decreasing SVRI. Milrinone increases cardiac contractility in patients after cardiac surgery, improves perfusion in patients with cold shock (low flow). Its vasodilatory effects could be useful in the treatment of pulmonary hypertension.
- The recommended dosage is initially 50 µg/kg i.v. slowly over 15 min., then 0.4–1.0 µg/kg/min. Milrinone is stable when diluted to 5% glucose or 1/1 FR.
- In practice, in older children with acute heart failure, we start JIRP by administering furosemide i.v. and we add dopamine in a dose of 5–10 µg/kg/min. In patients, it is necessary to ensure CVK (inotropic administration, CVP values, SvcO2) and an arterial line. Cardiac output is mostly monitored indirectly using thermodilution methods (PiCCO), rarely directly during the introduction of a Swan-Ganz catheter.

Overview of the most important inotropic substances				
Pharmakon	**alpha-1**	**beta-1**	**beta-2**	**dope**
norepinephrine	+++	+++	0	0
adrenaline	+++	+++	++	0
dopamine	+++	++	+	+++
dopexamine	0	+	+++	+
dobutamine	0	+++	+++	0
isoproterenol	0	+++	+++	0
amrinone	0	+	+++	0
milrinone	0	+	+++	0
enoximone	0	+	+++	0
pyroximone	0	+	+++	0

Normal values of heart and respiratory rate		
age	**normal respiratory rate (per minute)**	**normal heart rate (per minute)**
newborns	40-60	100–180
infants	30–50	80–150
toddler	25-40	80–130
preschoolers	25–35	80–120
youngši schoolchildren	20-30	70–100
older schoolchildren	12–20	60–100
adult	12–16	60–90

Indications for administration of cardiotropic drugs:

- **adrenaline**: hypotension, low CI and high SVRI (cold shock = low flow);

- **noradrenaline**: severe hypotension, normal or increased CI and low SVRI (warm shock = high flow);
- **dopamine**: 5-10 µg/kg/min. : hypotension, low CI and high SVRI (cold shock = low flow) > 15 µg/kg/min. : hypotension, normal or elevated CI and low SVRI;
- **dobutamine'**: normotension or mild hypotension, low CI and high SVRI;
- **PDE III inhibitors**: normotension, low CI, and high SVR despite epinephrine or nitrate infusion.

Links

Related Articles

- Heart failure (pediatrics)

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