

# Acute heart failure: vasoactive agents – does it matter?

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Acute heart failure (AHF) is defined as the rapid onset of symptoms secondary to abnormal cardiac function. It is a syndrome and has a variety of potential etiologies. AHF is a very polymorphic conception and can be related with abnormalities in cardiac rhythm, systolic or diastolic dysfunction or preload and afterload mismatch. The cornerstone of management includes therapy directed towards the underlying cause of heart failure. On the other hand, if the underlying cause is irreversible – a heart assist device or even heart transplantation may be needed. Therefore, while awaiting their availability, vital organ perfusion remains crucial. In these settings, intravenous cardio-/vaso- active agents are necessary.

With few exceptions, most vasopressor and positive inotropic agents are symphatomimetic amines that exert their action by binding and stimulating adrenergic receptors. They are powerful drugs with a considerable potential for toxicity.

Vasopressor and inotropic support in case of AHF helps to win the time until a more definitive treatment becomes available. Therefore, AHF management must be directed to establish and eliminate deteriorational factors, however, not the correction of particular hemodynamic parameters.

**Key words:** acute heart failure (AHF), vasopressors, inotropes, cardiogenic shock

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## INTRODUCTION

Acute heart failure (AHF) is defined as the rapid onset of symptoms secondary to abnormal cardiac function. It is a syndrome and has a variety of potential etiologies. In the elderly population coronary

heart disease is the main cause of AHF, while dilated cardiomyopathy, arrhythmias, myocarditis, congenital or valvular heart diseases are the main etiologies in younger ages. AHF is a very polymorphic conception and can be related with abnormalities in cardiac rhythm, systolic or diastolic dysfunction or preload and afterload mismatch. The cornerstone of management includes therapy directed towards the underlying cause of heart failure. In order for patients with AHF to respond to treatment, heart dysfunction must be reversible: causes such

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as bradycardia must be treated with cardiac pacing, tachyarrhythmias with cardioversion, myocardial infarction with anti-ischemic treatment, valvular dysfunction with valvular repair, medical intoxication with detoxication therapy. On the other hand, if the underlying cause is irreversible – a heart assist device or even heart transplantation may be needed. Therefore, while awaiting their availability, vital organ perfusion remains crucial. In these settings, intravenous cardio-/vaso- active agents are necessary (1–4).

With few exceptions, most vasopressor and positive inotropic agents are sympathomimetic amines that exert their action by binding and stimulating adrenergic receptors. Usually they are short acting agents with a rapid onset and offset of actions, initiated without a bolus and can be titrated frequently. Vasopressors and positive inotropic agents are powerful drugs with a considerable potential for toxicity. They are associated with an increased risk of cardiac ischemic events and with tachyarrhythmias (4–6).

### INOTROPES WITH VASOPLEGIC PROPERTIES

**Dobutamine** is a synthetic catecholamine with potent inotropic and chronotropic activity with mild vasodilatation. Doses up to 15 µg/kg/min increase cardiac contractility without greatly affecting peripheral resistance. In contrast to dopamine, dobutamine decreases cardiac filling pressures, making it a preferred agent in the treatment of patients with acute decompensated heart failure (7–8). Depending on the shock state, dobutamine can be used with norepinephrine or dopamine to manage the balance between inotropy and afterload. Tolerance to dobutamine develops after a few days of therapy, and malignant ventricular tachyarrhythmias can be observed at any dose. Increased myocardial oxygen consumption promotes cardiac ischemia, thus the usage of this agent can be associated with excess mortality. Chronic therapy may also cause an eosinophilic or hypersensitivity myocarditis (9).

**Phosphodiesterase inhibitors (PDEs)** increase the level of cAMP by inhibiting its breakdown within the cell, which leads to increased myocardial contractility. These agents are potent inotropes and vasodilators and may also improve diastolic relaxation. Therefore, these agents are particularly

useful in case of desensitized adrenergic receptors due to chronic heart failure or  $\beta$ -blockators administration (10). Their additional vasodilatation of the systemic and pulmonary vasculature makes them suitable for right heart failure treatment. Being a potent vasodilator, milrinone should be avoided in patients with severe hypotension or severe aortic stenosis.

**Calcium-sensitizing agents** act on contractile proteins and sensitize them to calcium, which leads to increased contractility without impairing diastolic relaxation. In addition, the opening of ATP-dependent potassium channels adds vasodilatory properties. It also shows the anti-inflammatory effect (11). Levosimendan is useful for the treatment of patients with severe decompensated heart failure (1–3, 7, 12). Theoretically, levosimendan should be less arrhythmogenic than other inotropes.

**Isoproterenol** is a potent, nonselective, synthetic  $\beta$ -adrenergic agonist with a very low affinity for  $\alpha$ -adrenergic receptors. It has powerful chronotropic and inotropic properties with potent systemic and mild pulmonary vasodilatory effects. Isoproterenol is useful to increase the heart rate in patients with bradycardia or AV block. As all inotropic agents, isoproterenol increases myocardial oxygen demand and may induce myocardial ischemia or tachyarrhythmias (5–6).

### INOTROPES WITH VASOPRESSOR ACTIVITIES

**Dopamine** is an endogenous catecholamine with complex and dose dependent actions. At low doses (<5 µg/kg/min), its vasodilatory effect is concentrated in the coronary, renal, mesenteric, and cerebral beds and promotes diuresis. At intermediate doses (5–10 µg/kg/min), dopamine increases cardiac contractility and chronotropy, with a mild increase in systemic vascular resistance. At higher infusion rates (>10 µg/kg/min), vasoconstriction predominates (5). Dopamine is useful in the management of patients with cardiogenic shock or, at low doses, to augment diuresis (6, 13). Like all positive inotropic agents, dopamine can result in myocardial ischemia and may be associated with splanchnic shunting, impairment of gastric mucosal oxygenation, and increased risk of gastrointestinal bleeding.

**Epinephrine** is an endogenous catecholamine with a high affinity for  $\beta_1$ -,  $\beta_2$ - and  $\alpha_1$ - adrenore-

ceptors. Epinephrine has an unpredictable positive inotropic and vasoconstrictory effect and is a preferred vasoactive agent following cardiac arrest and anaphylaxis (5). It is also used to reverse hypotension with or without bradycardia after cardiopulmonary bypass or cardiac transplantation (6, 14). Epinephrine reduces peripheral, pulmonary, splanchnic and renal blood flow, induces myocardial ischemia and promotes tachyarrhythmias. Due to its adverse effects epinephrine has generally been regarded as a last-line agent in the management of shock.

### AGENTS WITH PRIMARY VASOPRESSOR ACTIVITIES

**Norepinephrine** is an endogenous catecholamine with potent  $\alpha_1$ - and mild  $\beta_1$ -adrenergic activity. The main cardiovascular effect of norepinephrine is dose-dependent arterial and venous vasoconstriction. The mild positive inotropic and chronotropic effects are generally counterbalanced by the increase in afterload and vagal activity induced by the elevated systemic vascular resistance (5–6). The advantage of norepinephrine in cardiogenic shock is questionable, unless the systolic blood pressure is less than 70 mmHg despite the medium dose of dopamine or dopamine/dobutamine administration (6). It is an agent of choice for the management of hypotension in hyperdynamic (vasoplegic) shock (15). Adverse effects of norepinephrine include increased myocardial oxygen consumption causing ischemia, also renal and mesenteric vasoconstriction.

### PURE VASOPRESSOR AGENTS

**Phenylephrine** is a selective  $\alpha$  agonist that can be administered peripherally as boluses for short-term treatment. Phenylephrine is a potent vasoconstrictor without any inotropic effect, therefore, activation of vagal reflexes causes the slowing of the heart rate. The advantage of phenylephrine in cardiogenic shock is very questionable. Phenylephrine can be useful to raise the mean arterial pressure in patients with severe aortic stenosis, to correct hypotension caused by the simultaneous ingestion of sildenafil and nitrates or to decrease the outflow tract gradient in patients with obstructive hypertrophic cardiomyopathy (6). It is

commonly used in the management of anesthesia-induced hypotension. Compared to epinephrine and norepinephrine, phenylephrine is less likely to decrease microcirculatory blood flow in the gastrointestinal tract.

**Vasopressin** is an antidiuretic hormone, synthesized to a lesser degree by the heart in response to evaluated cardiac wall stress and by the adrenal gland in response to increased catecholamine secretion. It has dose-dependent increase in systemic vascular resistance. The advantage of vasopressin in cardiogenic shock is very questionable. Vasopressin could be useful in cardiopulmonary resuscitation and in the treatment of hyperdynamic (vasoplegic) shock, because its pressor effects are relatively preserved during hypoxic and acidotic conditions (5–6). Potential adverse effects of vasopressin include excess vasoconstriction causing severe end-organ ischemia and hyponatremia.

### CHOOSING AN AGENT

First of all, the history and physical examination should be directed towards establishing the primary mechanism and etiology of heart deterioration. Invasive monitoring with an arterial line and central venous catheterization should be considered especially if vasoactive agents are employed. Foley catheterization should also be established to assess the hourly urine output as a surrogate for end-organ perfusion. Most patients with advanced heart failure can be classified according to their physical findings. Patients should be characterized by the presence or absence of congestion and low-perfusion (4):

1. Most patients with AHF (70–80%) demonstrate adequate end-organ perfusion, but are volume overloaded. In this case, primary treatment is relief of congestive symptoms with intravenous vasodilators, loop diuretics, narcotics and respiratory support. In these settings, inotropes with vasodilatory properties are very effective, but should not be routinely used, unless there are difficulties to start diuresis. Any inotropes with vasoconstrictory properties are absolutely contraindicated (1–3).

2. A small minority of patients (5%) demonstrate impaired cardiac output but does not adequately use the Starling mechanism to increase preload. In these settings, cautious hydration should be first

attempted. Patients, who fail to improve in end-organ perfusion, may require positive inotropic agents, such as dobutamine or calcium sensitizers, and in case of  $\beta$ -blockade – phosphodiesterase inhibitors (1–3, 7).

3. In the worst case scenario (10–15%), compromised end-organ perfusion with evidence of congestion is present. These patients have impending cardiogenic shock. In this case, the possibility to optimize preload and afterload is very limited, the pump lacks the power, and the inotropic support or the heart assist device is crucial. Positive inotropic agents with mild vasoconstriction should be continued until the cause of cardiac deterioration is determined and a definitive therapy implemented. Agents of choice are as follows: single therapy moderate dose of dopamine, dual therapy of dobutamine in combination with dopamine, dual therapy of levosimendane in combination with dopamine and in case of  $\beta$ -blockade – dual therapy of phosphodiesterase inhibitors with cautious usage of norepinephrine (13).

## CONCLUSIONS

Vasopressor and inotropic support in case of AHF helps to win the time until a more definitive treatment becomes available. Therefore, AHF management must be directed to establish and eliminate deteriorational factors, however, not the correction of particular hemodynamic parameters.

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## ŪMINIS ŠIRDIES NEPAKANKAMUMAS: AR PRASMINGA PANAUDOTI VAZOAKTYVIAS MEDŽIAGAS?

### *Santrauka*

Ūminis širdies nepakankamumas (ŪŠN) pasireiškia staigiais simptomais, kuriuos sukelia sutrikusios širdies funkcijos. ŪŠN yra labai polimorfiškas ir gali būti siejamas su širdies ritmo, sistolinės ir / ar diastolinės širdies funkcijos sutrikimais bei prieškrūvio ir pokrūvio neatitikimu.

Gydant ūminį širdies nepakankamumą daugiau dėmesio turėtų būti skiriama etiologinio veiksnio išaiškinimui ir pašalinimui. Siekiant užtikrinti adekvačią gyvybinių organų perfuziją kol bus paskirtos tikslinės gydymo priemonės, prasminga nustatyti hemodinamikos profilį ir tinkamai panaudoti (ino)vazoaktyvias medžiagas. Dauguma vazopresorių ir inotropiškai veikiančių vaistų yra agresyvūs medikamentai, todėl juos būtina vartoti racionaliai.

**Raktažodžiai:** ūminis širdies nepakankamumas (ŪŠN), vazopresoriai, inotropiškai veikiantys vaistai, kardiogeninis šokas