

CURRENT LITERATURE QUESTIONS THE ROUTINE USE OF LOW-DOSE DOPAMINE

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Dopamine use in acute renal failure (ARF) patients has been considered standard practice for many years. Despite this widely accepted practice, there has been limited evidence to support its usage. Low-dose dopamine has been accepted because it is considered to pose minimal risk to the patient. Dopamine infused at low doses is thought to be specific to dopaminergic receptors. However its results are often unpredictable and can lead to several alpha and beta induced side effects.

With advances in technology there is another option that

may be superior in the prevention and treatment of acute renal failure. Fenoldopam is a drug specific to dopamine-1 receptors in the kidneys. It is currently being examined to determine its usefulness among patients with ARF. With the discovery of fenoldopam and the known serious side effects of dopamine, there is reason to use caution with the routine use of low-dose dopamine.

Key words: Acute renal failure, fenoldopam, low-dose dopamine.

The use of low-dose dopamine to prevent and treat renal dysfunction has become widely accepted clinical practice.¹ Research in healthy volunteers has shown that low-dose dopamine increases renal blood flow and induces both natriuresis and diuresis.² Since renal ischemia is the most common cause of acute renal failure (ARF), it is expected that these beneficial effects of dopamine would aid in the prevention and treatment of ARF. Contrary to the expected results, there is a lack of strong evidence to support the use of dopamine to attenuate renal injury.² Researchers continue to explore the benefits of low-dose dopamine in the prevention and treatment of renal failure, but further evidence is needed to prove the benefits outweigh the associated adverse effects.

Due to the concerns with the effectiveness of low-dose dopamine and knowledge related to dopamine specific agonists, alternative therapies in the prevention and treatment of ARF are being explored.² Fenoldopam, a selective dopamine-1 (DA₁) receptor agonist, is being examined to determine its usefulness among patients with ARF. The purpose of this paper is to examine the controversy related to the use of low-dose dopamine in the prevention and treatment of ARF, and explore the use of fenoldopam, as an alternative, that appears to offer a better risk/benefit ratio.

Acute renal failure

Acute renal failure is a decline in renal function that

cannot be reversed immediately with changes in extrarenal factors, meaning cardiac output, intravascular volume, urinary flow, or blood pressure. Renal failure is ultimately characterized by azotemia, either prerenal, renal, or postrenal, and oliguria (decline in urine output < .5 mL/kg per hour).³ Acute renal failure or renal azotemia can be diagnosed following the exclusion of prerenal and postrenal causes. Prerenal azotemia usually results from kidney hypoperfusion, and, if left untreated, can progress to ARF. Postrenal azotemia results from a urinary tract obstruction that does not allow the excretion of urine. Again, both postrenal and prerenal azotemia must be ruled out before the diagnosis of ARF can be made.

Half of all cases of ARF are due to major trauma or surgery. In these cases, the causes are ischemia and nephrotoxins.³ Nephrotoxins can be classified as both endogenous and exogenous. Exogenous nephrotoxins include radiographic contrast dyes, cisplatin, aminoglycosides, and amphotericin B.³ Myoglobin and hemoglobin are both potent nephrotoxins that can be released during rhabdomyolysis and intravascular hemodialysis, respectively.³ Renal ischemia and hypoxia can lead to epithelial cell demand and adenosine triphosphate production imbalance. This causes an altered ion transport, cellular swelling, altered metabolism of phospholipids, and an accumulation of intracellular calcium.³

Acute renal failure is often classified according to urinary volume. If urinary volume is greater than 400

mL/dL, it is called nonoliguric and is thought to indicate a less severe form of renal injury.³ If urinary volume is less than 400 mL/dL, it is called oliguric.³ Anuria is classified by urinary volume less than 100 mL/dL.³ Urine output is often considered a major indicator of renal function. Some patients with severe renal dysfunction can maintain or have increased urine output.⁴ Urine output alone, whether increased or decreased, cannot be considered a reliable indicator of renal function. See Table 1 for the signs and symptoms of acute renal failure and Table 2 for the differential diagnosis and causes of acute renal failure.

Pharmacologic treatment possibilities

Current pharmacologic treatment modalities for acute renal failure include the use of dopamine, mannitol, furosemide, and fenoldopam. Dopamine is a DA₁ and DA₂ receptor agonist and theoretically increases renal blood flow.⁵ Mannitol is an osmotic diuretic that increases tubular flow by increasing filtrate volume through its osmotic diuretic effect. The use of furosemide, a loop diuretic, prevents reabsorption of fluids at the loop of Henle. The newest pharmacologic treatment is fenoldopam, which is a selective DA₁ receptor agonist and is thought to preserve renal perfusion and glomerular filtration rate (GFR).⁵

Renal function tests

Adequate renal function can be determined by laboratory findings. Laboratory tests to evaluate baseline renal function should involve GFR and renal tubular function.⁴ The most reliable test for GFR is creatinine clearance.^{3,4} To ensure accuracy, this test is usually per-

Table 1. Signs and symptoms of acute renal failure

- Increase in serum urea and creatinine concentrations
- Sodium and water retention
- Acidosis
- Hyperkalemia
- Decreased urine output (oliguria, anuria)
- Fluid retention causing lower extremity swelling
- Decrease sensation in hands or feet
- Changes in mental status or mood (agitation, drowsiness, lethargy, confusion)
- Nausea, vomiting
- Prolonged bleeding, or bruising easily

(Adapted from: (1) Stoelting RK, Dierdorf SF. *Anesthesia and Co-existing Disease*. 4th ed. New York, NY: Churchill Livingstone; 2002:357-358. (2) Acute Kidney Failure. Medline Plus. Available at: <http://www.nlm.nih.gov/medlineplus/ency/article/000501.htm#Symptoms>. Accessed February 28, 2005.)

Table 2. Differential diagnosis and causes of acute renal failure*

Prerenal	Renal	Postrenal
Causes		
Volume depletion or sequestration Impaired cardiac output	Sepsis Toxins Multiple organ failure Rhabdomyolysis	Bladder outlet obstruction Ureteric ligation
Differential diagnosis		
BUN/Cr ratio >20:1 Variable increase in serum creatinine UA usually normal Urine osmolality >500 mOsm/L Urine Na <20 mEq	BUN/Cr ratio <15:1 Cr <0.5/dL per day UA with granular cell casts Urine osmolality <350 mOsm/L Urine Na >30 mEq	
Physical examination		
Orthostatic hypotension Poor skin turgor Dry buccal mucosa Congestive heart failure Edema	Edema Petechiae Palpable purpura Muscle tenderness	Distended bladder Enlarged prostate Abdominal or pelvic masses

* BUN indicates blood urea nitrogen; UA, urinalysis; Na, sodium; Cr, creatinine.

(Adapted from: (1) Hilton R. Acute renal failure. *BMJ*. 2006;333:786-790. (2) Singri N, Ahya SN, Levin ML. Acute renal failure. *JAMA*. 2003;289:747-751.)

formed over a 24-hour period. Creatinine clearance levels less than 25 mL/min indicate moderate to severe renal dysfunction.^{3,4} Plasma creatinine is another specific indicator of renal function (or GFR).^{3,4} Serum creatinine concentration is directly related to body muscle mass (source of creatinine) and inversely related to GFR.³ Only when the body muscle mass is constant will the serum creatinine concentration be dependant on GFR. When there is a 50% decrease in serum creatinine concentration, there will be a similar decrease in GFR.⁴ Blood urea nitrogen (BUN) is another test associated with determining a patient's renal function. In patients who consume a normal diet, BUN will vary inversely with GFR. BUN is not as sensitive a test as compared to GFR. This is because the clearance of urea also depends on resorption rate of the renal tubules and production rate of urea, not just GFR.⁴ There is a bigger chance for abnormal BUN levels despite the normal function of GFR.

Other tests to measure renal function include serum and urine electrolytes, osmolality, creatinine, and urinalysis. Urinalysis is intended to detect the presence of protein, glucose, acetoacetate, blood, leukocytes, pH, and specific gravity.⁴ These tests are indicators of the efficacy of renal function. A properly working kidney will maintain normal laboratory values, whereas a patient with renal failure will have abnormal test results.

Dopamine

Dopamine is an endogenous catecholamine that is a precursor to epinephrine and norepinephrine. Dopamine exerts its actions by affecting alpha (α) and beta (β) adrenergic receptors, as well as DA₁, and DA₂ receptors.⁶ Each of these receptors elicit varying responses and are located at different places throughout the body. The effect of exogenous-delivered dopamine on the body can vary depending on the dose of dopamine received.

When dopamine stimulates α_1 receptors, a systemic vasoconstriction effect occurs. This effect from dopamine infusion usually occurs at high doses (5-20 $\mu\text{g}/\text{kg}$ per minute).^{7,8} At intermediate doses (3-10 $\mu\text{g}/\text{kg}$ per minute) dopamine infusions usually stimulate β_1 receptors.⁸ Stimulation of β_1 receptors will produce increased cardiac index that helps to augment renal perfusion. With low-dose dopamine infusions (<3 $\mu\text{g}/\text{kg}$ per minute), there is an increase in renal blood flow (RBF) and GFR.^{6,9} This increase in RBF is due to intrarenal vasodilation from stimulation of DA₁ receptors.^{7,8} DA₁ receptors are located on the renal, coronary, cerebral, and mesenteric arteries.⁶ Low-dose dopamine also results in stimulation of DA₂ receptors.

DA₂ receptors are located in both sympathetic nerve endings and autonomic ganglia where they inhibit the release of noradrenaline.⁶ In the adrenal gland, DA₂ receptors inhibit the production of aldosterone.⁶

Dopamine is classified as a nonselective dopamine receptor agonist. It has effects on both DA₁ receptors, as well as DA₂ receptors at similar doses.⁶ Both DA₁ and DA₂ receptors are found in the kidneys and produce varying actions. The stimulation of DA₁ receptors cause vasodilation, variable effects on renin release, inhibition of Na-K adenosine and Na-phosphatase cotransport, and inhibition of angiotensin II and antidiuretic hormone actions.¹⁰

Dopamine is nonspecific in relation to dopamine receptors, which produces a multitude of undesirable effects. Some of these effects include tachyarrhythmias and myocardial and gut ischemia.¹¹ It also inhibits the sodium-potassium adenosine triphosphatase (ATPase) in the proximal tubule, which causes an increase in medullary oxygen requirement.⁵ Dopamine also is proven to decrease minute ventilation and adversely affect oxygen saturation.⁵ Dopaminergic receptors also can differ in distribution, affinity, and number at varying times.¹⁰ Dopamine produces very unpredictable results.

Rationale for use of renal-dose dopamine

Renal-dose (or low-dose) dopamine is a widely used practice by surgeons and physicians to help prevent, or as treatment for, ARF. This practice has been accepted because of the ability of renal-dose dopamine to increase RBF, increase Na excretion (naturesis), and increase GFR, all of which helps to induce diuresis.^{1,10,12} The mechanism that allows low-dose dopamine to exhibit these effects is through the selective action at dopamine receptors causing renal vasodilation.¹³ Dopamine, at low-dose, is thought to remain specific to dopamine receptor sites with minimal spillover to β sites and even less at the α sites.⁶ The effects elicited from low-dose dopamine should be largely renal.

Studies to support the use of renal-dose dopamine

There have been a number of studies to support this current practice trend. Renal-dose dopamine's usefulness in the treatment and prevention of ARF began in the 1960s and has continued to hold true for the past 4 decades.^{6,14} Over the years, studies have demonstrated renal-dose dopamine's efficacy with ARF in relation to congestive heart failure, septic shock, contrast-related nephrotoxicity, vascular surgery, cardiac surgery, and liver transplantation.⁶ Several studies will

be reviewed in order to demonstrate the renal protective effects of dopamine.

A study involving hypertensive patients showed that at renal-dose, dopamine caused an increase in RBF, GFR, and naturesis with minimal changes in cardiac output.¹⁵ This shows that at low doses, dopamine can have specific effects on dopamine receptors at the kidneys unrelated to improved cardiac function. For patients in cardiogenic shock, the addition of renal-dose dopamine to the norepinephrine and intra-aortic balloon counterpulsation (IABP) caused a significant increase in urine output.¹⁶ Another study involving postcardiac surgical patients, showed how renal-dose dopamine was effective in the treatment of oliguria.¹⁷

Septic shock patients often require treatment involving potent α agonists, such as norepinephrine. Alpha agonists produce their effects by increasing blood pressure due to vasoconstriction. The use of renal-dose dopamine with septic shock patients has been shown to maintain renal vasodilation despite the use of potent vasoconstrictors, which could lead to ARF.⁶ A multitude of studies have proven that renal-dose dopamine causes diuresis in oliguric patients.¹⁸⁻²⁰

In regard to contrast-related nephrotoxicity, renal-dose dopamine has been shown to decrease toxicity by increasing the tubular flow rate so that there is less contact of the contrast to the tubular epithelium.^{21,22} A study performed by Pelson et al concerning the high incidence of postoperative renal failure showed that toxicity has decreased with the use of prophylactic renal-dose dopamine prior to surgery.²³ During abdominal aortic aneurysm surgery, where there is cross-clamping of the aorta, the use of dopamine helps to attenuate possible ARF by increasing urine output, sodium excretion, and creatinine clearance.²⁴

The list of studies showing the effectiveness of renal-dose dopamine in the prevention and/or treatment of ARF is indefinite. Although these studies show favorable experimental evidence and effects that might help with renal recovery, there are virtually no studies to support the use of renal-dose dopamine that are randomized or controlled.¹³ These types of studies are the gold standard of medical practice.¹³ Also the majority of studies performed have been on limited samples of people that decreases their power and limits the findings.¹ Despite the lack of strong evidence, renal-dose dopamine is still regarded as the standard of practice in the treatment and prevention of ARF.

Side effects of dopamine usage

Dopamine has a number of known adverse effects even at low doses. The pharmacokinetics of dopamine vary considerably from patient to patient. Low-dose

dopamine typically has a higher affinity for dopamine receptors; however, α and β effects are often detected even at low doses. This variation and unpredictability of receptor affinity is often the culprit of tachyarrhythmias, increased afterload, and increased myocardial consumption that can occur with low-dose dopamine.⁷ These effects can be especially detrimental to patients with preexisting cardiac disease.

Gut ischemia also has been reported during the use of low-dose dopamine. Dopamine causes precapillary vasoconstriction resulting in the shunting of blood flow away from the gut mucosa.^{2,7,9,25} Mucosal ischemia has long been linked to the development of multisystem organ dysfunction.⁹

In low doses, dopamine inhibits lymphocyte proliferation and immunoglobulin synthesis leading to impaired resistance to infections.^{2,7,9} Dopamine also decreases serum prolactin concentrations, growth hormone secretion, and thyrotropin release.⁹ These important immuno-stimulatory hormones help protect the body against infection and aid in the prevention of negative nitrogen balance in critical illness.⁹ Dopamine blunts the hypoxic ventilatory drive and may increase pulmonary shunting due to depression of chemoreceptor responsiveness in the carotid bodies to carbon dioxide and oxygen.^{2,7,9}

Studies that refute the use of low-dose dopamine

As previously mentioned, dopamine use in ARF is common despite the consistent lack of strong evidence that supports its use. There have been numerous studies showing the theories behind why dopamine should aid in the prevention and treatment of ARF. Large randomized, controlled studies are virtually nonexistent and do not demonstrate these benefits.¹

Both low-dose dopamine supporters and critics agree that dopamine increases RBF while also inducing diuresis and naturiesis. The controversy arises related to the clinical significance of the effects in relation to the prevention and treatment of ARF. Supporters of low-dose dopamine stress the effect of increased RBF, with the belief that improved blood flow will restore oxygen delivery to portions of the kidney that are hypoxic. It is expected that these beneficial effects would prevent ARF in the example of contrast-related nephrotoxicity, where the cause of ARF is related to decreased RBF and medullary ischemia. Research related to contrast-related nephrotoxicity does not reflect these benefits.^{1,2} In fact, a few studies show that these effects may actually be deleterious to renal function because of the diuretic effects of dopamine. Diuresis may result in an increased presentation of

ions for reabsorption, which inadvertently increases medullary oxygen consumption and may exacerbate medullary ischemia.^{1,2} These are the reasons critics of low-dose dopamine do not recommend its use as a nephroprotective agent in the prevention of contrast-related ARF.

Low-dose dopamine has been shown to increase urine output, and urine output is often erroneously considered an indicator of renal function. Urine output is a poor indicator of GFR.⁷ As previously mentioned, GFR is determined by creatinine clearance. The diuretic effects of low-dose dopamine must not be mistaken for improvement in renal function and decreased incidence of ARF.

The diuretic effects of low-dose dopamine also have been considered beneficial in the prevention of anuric renal failure. As previously mentioned, non-oliguric renal failure carries a lower mortality than anuric renal failure but does not affect overall renal recovery or outcome.¹ The question remains whether low-dose dopamine is the best way to prevent anuria. There are many other available diuretics that can be used in the prevention of anuria that carry fewer adverse effects than dopamine. It is in the patient's best interest to avoid low-dose dopamine for the sole purpose of increasing urine output.

The effect of low-dose dopamine on serum creatinine levels and GFR has been studied numerous times. A meta-analysis was composed on the effects of low-dose dopamine and serum creatinine levels.²⁵ Of the 7 studies that met inclusion criteria, 6 of the studies revealed no difference in serum creatinine levels between subjects that received low-dose dopamine and those that did not.²⁵ The one study that showed a decrease in serum creatinine levels was a small study.²⁵ All of the studies included in the meta-analysis that examined the effects of low-dose dopamine on GFR were unable to show any statistical significance between GFR in patients receiving low-dose dopamine and those that did not.²⁵

Several studies also have been conducted to determine the effects of low-dose dopamine on the incidence of ARF, need for hemodialysis, and mortality related to kidney failure.^{1,7,9,26} Based on these criteria, a review of the literature confirmed that low-dose dopamine has no renoprotective effect.⁹ Several randomized controlled trials showed no benefit of dopamine in patients undergoing infrarenal aortic cross-clamping for elective abdominal aortic aneurysm surgery.²⁷ Elective coronary artery bypass graft surgery also was studied related to the use of low-dose dopamine.²⁸ It was found that low-dose

dopamine does not provide sufficient protection of tubular function and may increase renal tubular injury during the early postoperative period.²⁸ Another randomized controlled study was conducted involving the use of low-dose dopamine for prophylaxis in liver transplant patients that showed no significant difference between the groups in the incidence of ARF requiring dialysis and no difference in mortality.²⁹ Finally, a large study was conducted with septic oliguric patients and the use of low-dose dopamine.²⁶ The results indicated that low-dose dopamine did not reduce the incidence of ARF or the need for dialysis.

DA₁ and DA₂ receptors sites

The effects of DA₁ and DA₂ receptors differ. In the prevention and treatment of ARF, DA₁ receptor stimulation provides the most desirable effects. These effects include decreases in renal vascular resistance, increases in renal blood flow and GFR, and increases in sodium excretion and urine volume.¹⁰ Low-dose dopamine is nonspecific to dopamine receptors, making it impossible to attain the desired DA₁ receptor effects without concomitant undesirable DA₂ receptor effects.¹⁰ DA₁ specific agonists have been considered an alternative to low-dose dopamine because of promising human data demonstrating their ability to significantly increase RBF, GFR, and natriuresis. See Table 3 for the differences between DA₁ and DA₂ receptors.³⁰

Fenoldopam

Fenoldopam mesylate (Corlopam) is the first commercially available selective DA₁ receptor agonist.³¹ It causes both systemic and renal arteriolar vasodilation through the activation of adenylate cyclase and natriuresis by inhibiting sodium-potassium ATPase-dependent processes.^{31,32} This enables fenoldopam to decrease renal oxygen demand and increase renal oxygen delivery.³² Unlike dopamine, fenoldopam has no DA₂, α -adrenergic, or β -adrenergic agonism.³¹

In addition to the benefit of preventing ARF, fenoldopam at higher doses can be used in the management of hypertensive emergencies because of its significant peripheral vasodilatory effects.³⁰ Despite the reduction in renal perfusion pressure that occurs with decreasing systemic blood pressure, GFR and renal blood flow are maintained or increased during treatment with fenoldopam.³¹ Sodium excretion and urine output also are increased during treatment of hypertensive emergencies with fenoldopam.¹⁰ When fenoldopam is given in lower doses, increased renal blood flow is experienced without lowering systemic blood pressure.¹⁰

Table 3. Dopamine I and dopamine II receptors in the kidney*

Dopamine I	Dopamine II
Cyclic adenosine monophosphate (cAMP)	Cyclic adenosine monophosphate (cAMP)
Arterial vasodilation	Inhibits Na/K ATPase activity in the proximal tubules
Natriuresis and diuresis in renal tubules	Increases K channel
Renin release in the juxtaglomerular apparatus	Decrease Ca channel
	Stimulates prostaglandin E2 production in the collecting duct

* Na indicates sodium; K, potassium; ATPase, adenosine triphosphatase, Ca, calcium.

(Adapted from Murphy MB, Murray C, Shorten GD. Fenoldopam: a selective peripheral dopamine-receptor agonist for the treatment of severe hypertension. *N Engl J Med.* 2001;345:1548-1557.)

Unlike dopamine, which causes renal vasoconstriction at higher doses, fenoldopam at higher doses produces even greater renal vasodilation.³¹ Fenoldopam is more than 6 times as potent as dopamine in increasing renal blood flow.¹⁰ Fenoldopam is safer and is more consistently effective as a renoprotective agent than low-dose dopamine.³¹

Studies that support the use of fenoldopam

A randomized, double-blind, placebo-controlled study was performed related to the dose at which dilation of the renal vascular bed can be achieved without inducing systemic hypotension.³¹ It was discovered that fenoldopam at a dose of 0.1 µg/kg per minute does not induce significant hypotension.³¹ Several other studies agree that fenoldopam maintains hemodynamic stability at this infusion rate.^{30,32}

Early research related to the renal protective effects of fenoldopam for the prevention of contrast-related ARF reported promising results.³³ More recent randomized trials have failed to demonstrate the benefit of intravenous fenoldopam.³⁴⁻³⁶ Current research is now shifting toward trials that evaluate the intrarenal infusion of fenoldopam for the prevention of ARF. A case report by Ng et al found that fenoldopam infused intrarenally produced a 10-fold increase in GFR over fenoldopam given intravenously at the same infusion rate.³⁷ Additional research on the intrarenal use of fenoldopam is needed.

No severe or serious side effects have been reported with the use of fenoldopam.³¹ Side effects are generally mild and transient. They include headache, nasal congestion, dizziness, and abdominal pain.³¹ Even at high doses, fenoldopam is considered safe and well tolerated.

Research on fenoldopam in the prevention and treatment of ARF is favorable, but several studies suggest that further research is needed. Large, random-

Table 4. Effects of dopamine and fenoldopam on receptors

Receptors	Dopamine	Fenoldopam
Dopamine I	Yes	Yes
Dopamine II	Yes	No
Alpha I	Yes	No
Alpha II	Yes	No
Beta I	Yes	No

(Adapted from Murphy MB, Murray C, Shorten GD. Fenoldopam: a selective peripheral dopamine-receptor agonist for the treatment of severe hypertension. *N Engl J Med.* 2001;345:1548-1557.)

ized, controlled studies, along with existing research, will help expand the knowledge of fenoldopam. In the meantime, with the numerous side effects associated with low-dose dopamine and its inability to prove success among patients at risk for ARF, the use of fenoldopam for the prevention and treatment of ARF cannot be overlooked. See Table 4 for the effects of dopamine and fenoldopam on specific receptors.

Conclusion

When examining agents for potential therapeutic effects, it is important to weigh the risks vs the benefits regarding deleterious side effects. This analysis is essential when the treatment is of questionable benefit, as in the case of low-dose dopamine. It is no surprise that there are controversies related to the use of dopamine in the prevention and treatment of ARF. Low-dose dopamine has been linked to several harmful side effects, has extreme variability even at steady-state infusion rates, and is not well supported in the literature. The use of low-dose dopamine on the basis that it will be beneficial while causing no harm is no

longer advisable. With research related to specific DA₁ agonists, such as fenoldopam, there may be no need to subject patients to the harmful effects of dopamine. Research on fenoldopam is still in its infancy, but, when given intrarenally, it shows a promising future in the prevention and treatment of ARE.

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