

Vasoactive Agents

INO HUSEDZINOVIĆ • NIKOLA BRADIĆ • TANJA GORANOVIĆ

INO HUSEDŽINOVIĆ (✉) •
NIKOLA BRADIĆ • TANJA GORANOVIĆ
Department for anesthesiology,
reanimatology and intensive care medicine
University Hospital Dubrava
Gojko Šušak Avenue No 6
10000 Zagreb, Croatia
Phone: +385 1 290 3197
Fax: +385 1 290 3440
e-mail: inoh@kbd.hr

ABSTRACT

This article is a short review of vasoactive drugs which are in use in today's clinical practice. In the past century, development of vasoactive drugs went through several phases. All of these drugs are today divided into several groups, depending on their place of action, pharmacological pathways and/or effects on target organ or organ system. Hence, many different agents are today in clinical practice, we have shown comparison between them. These agents provide new directions in the treatment of cardiovascular compromise, suggesting that the primary goal of therapy is to produce a vasodilatory effect of the circulation rather than to reverse hemodynamic failure by using inotropic agents, with their inherent risks and side effects.

Key words: vasoactive agents, inotropic agents, levosimendan, phosphodiesterase III inhibitors

Vasoactive agents are a group of bioactive chemicals, which change vasomotor tone through their influence on various peripheral receptors. Most of these agents have inotropic effects (e.g. norepinephrine) as they bind with receptors positioned on the surface of the myocardium. Some pharmacologic agents are difficult to classify as their effects overlap, however all vasoactive drugs affect stroke volume and heart rate. This determines cardiac output and, as a consequence, overall cardiovascular function.

In the ideal situation, inotropic drugs would only have effects directly on myocardial cells, without simultaneous stimulation of other receptors. As one quickly learns, such is not the case with many of our most important vasoactive agents. Some inotropic agents such as dopamine (depending on the dose) provoke vasoconstriction while other such agents, like isoprenaline, cause vasodilatation.

Pure vasoconstrictors produce arterial wall constriction by stimulation of α -adrenergic receptors (e.g. phenylephrine) or by stimulating V1a receptors (e.g. vasopressine) on the vascular endothelial surfaces. Pure vasodilators, on the other hand, are classified according to their predominate

effect on the arteries (e.g. hydralazine), veins (e.g. nitroglycerine), or both arterial and venous (e.g. nitropruside) vessels. The main favorable result of hydralazine and nitropruside is a reduction of cardiac afterload and an increase in cardiac output. The main effect of nitroglycerine is achieved by venodilatation, which

Table 1. cAMP dependent inotropic agents

INOTROPIC AGENTS

cAMP dependent
adrenergic agonists
epinephrine
isoproterenol
dobutamine
norepinephrine
xamoterol
dopaminergic agonists
dopamine
dopexamine
ibopamine
phosphodiesterase III isoenzyme inhibitors
derivate of biperidine - amrinone, milrinone
derivate of imidazolone - enoximone, piroximone
toborinone

decreases preload and consequently cardiac output.

In 1908, Sir James McKenzie first described "low cardiac output syndrome". Clinically, this syndrome results in global hypoperfusion, whose treatment requires inotropic support by vasoactive medications, or mechanical intervention to support and improve cardiac work. In the early 1900s' the mainstay of cardiac treatment was digitalis with the addition of a salt reduced diet. Accumulated fluids within pleural and peritoneal spaces were eliminated by mechanical means or by drainage. The use of diuretics was instituted during the 1920's. The treatment of congestive heart failure entered a second phase in the 1950's, when vasodilators were introduced into the physicians' therapeutic armamentarium. With the introduction of the inotropic agents in the 1980s', a third great period in the therapy of heart failure had begun.

Using the pharmacokinetics and pharmacodynamics of many inotropic agents, Lehtonen was able to categorize them into two basic groups: cAMP dependent (Table 1), and cAMP independent (Table 2) (1).

The cAMP dependent group consists of those agents, which increase production of cAMP by stimulating adrenergic receptors (adrenergic and dopaminer-

Table 2. cAMP independent inotropic agents

INOTROPIC AGENTS

cAMP independent
 Na⁺-K⁺-ATPase inhibitors
 digoxin
 potassium channels inhibitors
 vesnarinone
 agonists of β- adrenergic receptors
 phenylephrine
 Calcium

gic agonists) or by decreasing cAMP degradation by inhibiting phosphodiesterase activity (phosphodiesterase III inhibitors). In contrast, the groups of inotropic agents, which are in the cAMP independent group, are inhibitors of Na⁺-K⁺-ATPase (digoxin), potassium channel inhibitors (vesnarinon), agonists of β- adrenergic receptors (*phenylephrine*), and include the calcium salts. The agents in this latter group affect ionic pumps and regulate the concentration of intracellular calcium (Table 3).

The catecholamine inotropic agents were among the earliest vasoactive agents and remain important and useful today although there can be some negative consequences of their use (Table 4). A major side effect is an increase

Table 3. Older therapeutic medications

OLDER THERAPEUTIC MEDICATIONS

NOTE: treatment of acute heart failure did not change for decades
 morphine
 diuretics
 nitroglycerine
 catecholamine inotropic agents
 Despite acute hemodynamic improvement, inotropic agents often increased mortality
 epinephrine
 dobutamine
 milrinone

in myocardial oxygen consumption. Furthermore, it is well established that during dopamine administration its effectiveness diminishes significantly as administration continues beyond 48 hours. This same effect has been seen after 90 hours with dobutamine. The most important component to explain

Table 4. Adverse effects of catecholamine administration

ADVERSE EFFECTS OF CATECHOLAMINE ADMINISTRATION

increase in oxygen consumption
 arrhythmogenic effect
 tachyphylaxis
 increased risk of sudden cardiac death
 difficulty during β-blocker administration
 Dependency on the functional condition of β-adrenergic receptors

the decreased effectiveness of inotropic agents is the functional condition of the β-adrenergic receptors. Today, there are many known conditions which change the density and responsiveness of β-adrenergic receptors. Such conditions, in fact, change the relationship within subgroups of β-adrenergic

Table 5. Conditions that alter receptor density and affect response to catecholamines

Legend: *β -adrenergic receptors are decreased in severe heart failure; + if on β - agonists therapy for asthma; ↑ - increased; ↓ - decreased. Modified from: Zaritsky A, Eisenberg MG. Ontogenetic consideration in the pharmacotherapy of shock. In: Chernow B, Shoemaker WC, eds. Critical Care: State of the Art. Fullerton, CA: Society of Critical Care Medicine; 1986;7:485-534

CONDITIONS THAT ALTER RECEPTOR DENSITY AND AFFECT RESPONSE TO CATECHOLAMINES

CONDITION	RECEPTOR DENSITY CHANGE
congestive heart failure	↑ β (heart)*
sepsis	↓ α (liver, vasculature)
myocardial ischemia	↓ β, ?? (heart)
asthma	↓ β (lungs leukocytes)+
cystic fibrosis	↓ β (leukocytes)
agonist administration	↓ α, β (heart, platelets, leukocytes)
antagonists administration	↑ α, β (heart, platelets, leukocytes)
hyperthyroidism	↑ β (heart)
hypothyroidism	↓ β (heart)
glucocorticoids	↑ β (heart, leukocytes)

receptors in myocardium, from 80% β1: 20% β2 changing in 60% β1: 40% β2 (Table 5) (2).

Phosphodiesterase III inhibitors produce their effects independently of β-adrenergic receptors. They are a useful class of agents that can be employed in various therapeutic settings. They are a non-specific heterogeneous group of agents. All three phosphodiesterase fractions are physiologically active. They have strong chronotropic effects, and therefore should be avoided in clinical practice when an inotropic agent is needed. Specific inhibitors of this class of agents are divided into the two groups (Table 6) (2).

There is also a group of vasoactive agents that exhibit an inotropic effect, but in addition, also have a vasodilator effect. Opie grouped these agents into a unique class, the inodilators (Table 7) (3).

A lack of tachyphylaxis and tachycardia, and being independent of β-adrenergic receptor conditions, gives a clinical advantage to this group of agents, when comparing them with the catecholamines (Table 8).

Furthermore, these agents have a very important myocardial effect, called the

Table 6. Phosphodiesterase iii inhibitors

PHOSPHODIESTERASE III INHIBITORS (PDE III)

NON-SPECIFIC

theophylline
papaverine
dipyridamole

SPECIFIC

derivates of biperidine - amrinone, milrinone
derivates of imidazolone - enoximone, piroximone

lusitropic effect, which was introduced into clinical terminology by Smith and Katz in 1986. Coining this term, the authors wanted to emphasize the role of diastolic dysfunction (4) during

Table 7. Effects of phosphodiesterase III inhibitors

EFFECTS OF PHOSPHODIESTERASE III INHIBITORS

MYOCARDIUM	positive inotropic
VASCULATURE	vasodilatation
CORONARY ARTERIES	vasodilatation
PLATELETS AND LEUKOCYTES	metabolic effect

heart failure. All agents, which improve diastolic function, primarily by decreasing the actin-myosin overlap during diastole, are deemed to have a positive lusitropic effect.

Numerous adverse effects and an increased mortality are the reasons why many clinicians are often unsuccessful with the inotropic agents presently in use. New therapeutic agents have been developed in the last few years to assist the clinician in the stabilization, support and treatment of cardiovascular disease (Table 9).

Table 8. Advantages of phosphodiesterase III inhibitors

ADVANTAGES OF PHOSPHODIESTERASE III INHIBITORS

myocardial - positive lusitropic effect
independent of the functional condition of adrenergic receptors
lack of tachyphylaxis
lack of tachycardia

One of the newest groups of inotropic agents (Table 10) is a group of agents, which increase the affinity of myofibrils for calcium and are called calcium sensitizers. Calcium sensitizers are the newest heterogeneous group of inotropic agents. The best known representatives of this group are levosimendan and pimobendan. Positive inotropic

effects of levosimendan are achieved by its binding to troponin C and calcium, thereby stabilizing the tropomyosin molecule and prolonging the duration of actin-myosin overlap without a change in the net concentration of intracellular calcium. The vasodilatory effect of levosimendan is reached through activation of ATP-dependent potassium channels. This leads to a decrease in both afterload and preload, increased coronary blood flow and a resultant anti-ischemic effect. Levosimendan is therefore categorized as an anti-ischemic

inotropic agent (5). Additionally, the incidence of arrhythmias is extremely low, there is no development of tolerance to its pharmacological effects, and the simultaneous administration of β -blockers and calcium channels blockers does not produce serious adverse effects. In two large randomized studies, RUSLAN and LIDO, it was documented that positive hemodynamic effects and a lower mortality was seen in patients who received levosimendan

Table 10. Newer inotropic agents

NEWER INOTROPIC AGENTS

CALCIUM SENSITIZERS

levosimendan
pimobendan

OTHERS

natriuretic brain peptide - nesiritide
tezosentan
vasopressin

in comparison to patients who received dobutamine or placebo (6, 7). Also, there is much interest in levosimendan administration in patients with open-heart surgery, especially in those with off-pump procedure (8-10).

There are three types of natriuretic brain peptides. The A and B types are located in the atria and ventricles of the heart, and the C type is located in endothelial cells. B-natriuretic peptide has a spectrum of physiologic effects of clinical importance, which include reduction of both pre- and afterload along with diuretic and natriuretic effects (Table 11). The serum level of B-natriuretic peptide is directly correlated with the degree of chronic heart failure. Because of this, it has been added to the diagnostic pro-

Table 9. New therapeutic goals

NEW THERAPEUTIC GOALS

AGENT	EFFECT	MECHANISM OF ACTION
ISDN - high doses	venous and arterial vasodilatation	synthesis of NO
Tezosentan	arterial vasodilatation	blockade of endothelin receptors
Nesiritide	arterial vasodilatation	decrease of preload, afterload, diuresis
Levosimendan	inotropic, vasodilatation	binding for troponin C, activation of potassium channels

tolocol of the European Cardiology Association and to the protocol of congestive heart failure treatment as well (11).

Nesiritide is an exogenous recombinant B-natriuretic peptide with the same pharmacological profile. There have been nine clinical studies conducted using nesiritide involving over nine hundred patients. Significant, positive clinical effects have been documented.

Endothelin is a strong vasoconstrictor. There are two types of receptors to which it attaches. The ET_A receptors are located in the vessel's smooth muscles cells and the ET_B receptors are located on the endothelial surfaces. Stimulation of the receptors by endothelin produces increased vascular tonus and progression of arteriosclerosis in subjects with coronary artery disease. Inhibition of endothelin function results in better hemodynamics, heart remodeling and a decreased proliferation of smooth muscles in blood vessel walls. In the RITZ

study, and the VERITAS study, involving almost 1500 patients (13), favorable hemodynamic effects (a lowering the systemic blood pressure, and increase of cardiac index) were measured but without significant clinical improvement and or a reduction in mortality (4, 5, 12). Arginin-vasopresine is an endogenous nonapeptide. It stimulates V1a receptors and produces vasoconstriction. At the same time stimulation of V2 receptors produces an antidiuretic effect. By these mechanisms vasopresine plays an important role in fluid homeostasis. It plays an important therapeutic role in states of refractory vasodilatation, in which patients are unresponsive to catecholamine vasoconstrictive therapy (14). Vasopresine has also a place in cardiopulmonary resuscitation procedures (15). In the animal model, it has shown better effects on circulation in the splanchnic region in comparison with norepinephrine (16).

CONCLUSION

Historically, the catecholamines inotropic agents were first line medications used in the treatment of cardiovascular compromise, but their benefits were often overshadowed by major complications, such as increased mortality. The introduction of many newer agents in newer classes, such as those which produce their effects independently of β -receptor functionality (e.g. phosphodiesterase III inhibitors), or do not change the intracellular calcium values (e.g. calcium sensitizers), represent safer, better choices for treatment. They also establish new directions in the treatment of cardiovascular compromise, suggesting that the primary goal of therapy is to produce a vasodilatory effect of the circulation rather than to reverse hemodynamic failure using inotropic agents, with their inherent risks and side effects.

LITERATURE

1. Lehtonen AE, Antila S, Pentikainen PJ. Pharmacokinetics and pharmacodynamics of intravenous inotropic agents. *Clin Pharmacokinet* 2004;43:187-203.
2. Priebe HJ. Vasoactive drugs (IARS Review Course Lectures). *Anesth Analg* 2004;64:79-83.
3. Opie LH, Chatterjee K, Gersh BJ. Drug for heart 2nd edition. Orlando, Florida: Grune Stratton; 1986, pp 306-309.
4. Smith VE, Katz AM. Inotropic and lusitropic abnormalities as the basis for heart failure. *Heart Failure* 1987;3:55-65.
5. Lehtonen LA. Levosimendan: a parenteral calcium-sensitizing drug with additional vasodilatory properties. *Expert Opin Investing Drugs* 2001;10:955-970
6. Moiseyev VS, Poder P, Andrejevs N, Ruda MY, Golikov AP, Lazebnik LB, Kobalava ZD, Lehtonen LA, Laine T, Nieminen MS, Lie KI; RUSLAN Study Investigators. Safety and efficacy of a novel calcium sensitizer, levosimendan, in patients with left ventricular failure due to an acute myocardial infarction. A randomized, placebo-controlled, double blind study (RUSLAN). *Eur Heart J* 2002;23:1422-32
7. Follath F, Cleland JG, Just H, Papp JG, Scholz H, Peuhkurinen K, Harjola VP, Mitrovic V, Abdalla M, Sandell EP, Lehtonen L; Steering Committee and Investigators of the Levosimendan Infusion versus Dobutamine (LIDO) Study. Efficacy and safety of intravenous levosimendan compared with dobutamine in severe low-output heart failure (the LIDO study): a randomised double-blind trial. *Lancet* 2002;360:196-202.
8. Barisin S, Husedzinovic I, Sonicki Z, Bradic N, Barisin A, Tonkovic D. Levosimendan in Off-Pump Coronary Artery Bypass; A Four – times Masked Controlled Study. *J Cardivasc Pharmacol* 2004;44:703-708.
9. Husedzinovic I, Bradic N, Barisin S. Levosimendan-hemodynamic support during off-pump coronary artery bypass graft surgery. *Intensive Care Med* 2005;31(suppl 1):S 97.
10. Husedžinović I, Barišin S, Bradić N, Barišin A, Sonicki Z, Milanović R. Levosimendan as a new strategy during off – pump coronary artery bypass grafting: Double – blind randomized placebo – controlled trial. *Croat Med J.* 2005;46:950-6.
11. Rodeheffer RJ. Measuring plasma B-type natriuretic peptide in heart failure: good to go in 2004?. *J Am Coll Cardiol.* 2004; 44: 740-9.
12. Kaluski E, Kobrin I, Zimlichman R, Marmor A, Krakov O, Milo O, Frey A, Kaplan S, Krakover R, Caspi A, Vered Z, Cotter G. RITZ-5: randomized intravenous Tezosentan (an endothelin-A/B antagonist) for the treatment of pulmonary edema: a prospective, multicenter, double-blind, placebo-controlled study. *J Am Coll Cardiol.* 2003;41:204-10
13. Teerlink JR, McMurray JJ, Bourge RC, Cleland JG, Cotter G, Jondeau G, Krum H, Metra M, O'Connor CM, Parker JD, Torre-Amione G, Van Veldhuisen DJ, Frey A, Rainisio M, Kobrin I; VERITAS Investigators. Tezosentan in patients with acute heart failure: design of the Value of Endothelin Receptor Inhibition with Tezosentan in Acute heart failure Study (VERITAS). *Am Heart J* 2005;150:46-53
14. Patel BM, Chittock DR, Russell JA, Walley KR. Beneficial effects of short-term vasopressin infusion during severe septic shock. *Anesthesiology.* 2002;96:576-82.
15. Stiell IG, Hebert PC, Wells GA, Vandemheen KL, Tang AS, Higginson LA, Dreyer JF, Clement C, Battram E, Watpool I, Mason S, Klassen T, Weitzman BN. Vasopressin versus epinephrine for in-hospital cardiac arrest: a randomised controlled trial. *Lancet* 2001;358:105-9.
16. Guzman JA, Rosado AE, Kruse JA. Vasopressin vs norepinephrine in endotoxic shock: systemic, renal, and splanchnic hemodynamic and oxygen transport effects. *J Appl Physiol* 2003; 95: 803-9.