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Acute Renal Failure

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Abstract

Each kidney is made up of about 1 million nephrons. Nephron consists of 6 functional units anatomically:

- glomerular capillary
- proximal twisted tubule
- helne handle
- distal renal tubule
- collector channels (cortical and medullary)
- juxtaglomerular apparatus

Glomerular filtration pressure (GFP) (60 mmHg) is 60% of the mean arterial pressure and is reduced by plasma oncotic pressure (about 25 mmHg) and renal interstitial pressure (about 10 mmHg);

$$\text{GFP} = \text{MAP} - \text{plasma oncotic pressure} - \text{renal interstitial pressure}$$

Tonus of renal afferent and efferent arterioles are important in determining the filtration pressure:

$$\text{GFR} \propto \text{efferent arteriolar tone and } 1/\alpha \text{ afferent arteriolar tone}$$

Approximately 20% (120ml / min, 180L / day) of plasma passing through the glomerulus of both kidneys is filtered into the Bowmann capsule.

Keywords: kidney; Failure; Acute

Renal Circulation

Renal functions are directly related to renal blood flow. The kidneys are the only organ in which oxygen use is determined by blood flow. In other organs, blood flow determines the organ's use of oxygen. Approximately 20-25% of the total cardiac output passes through the kidneys [1]. Renal blood flow and glomerular filtration (2)

a. Clearance is the volume of blood that the kidneys clear from the substance (x) per minute (min).

b. Renal blood flow: Renal plasma flow is usually measured by p-aminohippurate (PAH) clearance. PAH is eliminated in a transition from the kidney through filtration and secretion at low plasma concentrations.

c. Renal plasma flow (RPF) = PAH clearance = (PAH urine / PAHplasma) x urine flow.

d. Renal blood flow (RBF) = RPF / (1-hematocrit)

$$\text{RPF} = 660 \text{ ml / min}$$

$$\text{RBF} = 1200 \text{ ml / min}$$

Glomerular Filtration Rate (Gfr)

GFR is normally up to 20% of the renal blood flow. Fully filtered and secrecy and non-reabsorbed inulin clearance is a good criterion for GFR.

$$\text{GFR} = 120 \pm 25 \text{ ml / min in men}$$

$$95 \pm 20 \text{ ml / min female}$$

Although less valid than inulin, it is practically used in clinical practice for estimation of creatinine clearance. Since creatinine is normally secreted from the renal tubules, it can cause high detection of GFR.

Creatinine clearance = $\frac{[\text{Creatinine}] \text{ urine} \times \text{urine flow rate}}{[\text{creatinine}] \text{ plasma}}$

The ratio of GFR to RBF is called the filtration fraction and is normally 20%. Although renal plasma flow decreases, afferent arteriolar dilatation and efferent arteriolar vasoconstriction increase the filtration fraction.

Control Mechanisms Of Renal Blood Flow [3]

Regulation of RBF is a complex process

Intrinsic auto regulation

Extrinsic regulation: hormonal, neural factors play a role

Intrinsic Autoregulation

Intrinsic renal vascular tone; It depends on the balance of vasoconstrictor (salt trap) (sympathoadrenal axis, renin-angiotensin, arginine vasopressin) and vasodilator (salt extractor) (Prostaglandin; PG, atrial natriuretic peptide; ANP, nitric oxide; NO) systems.

a. The vasoconstrictor system preferably creates vasoconstriction in the cortex, causing redistribution of blood from the cortex to the salt-trapping deep areas of the medulla.

b. Autoregulation may occur when the mean arterial pressure (MAP) is between 80-180 mmHg. RBF usually decreases when MAP drops below 70 mmHg.

c. Vasoconstriction and vasodilation in the afferent arteriole ensures constant renal blood flow within the limits of autoregulation (80-180mmHg).

d. Outside these autoregulation limits, RBF becomes pressure dependent.

a. When MAP is 40-50mmHg, glomerular filtration stops.

e. Keeping MAP at 65 mmHg in septic shock may not be sufficient, especially in elderly, hypertensive and diabetic patients.

MAP <60 mmHg value poses a risk in all patients in terms of renal failure. Preglomerular afferent arteriole resistance changes keep GFR within physiological limits:

This mechanism is explained by Bayliss's myogenic theory and the tubuloglomerular feedback controlled by the

juxtaglomerular apparatus. According to Bayliss's theory, when the perfusion pressure drops, afferent arteriolar tone and vascular wall tension decreases; This myogenic reflex response is regulated by vascular smooth muscles and occurs in interlobular and afferent arterioles.

Tubulolomerular Balance And Feedback

Changes in renal tubular fluid flow affect GFR: GFR decreases as tubular fluid flow increases, GFR increases when tubular fluid flow decreases [4]. This feedback plays an important role in keeping the GFR constant, although the perfusion pressure varies over a wide range. Although its mechanism is not completely clear, macula densa is thought to play a role by inducing reflex changes on afferent arteriolar tone and glomerular capillary permeability. Angiotensin II may contribute to this process. Local release of adenosine (released in response to volume expansion) inhibits renin release, creating afferent arteriole dilation. The decrease in sodium reabsorption in response to the phenomenon of pressure natriuresis or the rise in blood pressure indicates the tubulochlomerular feedback. and ultimately GFR increases. The increase in GFR causes adenosine to form vasoconstriction in afferent arteriole through adenosine-1 receptors. The aim of corticomedullary blood flow redistribution and tubulolomerular feedback is to protect against excess salt and water loss and reduce the oxygen requirement of nephron by reducing the filter solute load. With increased cortical vasoconstriction, medullary blood flow; GFR decreases and medullary reabsorption decreases secondary to increased medullary blood flow and the work of the medulla decreases. The GFR decline that develops in prerenal insufficiency actually develops to protect against advanced medullary tubular damage (acute renal success) [5].

Hormonal Regulation

Afferent arteriolar pressure increase stimulates the release of renin and the formation of angiotensin II. Angiotensin II creates generalized arteriolar vasoconstriction and secondarily reduces RBF

In this case, afferent and efferent arterioles are constricted, but since the efferent artery is smaller, the efferent resistance increase is greater than that of the afferent, and consequently GFR is relatively conserved.

Very high levels of angiotensin II concentrate both arterioles and significantly reduce GRF. Adrenal catecholamines (adrenaline, noradrenaline) directly and selectively increase the afferent arteriolar tone, but GRF reduction is indirectly minimal because of activating renin and angiotensin II. The relative protection of GFR in the

increase of aldosterone and catecholamine secretions is partially due to the stimulation of prostaglandin synthesis by angiotensin. Renal synthesis of vasodilator prostaglandins (PG D₂, E₂, I₂) is an important protection mechanism during systemic hypotension and renal ischemia. Atrial natriuretic peptide (ANP) is released from atrial myocytes in response to distension.

ANP directly relaxes smooth muscles and antagonizes vasoconstrictive factors such as norepinephrine and angiotensin. ANP preferably dilates the afferent arteriole, which may produce vasoconstriction in the efferent arteriole. ANP inhibits the synthesis of aldosterone induced by renin and angiotensin, and antagonizes the effects of aldosterone in distal and collector tubules. Arginine-vasopressin, at its physiological levels, activates the V₂ receptors in the collector tubules, causes water absorption, and tries to increase the glomerular filtration pressure by creating a vasoconstriction in the efferent arteriole through V₁ receptors predominantly. Paracrine vasodilator mediators (adenosine, PGs, NO), which are adaptive mechanisms to protect from medullary hypoxia and ischemic tubular damage, dilate the medullary vessels and reduce medullary solute reabsorption [6].

Neural Regulation [7]

- A Sympathetic discharge of the spinal cord at T₄-L₁ level reaches the kidneys through the celiac and renal plexus.
- Sympathetic nerves innervate the juxtaglomerular apparatus (beta-1) and renal vessels (alpha-1).
- This innervation is responsible for RBF reduction in stress situations.
- Stimulation of alpha-1 adrenergic receptors increases sodium reabsorption from the proximal tube, while stimulation of alpha-2 receptors reduces sodium reabsorption and increases water excretion.
- Dopamine creates vasodilation by activation of D-1 receptors in afferent and efferent arterioles.
- Activation of D-2 receptors in presynaptic postganglionic sympathetic neurons dilate the arterioles by inhibiting norepinephrine secretion.
- Reduces reabsorption of dopamine sodium from the proximal tubule.
- The functions of vagal fibers in the kidney are not understood

Distribution Of Renal Blood Flow

80% of RBF is distributed to cortical nephrons and

10-15% to juxtamedullary nephrons. Redistribution of RBF from cortical nephrons with short helne handles to juxtamedullary nephrons with big helne handles occurs under some conditions: sympathetic stimulation, catecholamines and increased level of angiotensin II, heart failure. The cause of this event is controversial, but the clinical result is sodium retention. There is hyperchloremic metabolic acidosis at the beginning of ABY, high anion gap acidosis is generally seen when GFR decreases to 15-20 ml / min. Anions that cannot be measured in ABY cannot be eliminated (phosphates, sulfates, non-oxidized organic acids, etc.). No mixed-type metabolic acidosis (hyperchloraemic + high anion gap) is seen in ABY. Therefore, SIDa is generally low in patients with renal insufficiency. Calculated Strong ion difference (SIDa) = (Na + K + Ca + Mg) - (Cl + Lactate) = 40-42 mmol / L [8].

Blood Urea Nitrogen [9]

- The primary source of urea is liver.
- Ammonia is formed by deamination of amino acids during protein catabolism.
- By turning the ammonia into urea by the liver, it is protected from toxic levels of ammonia;
- BUN level is correct with protein catabolism and inversely proportional with glomerular filtration.
- BUN is not an appropriate indicator of GFR unless protein catabolism is normal and constant.
- 40-50% reabsorbs from tubules and increases reabsorption in hypovolemia.
- Low BUN level can be seen in starvation and liver diseases.
- High levels are usually associated with protein catabolism and GFR reduction.
- BUN values above 50 mg / dl are generally associated with impaired renal function.

Serum Creatinine

Creatine, a product of muscle metabolism, turns nonenzymatically into creatinine. Muscles make up 98% of the creatinine pool. Creatinine production is generally stable and associated with muscle mass; 20-25 mg / kg / day in men, 15-20 mg / kg / day in women. Creatinine undergoes glomerular filtration, is excreted and secreted from tubular cells, does not reabsorb. Serum creatinine is inversely proportional to muscle mass and correct GFR. Normal values are 0.8-1.3 mg / dl in men and 0.6-1 mg / dl in women. Creatinine distribution volume is whole body water

Doubling in serum creatinine value reflects a 50% reduction in GFR:

GFR Serum creatinine

120 1

60 2

30 4

High protein diet, cimetidine, elevate serum creatinine values without alteration in acetoacetate GFR. Cimetidine reduces the secretion of creatinine from the renal tubules. GFR decreases with age. After 20 years of age, it decreases by 5% every 10 years, but since muscle mass decreases with age, serum creatinine value remains within normal limits. Creatinine production can drop to 10 mg / dl. Therefore, small serum creatinine value fluctuations in elderly cases may indicate a marked GFR decrease [10].

Using age and lean body mass, GFR can be estimated:

Creatinine clearance = ((140-age (years)) x (lean mass (kg))) / 72 x plasma creatinine

* Multiplied by 0.8 in women.

GFR: [(140-age) x (weight) x 1.73 *] / [72x serum creatinine (mg / dl) x body surface area (m2)]

* 1.47 for female sex

Lean mass: male; 2.3 kg for every 2.5 cm over 50 + 152 cm,

Women; 2.3 kg for every 2.5 cm over 45.5 + 152 cm

Serum creatinine value is more specific than BUN for GFR estimation but it is not exactly correlated.

For example; serum creatinine value of 1.5 mg / dl at steady state;

a. corresponds to 36 ml / min GFR in an 80-year-old white woman

b. corresponds to 77 ml / min GFR in a 20-year-old black man

Events That Affect Serum Creatinine [11]

a. increases in trauma, fever and immobilization

b. liver dysfunction and decreased muscle mass build

c. As the decrease in glomerular filtration rate increases the secretion of tubular creatinine, the increase in serum creatinine is less than expected. Thus, since the creatinine excretion is greater than the amount of filter, it

causes the wrong high calculation of the glomerular filtration rate (up to 2 times). Therefore, creatinine clearance in ABI is not a good indicator of glomerular filtration rate.

d. The volume of distribution increases when total body water increases ABY is not a constant condition for plasma creatinine value. Therefore, creatinine clearance can be calculated using unstable plasma creatinine value and without urine collection [12]

Cretin clearance = (V x (Cr2 - Cr1) + P) x (100/1440) / Cmean

V; distribution volume (dl) = 0.4 X 100 grams body weight

CR2-CR1; Difference in plasma creatinine values today and yesterday (mg / dl)

-Cme that; (CR1 + CR2) / 2

-P = AxBxC

-A = 140 x (age / 5) x weight (kg) B = 1.037- (0.0338 x Cmean) C = 0.85 for male, 0.765 for female

This formula differs within 25% limits with the measured creatinine clearance.

Bun / Serum Creatinine [13]

Low renal tubular currents increase urea reabsorption while not affecting creatinine. Increased medullary collector tube urea reabsorption in prerenal events (volume deficit) causes an increase in BUN in proportion to the increase in serum creatinine level (BUN / Creatinine > 10-15 / 1). Values above 15/1; hypovolemia, edematous conditions and obstructive uropathies, where tubular flow decreases, may increase in protein catabolism. BUN is affected by exogenous urea intake, endogenous urea production (catabolism) and tubular reabsorption

Glomerular Filtration

(male; 120 ± 125, female 95 ± 20 ml / min, 75-100ml / min / 1.73 m2) It varies with normal physiological conditions. While 45-50 ml / min GFR is required in vegetarian nutrition, 140-150ml / min GFR is required in a protein-rich diet. Efferent arteriolar vasoconstriction and afferent arteriolar vasodilation increase GFR. ACE inhibitors adversely affect this mechanism, reducing GFR. For GFR measurement, 2-hour Creatinine Clearance is currently the most convenient and practical method [14].

Urine Flow

Anuria: glomerular filtrate has been discontinued (rapidly progressing glomerulonephritis, acute cortical

necrosis, renal arterial occlusion, complete urinary tract obstruction). short-term (<24-48 hours) and severe oliguria (<100 ml / day) episodes can be seen in some cases of acute tubular necrosis and especially in heat stroke

prerenal ABY is usually oliguric (<400 ml / day)

Postrenal and renal deficiencies can be anuric-polyuric

Urine analysis [15]

may be normal: prerenal ABY, postrenal ABY, high plasma oncotic pressure abnormal Events at the end of the nephron cause tubular waste

i. erythrocyte, erythrocyte waste, proteinuria: glomerulonephritis, vasculitis, thrombotic microangiopathy

ii. leukocyte, leukocyte wastes: pyelonephritis, interstitial nephritis

iii. eosinophiluria: allergic interstitial nephritis, atheroemboli, glomerulonephritis

iv. pigment wastes, renal tubular epithelial cells: acute tubular necrosis, myoglobinuria, hemoglobinuria

v. crystalluria: uric acid, drugs-toxins

vi. non-albumin proteinuria: plasma cell dysresiasis

vii. Proteinuria: If detected in routine analysis, it should be re-examined in 24-hour urine. Over 150mg/dl is meaningful. 1-2g/day urine protein suggest ABY with glomerular cause

viii. pH: Arterial pH should be known for interpretation. In the presence of systemic acidosis, if urine is higher than pH 7, renal tubular acidosis may be considered.

ix. Specific gravity: associated with urinary osmolality. 1010 generally corresponds to 290mOsm/kg. Having a specific weight above 1018 after an overnight fast indicates sufficient renal concentration ability. Despite hyperosmolality, low specific gravity indicates diabetes insipidus.

x. Glycosuria: the cause may be low tubular threshold (N 180mg/dl) or hyperglycemia Moderate hyperkalemia (<5.5mEq/L) is common in ABY. In more severe hyperkalemia, RBC is associated with rhabdomyolysis, tumor lysis syndrome, intravascular hemolysis, NSAID or ACE inhibitors.

Creatinine kinase, lactate dehydrogenase and sGOT increase in rhabdomyolysis and tumor lysis syndrome. Moderate hyperuricemia (<10 mg / dl) is generally seen in ABY. If higher, tumor lysis syndrome, rhabdomyolysis,

heat stroke are considered. Moderate high anion gap metabolic acidosis (5-10 mEq / L) is seen in ABY. In the presence of serious anion deficit, ethylene glycol, methanol poisoning, rhabdomyolysis and lactic acidosis due to sepsis are considered. If prerenal ABY is not prolonged, tubular functions are generally not affected and the reabsorption of the filter salt-water and organic acids increases; sodium, chlorine and uric acid decrease in urine concentrations, relative urine / plasma osmolality, urine / plasma urea nitrogen and urine / plasma creatinine rates increase, on the contrary, the tubular functions that are impaired in acute tubular necrosis (ATN) to high urine sodium, chlorine, uric acid concentration. and low urine / plasma osmolality, urine / plasma urea nitrogen and urine / plasma creatinine ratios. Fractional sodium urea is more sensitive than others in distinguishing prerenal insufficiency from ATN [16].

$$\text{FeNa} = \left[\frac{\text{UNa}}{\text{PNa}} \right] / \left[\frac{\text{UCr}}{\text{PCr}} \right] \times 100$$

In cases of diuretic use, fractional urea excretion is more sensitive than fractional sodium excretion in separating prerenal insufficiency from ATN.

Clinical Recommendation For Aby [17]

i. If the serum creatinine value increased by 0.5 mg / dl, examine the patient

ii. Eliminate prerenal and postrenal causes

iii. Examine urinary sediment (muddy brown wastes = ATN, erythrocyte wastes = glomerulonephritis and vasculitis, pyuria = acute interstitial nephritis, clean sediment = pre-post renal azotemia)

iv. Examine urine electrolytes without diuretics (urinary osmolality, urinary sodium, urinary / plasma creatinine ratio, fractional sodium urine)

v. After pre-post renal causes are excluded and urinary sediment and electrolytes are investigated, if a renal diagnosis of ABY is diagnosed and serum creatinine value is 2 mg / dl or above, request a nephrology consultation

vi. Remember that 30-40% of cases can be nonoliguric

vii. Avoid Excessive Fluid Load

viii. Avoid Hypotension

ix. Maintain fluid balance, promote hyperkalaemia

x. Using Renal Dopamine

xi. Review patient archive

xii. Prefer enteral nutrition

xiii. discuss the dialysis program

Anesthesia-Surgery-Kidney

i. GFR, RBF, urine flow and sodium excretion are reduced reversibly during regional and general anesthesia.

ii. These changes are less in regional anesthesia

iii. Most of these changes are indirectly due to autonomic and hormonal factors

iv. These changes can be overcome with partial fluid resuscitation and normal blood pressure, even partially.

v. Methoxyflurane and theoretically influrane and sevoflurane have high doses of specific renal toxicity [18]

Indications For Renal Replacement Therapy In Intensive Care [19]

a. 1 oliguria <200 ml / 12 hours

b. 2 anuria <50 ml / 12 hours

c. 3. potassium > 6.5 mmol / L

d. 4. acidemia <pH = 7

e. Urea > 30 mmol / L

f. Uremic encephalopathy

g. Uremic neuro-myopathy

h. Uremic pericarditis

i. Sodium > 155 mmol / L, <120 mmol / L

j. Hyperthermia and ABY

k. Drug overdose, dializable toxins

Symptoms of ABY usually appear when GFR is <25 ml / min and becomes dialysis dependent below <10.

Dialysis Complications

i. neurological: disequilibrium syndrome, dementia

ii. Cardiac: volume depletion, hypotension, arrhythmia

iii. Pulmonary: hypoxia

iv. Gastrointestinal: acid

v. Hematological: anemia, neutropenia, residual anticoagulation, hypocomplementemia

vi. Metabolic: hypokalemia, protein loss

vii. Skeleton: osteomalacia, arthropathy

viii. Myopathy

ix. Peritonitis, transfusion-induced hepatitis

Hypotension, neutropenia, hypoxia and disequilibrium syndrome occurring in dialysis are usually temporary and resolves within hours after dialysis:

i. Hypotension in dialysis: vasodilating effect of acetate dialysis fluids, autonomic nephropathy, rapid withdrawal of fluid

ii. neutropenia: Integration of Cellophane derivative dialysis membranes with leukocytes

iii. hypoxia: pulmonary dysfunction due to leukocytes

iv. Dysequilibrium syndrome: Temporary neurological symptoms occur due to the fact that the extracellular fluid osmolality decreases faster and much more than the intracellular fluid osmolality [20].

Pathophysiology In Prerenal Insufficiency

i. Prerenal azotemia is an appropriate physiological response to renal hypoperfusion.

ii. The reason may be true hypovolemia or a decrease in effective circulation volume.

iii. Lower arterial pressure due to hypovolemia causes activation of the sympathetic nervous system with stimulation of baroreceptors and increased release of vasopressors such as renin-angiotensin, vasopressin and endothelin.

iv. The goal of these mechanisms is to increase cardiac output, blood pressure and cerebral perfusion.

v. Hypovolemia creates dilatation in the preglomerular arteriole with the intrinsic myogenic mechanism, while angiotensin II creates vasoconstriction in the postglomerular arteriole and consequently glomerular hydrostatic pressure is maintained.

vi. However, autoregulation of renal blood flow and GFR may not be sufficient in severe circulatory failure.

vii. When systemic hemodynamics deteriorate, protective vasodilation occurs with NO and PGI₂ in the kidney.

viii. Acute tubular necrosis (ATN):

ix. The reason for ATN in intensive care is 35-50% sepsis. 20-25% of ATNs formed in the hospital are after surgery and most of them are of prerenal origin. Radiocontrast agents

are 7% active [21].

- x. Important factors in ATN pathogenesis.

Vascular Factor

- a. intrarenal vasoconstriction (catecholamines, angiotensin II, endothelin, PAF, adenosine, serotonin); Causes GFR reduction

- b. vascular congestion in the external medulla

- c. activation of tubulomerular feedback

Tubular Factor

- a. tubular obstruction

- b. transtubular reversal of ultrafiltrate

- c. interstitial inflammation

New Concepts

- a. sublethal cell death

- b. apoptosis

- c. cell repair

The Phases of Atn [22]

- i. Initial phase: renal functions begin to deteriorate.

- ii. Continuation phase: renal functions are impaired, usually oliguria (1 week - 1 year).

- iii. Recovery phase: diuresis increases before serum creatinine starts to decrease (2-3 weeks).

Risk Factors for Acute Toxic Renal Dysfunction

- i. presence of pre-existing renal dysfunction

- ii. advanced age

- iii. cardiovascular diseases

- iv. Diabetes Mellitus

- v. Hypovolaemia

- vi. Jaundice

- vii. Concomitant use of several nephrotoxic agents

Myoglobinuria

- i. It is the breakdown of the striped muscles and the pouring of the structural elements into extracellular fluid and circulation.

- ii. Myoglobin is an oxygen carrier weighing 18.8 kDa.

- iii. It normally depends on plasma globulins and reaches urine in small quantities.

- iv. In massive formation, protein binding capacity is exceeded and it is a filter from glomerulus and reaches the tubules.

- v. Especially acid precipitates in tubules in urine.

- vi. Myoglobin can cause intrarenal acute vasoconstriction in two ways: a. As NO grasper; b. Reducing effective vascular volume with fluid loss to damaged muscle tissue

- vii. Iron in both protein acts as a mediator for proximal tubular toxicity. While myogenic mechanism creates dilatation in the preglomerular arteriole, angiotensin II creates vasoconstriction in the postglomerular arteriole and consequently glomerular hydrostatic pressure is maintained.

- viii. However, autoregulation of renal blood flow and GFR may not be sufficient in severe circulatory failure.

- ix. When systemic hemodynamics are impaired, protective vasodilation occurs with NO and PGI₂ in the kidney.

- x. Acute tubular necrosis (ATN):

- xi. The reason for ATN in intensive care is 35-50% sepsis. 20-25% of ATNs formed in the hospital are after surgery and most of them are of prerenal origin. Radiocontrast agents are 7% active.

- xii. Important factors in ATN pathogenesis [23]

Causes of Myoglobinuria

- i. physical: trauma, compression of muscles, occlusion of muscle vessels, electrical burn, hyperthermia

- ii. nonphysical causes: metabolic myopathies, drugs and toxins, infections, electrolyte disorders, endocrine diseases, sepsis

- iii. Long-term positions (excessive lithotomy, prone) and malignant hyperthermia during the 3rd operation

- iv. Since myoglobin is metabolized rapidly and unpredictably in the liver, analysis of myoglobin in serum and urine is not a sensitive parameter.

- v. Serum creatinine kinase concentration gives better information about the presence and degree of damage.

- vi. With the breakdown of muscles, the serum levels of

potassium, phosphate, uric acid and proteases increase.

vii. Accumulation of calcium phosphate in the damaged muscle causes hypocalcemia.

viii. Hypovolemia, hypotension, tubular obstruction, aciduria and free radical release should be avoided.

ix. The ideal liquid to be given is mmol saline solution with 75 mmol / L sodium bicarbonate added.

x. If there is sufficient urine output, 10 ml / hour 15% mannitol can be given.

xi. Fluid requirement can be up to 10 liters per day.

xii. Allopurinol reduces the formation of uric acid and can be used as a free radical trapping agent.

xiii. When ABI develops, the only treatment method is extracorporeal blood purification.

Hemoglobinuria

1. It is less toxic than myoglobin, but when hemolysis is common, ABY may develop.

2. Due to the molecular size of the free hemoglobin, the glomerule is less filtered.

3. Being bound to haptoglobin in the serum also prevents its filtration.

4. When urine pH is low, autooxidation to methemoglobin decreases and its toxicity increases.

5. Immune hemolytic reactions (wrong blood, drugs), mechanical hemolysis (prosthetic valve, extracorporeal circulation) may be the cause of ABY [24].

Radiocontrast Nephropathy [2,24]

i. Typically, serum creatinine increases acutely within 24-48 hours after administration. Peak in 3-5 days and return to normal in 7-10 days.

ii. Serum creatinine value may continue to increase for 5-10 days in severe nephrotoxicity.

iii. Generally, it is nonoliguric.

iv. In urine analysis, granular waste and tubular epithelial cells are seen.

v. Since the contrast medium is interfaced with the proteins in the urine, urine protein analysis is irrelevant within the first 48 hours.

vi. In most cases, fractional sodium excretion has

decreased.

vii. In radiocontrast nephropathy, impaired renal hemodynamics and direct tubular cell toxicity (possibly free oxygen radicals) are considered to be primary factors.

viii. Renal hemodynamic changes due to radiocontrast are biphasic: RBF increases initially then RBF decreases for a long time.

ix. The mediators responsible for this hemodynamic change are unknown.

x. Impairment of the metabolism of PGs, NO, endothelin, and adenosine can be a factor.

Risk Factors [3,4]

i. previously impaired renal function

ii. DM, KKY

iii. High volume contrast agent

iv. Advanced age

v. Hipalbumine my

vi. Intraarterial application

vii. hypovolemia

viii. Application with potential nephrotoxic

ix. 9 MM

x. Nephropathy is less common in nonionic isoosmolar contrast agents.

xi. Potential nephrotoxic agents (ACE inh.) Should be discontinued 24-48 hours before radiocontrast administration.

xii. 600 mg N-acetylcysteine can be given 12 hours before and after administration.

Ace Inhibitors and Angiotensin II Receptor Blockers [23]

Interruption of the renin-angiotensin axis with these agents creates renal dysfunction more frequently than other antihypertensives. Because intraglomerular pressure drop caused by arterial pressure drop is accompanied by vasodilation developing in the glomerular efferent arteriole.

The use of these agents is dangerous for the occurrence of renal dysfunction in the following cases:

I. Renal artery stenosis

II. Polycystic kidney

III. hipovolemia

IV. NSAID usage

V. Sepsis

Nsaids [22]

As a result of inhibition of cyclooxygenase (I, II), thromboxane A₂ may cause glomerular artery vasoconstriction and decreased renal blood flow. Salt-water uptake, renin release from Juxtaglomerular apparatus. Renal PG release is low in healthy individuals and is not very important in the regulation of RBF.

Risky Cases for Nsaid Nephropathy

i. 60 years old arteriosclerotic

ii. Chronic kidney failure

iii. Renal hypoperfusion states such as sodium depletion, diuretic use, hypotension, cirrhosis, nephrotic syndrome, congestive heart failure.

iv. Hyperkalaemia may be higher than expected in those using potassium-sparing diuretics, angiotensin II receptor blockers, and angiotensin converting enzyme inhibitors.

v. In a healthy person, the evidence for NSAIDs to cause kidney failure is very limited

vi. ABY develops in 3-7 days. Abnormalities in urine sediment and absence of proteinuria indicate hemodynamic factors.

vii. If vasoconstriction due to NSAIDs is strong enough and lasts long, ATN may occur.

viii. It usually improves with discontinuation of the drug.

ix. Typically, an increase in hematuria, pyuria, leukocyte wastes and serum creatinine is observed. There is an appearance of an allergic reaction such as fever, rash, eosinophilia and eosinophiluria.

x. When the drug is stopped, it will recover within 1-2 weeks and 1-2 months.

xi. If renal failure still continues 1-2 weeks after discontinuation of NSAID, prednisone can be used.

xii. 35/10000 ABY was observed with ketorolac. If used for more than 5 days, the probability of ABY increases significantly [4,5].

Aminoglycosides

i. ABY incidence is 5-25%.

ii. Especially proximal folded tubes and pars rectada

cause tubular cell necrosis.

iii. After filtering, they are taken from the tubule cell side and they remain in the tubule cells for a long time in the form of residues. In other words, their half-life in the kidney tissue is long.

iv. Nephrotoxic mechanisms are not fully known.

v. Potential toxic mechanisms are explained by interfering with the membrane and disrupting its membrane structure and function.

vi. Reactive oxygen metabolites are considered another mechanism.

vii. It is typically nonoliguric.

viii. 5-10% of their use. There is no decrease in GFR and a significant increase in serum creatinine value until. Urinary sediment is usually benign

Risk Factors

i. duration of treatment

ii. previous renal, hepatic disease

iii. older age

iv. volume deficit

v. sepsis

vi. potassium, magnesium depletion

vii. The use of diuretics, cyclosporin, vancomycin, amphotericin B, NSAID, ACE inhibitor In general, serum creatinine value returns to normal 21 days after discontinuation of the drug [6,7]

Vancomycin

i. The incidence is 5-15%.

ii. Renal insufficiency is generally moderate but can be severe at high doses.

iii. Its mechanism is unclear. Oxidative stress is blamed.

Antifungal Drugs

i. The incidence of renal dysfunction with amphotericin B has been reported between 5-80%.

ii. Clinically, renal failure or electrolyte abnormalities (hypopotasemia, hypomagnesemia, renal tubular acidosis, nephrogenic DI) may be seen.

iii. Direct tubular damage and renal vasoconstriction are held responsible for the mechanism [8].

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Risk Factors

- i. total cumulative dose
- ii. duration of treatment
- iii. dehydration
- iv. diuretic use
- v. baseline kidney dysfunction
- vi. Concomitant use of other nephrotoxic in general, when the drug is discontinued, renal functions return slowly and incomplete; renal magnesium leakage may remain chronically.
 - i. Nephrotoxicity decreases if given in amphotericin B phospholipid vesicles (Liposomal).
 - ii. The lipid form of amphotericin B
 - a. does not contain deoxycholate,
 - b. use of detergent as melter
 - c. Selective distribution to the reticuloendothelial system, directly transferred to the fungi caught by this system, and not to be distributed to cholesterol-containing tissues such as kidney reduces nephrotoxicity.

Colloids

- i. All colloids and hyperoncotic albumin can form ABY (hyperoncotic ABY) by raising plasma oncotic pressure.
- ii. Especially dehydrated patients are at risk.
- iii. To prevent nephropathy due to contrast medium, hydration with isotonic liquid and N-acetyl cysteine, which started 12 hours before and continued for 12 more hours after contrast administration, have been shown to be protective.
- iv. Protective effects of furosemidine, mannitol, natriuretic peptides, dopamine and adenosine agonists have not been demonstrated. Diuretics have been found to worsen the prognosis of ATN due to contrast agent and seen after cardiac surgery.
- v. Shock milking and ABY:
- vi. In addition to fluid resuscitation, vasopressors are used.
- vii. In general, the first preferred agent is norepinephrine. There is no evidence that norepinephrine reduces renal blood flow. On the contrary, animal studies have shown that it increases renal blood flow in sepsis.

viii. Vasopressin creates vasoconstriction by potentiating the effectiveness of catecholamines over vasopressin receptors. It is effective in sepsis, shock resistant to catecholamines. The dose of vasopressin (0.05-0.1 U / min) used for this purpose may decrease renal blood flow, but there are no studies comparing vasopressin and catecholamines in this regard.

ix. Tight glucose control increases survival and decreases the incidence of ABY [7,8].

Average Arterial Pressure [9]

- i. There is insufficient evidence on what is the optimal mean arterial pressure required for renal perfusion.
- ii. It is known that the risk of kidney failure increases when the systolic artery pressure is not kept above 80 mmHg and the mean arterial pressure is kept above 65 mmHg.
- iii. It should be noted that the arterial pressure required for adequate renal perfusion is associated with the underlying comorbid condition.
- iv. Terlipressin has been shown to increase blood pressure and increase renal function in renal dysfunction due to hepatorenal syndrome.
- v. In acute renal failure due to septic shock, an increase in creatinine clearance was detected by keeping the mean arterial pressure above 65 mmHg with norepinephrine, but no difference was found in terms of renal fate when compared to keeping the mean arterial pressure above 65 and 85 mmHg in sepsis.
- vi. Decreased cardiac output is a risk factor for kidney failure. There is no evidence that increasing cardiac output to supranormal levels may have beneficial renal effects.
- vii. Aggressive fluid therapy protects against progressive renal damage due to crush injury.
- viii. Albumin replacement may have beneficial effects in liver failure and primary peritonitis.

Increasing Renal Blood Flow

- i. The use of recombinant human atrial natriuretic peptide has been found effective for primary kidney protection in cardiac surgery cases requiring significant vasopressors and inotropes.
- ii. The effect of diuretics to increase renal blood flow has not been established. Proposal
- iii. Extreme hypotension should be avoided.

iv. Cardiac output, mean arterial pressure and volume should be optimized.

v. Noradrenaline should be preferred when vasopressor is required.

vi. Selective renal vasodilating agents should be avoided.

Reduction of Renal Metabolism [10]

i. Hypothermia and insulin like growth factor 1 were found to be ineffective in renal protection

ii. Diuretics can reduce renal oxygen use, but there are insufficient data.

iii. Conclusion: There is no suggestion to reduce renal metabolism.

Endothelial Protection Strategies

i. Complement depletion protects from ischemic renal injury. In tubular necrosis, the complement is activated via an alternate route. Ischemic damage was found to be decreased in animals with C3, C5, C6 deficits.

ii. Blockade of adhesion molecules such as E-selectin, P-selectin and intercellular adhesion molecule-1 protected the ischemia-reperfusion injury in mice.

iii. Active protein C, with its anti-inflammatory effect, reduces endothelial damage in sepsis and ischemia-reperfusion. Reduced mortality in severe sepsis cases with ARF.

Potential therapeutic treatments in secondary kidney protection

i. Vasodilators: natriuretic peptides, endothelin antagonists, adenosine antagonists, growth factors

ii. Decreasing leukocyte-endothelial relationship: Anti-ICAM-1, alpha-MSH, anti B7-1 antibody, IL-10, PAF antagonists, atorvastatin, A2A adenosine antagonists

iii. Reducing cell death: caspas inhibitors, iron chelators, acetylcysteine

iv. Reducing tubular obstruction

v. Repair: growth factors

For what purpose will loop diuretics be given in atn?

i. Tubular cells, which are swollen and blocked tubules, prevent the medullary venous return and reduce RBF.

ii. Loop diuretics move tubular obstruction materials

by increasing tubular flow and hydraulic pressure.

iii. They increase renal blood flow in two ways:

iv. increase the production of vasodilator PGs by inducing cyclooxygenase

v. they inhibit the sodium-potassium-2 chlorine system, which initiates the signaling in the macular densa, interrupting the tubulolomerular feed

vi. Inhibition of sodium-potassium-2 chlorine cotransporter system reduces active sodium transport. Thus, the oxygen use of the tubules is reduced and the metabolic requirement is reduced in medullary tubular cells that are sensitive to ischemia.

vii. Cyclooxygenase II expression inhibits TNF-alpha-induced renal mesengial cell apoptosis [14].

Are there any clinical evidence showing the usefulness of loop diuretics?

i. Loop diuretics have increased urinary flow in most clinical trials, but there is limited evidence to show that they have beneficial effects on renal function.

ii. In cases that respond to loop diuretics with good urine output, it seems more rational to think that these patients already have less severe kidney failure, rather than thinking that diuretics improve renal function. Because in some clinical studies, loop diuretics have been found to worsen renal function.

iii. Consequently, there is no data to generate enough statistical power to advocate the usefulness of loop diuretics.

iv. It has been shown that the effectiveness and toxicity of furosemide increase in continuous infusion.

Why do loop diuretics not have beneficial effects?

There are opinions that explain the lack of protective effects of diuretics on renal function in ARF:

i. Preload reduction due to venous return reduction due to diuretics and vasodilator PGs induced by them, by increasing the renin-angiotensin system and sympathetic Tonus, indirectly creates renal vasoconstriction. If you are going to be given loop diuretics in Aby, it is very important to ensure adequate preload.

ii. Loop diuretics may reduce reabsorption only in non-obstructed tubules, but they may not be effective in those with obstructions.

iii. The answer to the question whether Loop diuretics

increase renal blood flow is still controversial. In some cases, it has been concluded that furosemide increases renal blood flow if renal autoregulation is intact.

iv. 90% of kidney blood flow passes through the cortex because it's here;

v. Current-dependent functions such as glomerular filtration and tubular transport are carried out.

vi. 10% of kidney blood flow passes through the medulla;

vii. The medullary concentration mechanism requires active tubular transport function, which requires high oxygen use as well as low blood flow to maintain the interstitial osmotic gradient.

viii. This heterogeneous perfusion distribution describes the following questions::

ix. why are kidneys susceptible to hypoperfusion despite global high blood flow support?

x. why ischemic damage occurs especially in the tubular segments of the outer medullary [pars recta of the proximal tubule (S3 segment) and the thick arm of the helve handle (mTAL)]

xi. Loop diuretics may have an adverse effect on intrarenal blood flow distribution, but this is difficult to detect.

xii. In a study with Laser doppler flowmetry, Furosemide was shown to significantly reduce medullary blood flow compared to cortical flow.

xiii. Furosemidine has been shown to increase cortical cyclooxygenases while reducing medullary cyclooxygenase mRNA. Since furosemide has different effects on cortical and medullary blood flow, medullary can turn prerenal failure into ATN by worsening oxygen balance.

xiv. Furosemide can disrupt renal blood flow autoregulation by inhibiting tubuloglomerular feedback.

xv. "Should we use Loop diuretics?" conclusions for the question:

xvi. It may be reasonable to think that kidney damage is minimal in patients who respond well to Loop diuretics

xvii. It is not yet proven that Loop diuretics have beneficial effects on renal function.

xviii. Use of prophylactic loop diuretics can be dangerous as they disrupt renal autoregulation and

protective corticomedullary blood flow redistribution [14,15,16].

Mannitol [22]

Why?

i. protects from Tubular obstruction by increasing diuresis

ii. protects from Tubular obstruction by reducing epithelial and endothelial cell swelling and vascular congestion

iii. cleans up free radicals

iv. creates vasodilation by increasing intrarenal PG synthesis

But,

i. osmotic diuresis may cause volume depletion

ii. increased distal solute load increases medullary oxygen requirement

iii. induces apoptosis of endothelin and epithelium

iv. high doses can cause Aby with hyperosmolality

Although it has been shown to reduce renal dysfunction in Renal transplant patients, there is no data supporting its use for renal replacement.

Result

i. low dose dopamine does not induce clinically significant renal protection references

ii. Continuous norepinephrine infusion in hypotensive vasodilated patients does not decrease renal blood flow and increases urine flow

iii. There is no clinical evidence that maximizing cardiac output protects the kidneys

iv. In intensive care patients, there is no information about the target average pressure required to optimize renal blood flow

Mechanical Ventilation And Renal Failure [23]

i. mechanical ventilation reduces urine flow

ii. Its effects on RBF and GFR are not clear

iii. Possible mechanisms: a. cardiac flow reduction; b. intrarenal blood flow redistribution; c. stimulation of sympathetic and hormonal pathways; d. release of systemic inflammatory substances

iv. Intrarenal changes: vasoactive mediator release

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caused by positive pressure mechanical ventilation (PPV) has been shown to redistribute renal blood flow from cortical regions to juxtamedullary nephrons.

v. During PPV, urine and blood ADH levels increase. As a result, free water clearance and urine volume are reduced.

vi. Why does PPV increase ADH?

vii. Relative intravascular volume depletion occurs with PPV

viii. In PPV, decreased blood flow to the abdomen in the intrathoracic vascular bed induces the release of ADH by stimulating atrial strain receptors

ix. Plasma renin levels increased in PPV.

x. Renin release is stimulated by increased sodium load to distal tubules and extrarenal beta receptor mediated sympathetic stimulation

Increased sympathetic tone increases renin activation by factors such as PEEP or agitation during mechanical ventilation, resulting in increased aldosterone release.

Therefore, sodium retention is common in ventilated patients.

B. Atrial natriuretic peptide (ANP) release is stimulated by increased atrial transmural filling pressure, resulting in diuresis and natriuresis

C. Decreased venous return in PPV reduces atrial transmural filling pressure, resulting in decreased ANP level

D. ANP decrease may explain the decrease in urine flow in PPV, but it cannot explain the decrease in GFR

PPV May be the Cause of ABY with the following Mechanisms

i. affecting arterial blood gases

ii. by affecting systemic and renal blood flow

iii. by triggering the pulmonary inflammatory reaction (biotravma)

iv. High tidal volumes that cause overdistribution,

v. repeated opening and closing of unstable alveoli,

vi. high peak alveolar pressures causes activation of pulmonary inflammatory substances

vii. These mediators move into the systemic circulation, affecting the organs

viii. High peak alveolar pressures and low PEEP are

the causes of ventilator-induced lung damage (VILI) and multiple organ failure (MOF)

ix. VILI causes mediator release and as a result, apoptosis begins with the effect of these mediators.

x. Dysregulation of apoptosis is responsible for the development of ARDS and MOF.

xi. Because Apoptosis is regulated by inflammatory cytokines, PPV can cause end-organ epithelial cell apoptosis by affecting the cytokine network.

xii. Changes in renal function in Ards cases are known to be significantly associated with changes in the regulation of apoptosis.

xiii. Cytokine and chemokine production has been shown to decrease in ventilation with low tidal volume and high PEEP.

Result

1. Mechanical ventilation in intensive care is the independent predictor of kidney failure

2. Vili should be avoided by applying lung protective ventilation. For this purpose, low tidal volume (4-8 ml/kg), low peak alveolar pressures (<30 cm H₂O) and sufficient PEEP (10-15 cm H₂O) should be used to prevent derekruitmesi.

3. ABY can cause noncardiogenic pulmonary payment by creating changes in pulmonary vascular permeability (down regulation of pulmonary epithelial sodium channels and aquaporins).

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