A STUDY OF HYPONATREMIA IN ACUTE HEART FAILURE PATIENTS IN PREDICTING THE ACUTE CARDIO RENAL SYNDROME TYPE 1

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CERTIFICATE FROM THE DEAN

This is to certify that this dissertation entitled **"A STUDY OF HYPONATREMIA IN ACUTE HEART FAILURE PATIENTS IN PREDICTING THE ACUTE CARDIO RENAL SYNDROME TYPE 1"** is the bonafide work of **DR.V.NARESHKUMAR,** in partial fulfillment of the university regulations of the Tamil Nadu Dr. M.G.R. Medical University, Chennai, for **M.D General Medicine, Branch I** examination to be held in **May-2018.**

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DECLARATION

I**, DR.V.NARESHKUMAR**, solemnly declare that this dissertation titled **"A STUDY OF HYPONATREMIA IN ACUTEHEART FAILURE PATIENTS IN PREDICTING THE ACUTE CARDIO RENAL SYNDROME TYPE 1"** is a bonafide record of work done by me at the Department Of General Medicine, Government Rajaji Hospital, Madurai, under the guidance of **Dr.R.PRABHAKARAN.M.D,** Professor, Department of General Medicine , Madurai Medical college , Madurai.

This dissertation is submitted to The Tamil Nadu Dr. M.G.R Medical University, Chennai in partial fulfillment of the rules and regulations for the award of **M.D Degree General Medicine Branch- I**; examination to be held in **May-2018.**

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ANNEXURES

INTRODUCTION

Cardiac function and kidney function are closely interconnected and a synergistic relationship exists between these organs. Dysfunction of heart often leads to a deterioration of function of the kidney. This clinical entity has been defined as cardio renal syndrome.

CRS type1 or acute CRS is described by rapid worsening of cardiac function leading to acute kidney injury. It is most common and rapid deterioration of pulmonary edema, acutely decompensated chronic cardiac failure, cardiogenic shock and primarily right heart failure leading to acute renal dysfunction.

Approximately one third of the ADHF patients develop AKI as defined by an increase in serum creatinine of >0.3 mg/dl. In patient with cardiogenic shock, the incidence of AKI can exceed 70%. The development of WRF in this setting usually associated with high mortality risk.

The pathophysiology of WRF in ADHF is complex and multifactorial. Major contributing mechanisms include congestion, haemodynamic factors and neurohormonal activation. Baseline chronic kidney disease, diabetes mellitus, prior cardiac failure and initial presentation with systemic hypertension are established risk predictors for CRS type 1.

Hyponatremia is the most common electrolyte disorder in hospitalized patients and is commonly observed in ADHF. Hyponatremia in patients with heart failure is an independent risk factor of mortality and repeated admission for decompensation.

The prevalence of hyponatremia and volume overload is high in hospitalized patients with worsening heart failure than outpatients. Hyponatremia , the volume overload status with venous congestion of kidney, neurohormonal activation, vasoconstriction , and the reduced renal blood flow make the kidneys more susceptible to develop WRF.

Hyponatremia was defined as serum sodium <136 mmol/L . WRF was defined based on the maximal increase of >0.3 mg/dl in serum creatinine from the admission value at any time during the hospital stay.

Patients with worsening renal function have a decreased ability for sodium and water excretion thus placing them at an increased risk of developing hyponatremia. Efforts to maintain normal renal function including blood pressure control, limiting use of nephrotoxic medication and avoiding excessive diuresis may help to limit the risk of hyponatremia.

AIMS AND OBJECTIVES

1. To study the prevalence of hyponatremia in acute decompensated heart failure patients

2. To evaluate the association between hyponatremia and worsening renal function

3. To predict morbidity and mortality in CRS type 1

REVIEW OF LITERATURE

Water is important constituent in the body comprising about 50% of body weight in females and 60% in males.It is divided in to ECF(55 -75%) and ICF(25-45%).ECF is further divided into intravascular (plasma) and extravascular (interstitial) fluid. The concentration of solute or particle in the fluid is known as osmolality(mOsm/kg). Important ECF particles are Na,Cl and Hco3 and ICF particles are potassium,organic esters.

Water balance is regulated by vasopressin secretion ,water intake and renal water transport to maintain osmolality between 280-295 mOsm/kg. Synthesis of vasopressin occurs in magnocellular neurons in hypothalamus. Distal axons of these neurons project into the posterior pituitary, from which vasopressin is secreted in the body circulaton.

There is linear relationship between vasopressin and serum osmolality. Blood pressure and blood volume are also direct stimuli for AVP. Half life of AVP is 10-20 minutes.

Sodium balance

Normal sodium concentration in plasma is more than 140meq/l.sodium is the principal osmole ,present in the extracellular fluid and maintaining the ECF volume.Regulation of blood pressure and osmotic equilibrium.sodium contration in ECF is maintainted by the action of Na/K ATP ase. Water can easily cross the cell membranes to maintain normal tonicity between ECF and ICF. Sodium cannot freely cross the cellmembrane. It requires energy dependent pump to cross cell membrane. Plasma sodium concentration is determind by multiple factors including osmolality, tonicity of plasma, sodium intake, renin angiotensin system, total potassium concentration and water.

Plasma osmolality is determained by mainly by serum sodium and minor contributors are glucose and blood urea nitrogen.

Plasma osmolality is calculated by following formula:

PLASMA OSMOLALITY =(2×Na)+(glucose/18)+(BUN/2.8)

The sodium is multiplied by two to account for the accompanying anions like bicarbonate and chlorides for electrical neutrality.

The corrections are made in the glucose concentration and blood urea nitrogen to convert mg/dl into mmol/1. Urea is lipid-soluble.It equilibrates across the cell membranes and it is ineffective osmole and does not contribute to fluid distribution, and therefore it is rejected from calculation of effective plasma osmolality .

Effective plasma osmolality = (2x [Na^+]) + ([glucose]/18).Normal plasma osmolality varies between 280 and 290mOsm/l. A discrepancy between the measured and calculated osmolality is referred to as an osmolal gap. A increased concentration of osmotically active molecules present in plasma such as ethanol, mannitol, methanol, ethylene glycol and isopropyl alcohol leads to significant osmolal gap.

Average sodium intake is 4-5 g per day (173-217 mmol/day). Sodium chloride is available as table salt, which dissolves in water to give sodium and chloride ions. Sodium is 0.39 weight of sodium chloride. So 1 g of table salt or salt tablets contains roughly 400 mg of sodium. One teaspoon of table salt comprises about 6 g of NaCl with approximately 2.4 g (104mmol) sodium.

One gram of sodium gives 43 mEq of sodium ions, whereas 1 g of sodium chloride gives 17 mEq of sodium ions. The amount of filtered sodium load (25,250) is the product of GFR and sodium cancentration in plasma. For

maintaining sodium balance with a dietary intake of sodium nearly 200 mmol or 3.2 g/day, a total of 25,000 mmol (about 99.6% of the filtered load) should be reabsorbed.

Proximal tubule of kidney reabsorbs about 60-70% of the filtered sodium . Ascending limb of the loop of Henle reabsorbs about 20-30%. The remaining sodium about 5-10% is reabsorbed in the distal tubule and collecting duct, under the influence of aldosterone.

Sudden decrease in blood volume is recognised by mechanoreceptors present in the left ventricle, carotid sinus, aortic arch and renal afferent arterioles leading to activation of the RAA system, stimulation of thirst and non osmotic release of arginine vasopressin. Juxtaglomerular cells of the kidney produce and secretes renin. Renin isoenzymes present in many tissues, including brain, adrenals, vascular beds, uterus and placenta.

Renin cleaves its substrate angiotensinogen to produce the angiotensin I, which is converted to angiotensin II by angiotensin I-converting enzyme. Angiotensin II stimulates aldosterone secretion from the adrenal cortex and also partially suppresses renin secretion by a direct effect on the juxtaglomerular cells. Aldosterone increases sodium reabsorption and potassium excretion in the distal tubule and the collecting duct of the nephron, the site where ADH regulates the rate of water reabsorption also.

Tonicity refers to the effect of a solution on the cell volume. An isotonic solution doesn't have any effect on cell volume, whereas hypotonic solutions increase and hypertonic solution decrease cell volume. Infusion of isotonic saline causes volume expansion without changing the plasma osmolality. And the steady state is restored by renal sodium excretion , ADH release and thirst are not altered. On the other hand, intake of large quantities of Nacl without water (e.g. consumption of salted pretzels, potato chips or peanuts) results in an elevation in the plasma osmolality and stimulation of thirst and ADH secretion leading to ECV expansion. ECF volume expansion will suppress the RAA system, resulting in increased urinary sodium excretion. Thus, the maintenance of the ECV is dependent on the regulation of sodium balance, while plasma osmolality is largely maintained by the regulation of water balance.

HYPONATREMIA

Hyponatremia is usually associated with increase in circulating AVP and/ or increased renal sensitivity to AVP. The underlying pathophysiology for increased or inappropriate AVP response differs in patient with ECF volume status.

Hyponatremia is classified into three groups

1. Hypovolemic hypontremia
2. Euvolemic hyponatremia
3. Hypervolemic hyponatremia

HYPOVOLEMIC HYPONATREMIA

Hypovolemia facilitates neurohumoral activation and increases the circulating levels of AVP. The increase in circulating of AVP preserve blood pressure via receptor mediated action like vascular and baroreceptor V1a and increase reabsorption of water through V2 receptor present in the renal tubules. Activation of V2 receptor may lead to hyponatremia in the setting of increased free water intake.

Hypovolemic hyponatremia causes are classified into renal and extra renal . Extra renal causes are vomiting, diarrhea, tube drainage and insensible water and

sodium loss like burns, sweating in the absence of adequate water intake. Renal causes are diuretic excess, ketonuria , mineralo corticoid deficiency , salt losing nephropathy, osmotic diuresis and cerebral salt wasting disorder. In both causes urine sodium concentration differs but blood volume is low in each condition.

Clinical finding of extracellular volume deficit such as flat neck veins, decreased skin turgor, dry mucous membranes, orthostatic hypotension and tachycardia.

Measurement of the urinary Na^+ concentration is useful in assessing whether losses are renal/extra renal in origin. Urinary Na^+ concentration of <20 mEq/1 reflects a normal renal response to hypovolemia and points to an extra renal source of Na^+ loss. In patients with hypovolaemic hyponatraemia, urinary Na^+ concentration in excess of 20 mEq/1, it indicate reanl origin.

HYPOVOLEMIC HYPONATREMIA

Renal cause(U Na>20)	Extra renal cause(U Na<20)
Diuretic excess Cerebral salt wasting Mineralo corticoid deficiency Ketonuria	Vomiting Diarrhea Burns Pancreatitis Trauma

Hypovolaemic hyponatraemia can be intensified when fluid losses are replaced with hypotonic fluids. When isotonic saline is used, it abolishes the stimulus for ADH release, thereby permitting the excess water to be excreted. This effect may normalise the plasma sodium concentration quickly and may be adverse in patients with chronic hyponatraemia (> 48 h). Administration of desmopressin or hypotonic solutions may be useful to slow the rate of sodium correction in these patients.

EUVOLEMIC HYPONATREMIA

Euvolemic hyponatremia cccurs in moderate to severe hypothyroidism and also occurs in pituitary dieease and with predominant glucocorticoid deficiency in Secondary failure. Glucocorticoid have negative feedback action on AVP release by acting on posterior pituitary. So hydrocortisone replacement will normalize the AVP response to osmolality.

Other important causes are SIADH , drugs and stress .The mechanism of hyponatremia in SIADH is persistant intake of free water at serum osmolalities that are lower than the usual threahold for thirst. Patient with SIADH have four different pattern of AVP release,

1. unregulated and erratic AVP release with no correlation between serum osmolality and blood AVP levels

2. some patients fails to suppress the AVP release at deceased serum osmolality with normal response curve to hyperosmolar state

3. some patients have reset osmostat with left shifted osmotic response curve and lower osmolality threshold

4.some patient have gain in function in renal warer reabsorption or other circulating substances like antidiuretics without detectable circulating AVP

Causes of euvolemic hyponatremia

EUVOLEMIC HYPONATREMIA	
Glucocorticoid deficiency	stress ,drugs
Hypothyroidism	SIADH

Decreased GFR and renal blood flow has been shown to be associated with Hypothyroidism. ADH level is elevated with severe hypothyroidism, and thyroxine treatment normalize the elevated ADH levels. The impaired water excretion in this disease is being mediated by the increased ADH combined with decreased distal fluid delivery.

Continued ADH release and excessive hypotonic fluid intake contributes to the exercise-associated hyponatraemia (EAH) seen after endurance exercise (e.g. triathlon events and marathons) . Hypovolaemia because of sweat losses, severe exercise pain and stress constitutes the non-osmotic stimuli for the ADH secretion

in endurance athletes . Clinical manifestations like dizziness, nausea and vomiting to seizures, coma and death are due to acute hyponatremia seen in exercise associated hyponatremia.

Fluid restriction and observation until the onset of a spontaneous diuresis is the initial management protocol for patients with mild to moderate symptoms Where as hypertonic saline can be given for those with severe neurological symptoms till the recovery from neurological symptoms. Prevention of these conditions can be done by training the endurance athletes to take fluids according to thirst during the race.

Primary polydipsia also comes under euvolemic hyponatremia. Water consumption in excess of 10 to 151 a day has been seen in many patients with chronic psychiatric illnesses notably schizophrenia .Suppression of ADH secretion occurs as a result of this excess water consumption and patient begins to excrete dilute urine (osmolality nearly 50mosm/kg). A defect in regulation of thirst centrally possibly plays a pivotal role in the pathogenesis of polydipsia.

Acutely psychotic patients are at an increased risk for developing hyponatraemia and treatement with some antipsychotic medications also add on the risk by increasing thirst through anticholinergic side effects. Augmented vasopressin release can be seen in schizophrenic patients with hyponatraemia during psychotic exacerbations.

HYPERVOLEMIC HYPONATREMIA

Patient with hypervulemic hyponatremia have increased total body Na, Cl but greater increase in total body water exceeds the sodium concentration in plasma which leads to hyponatremia. It is classified into two groups by urine sodium concentration.

CAUSES

U Na>20	U Na<20
Acute or chronic renal failure	Nephrotic syndrome Cirrhosis Cardiac failure

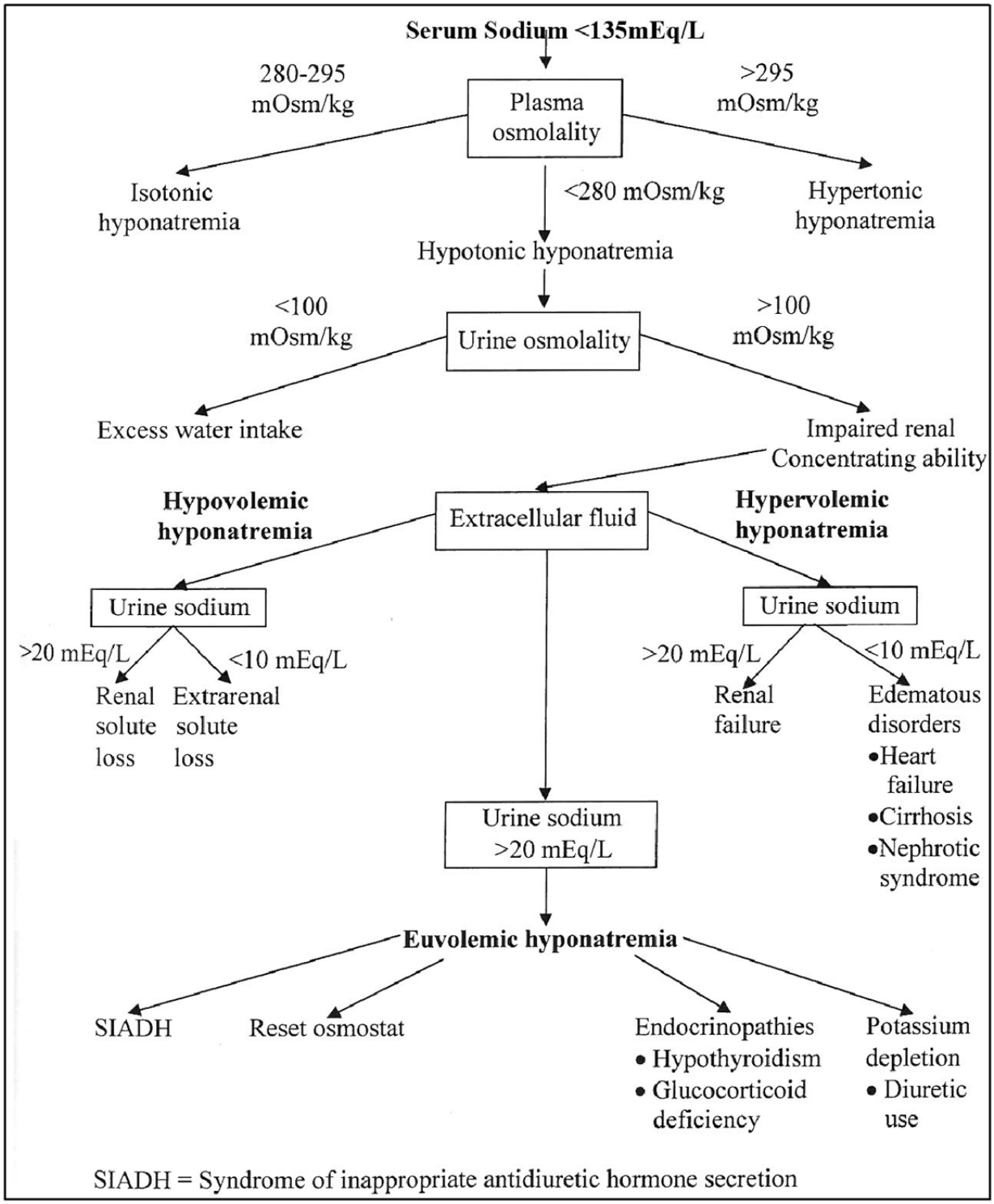
The main pathophysiology in this disorder is decrease in arterial filling and circulating integrity . The degree of hyponatremia gives gives an indirect index of neurohumoral activation and essential prognostic indicator in hypervolemic hyponatremia.

Hyponatremia is commonly occurs in patient with very low intake of dietary solutes. Classically it happens in alcoholics whose main nutrient is beer, called as beer potomania. Beer contains very low protein and salt content.extreme vegetarian diet also contains low salt and proteon content.

Hyponatraemia of unknown aetiology should prompt a work up for neuroendocrine amine precursor uptake and decarboxylating (APUD) tumours as well as oat cell, breast and ovarian tumours that are often difficult to detect. Infection like HIV, hepatitis C , cytomegalo vivus and toxoplasmosis are some of the causes of hyponatremia.

DRUGS CAUSING HYPONATREMIA

Thiazides, clonidine, ACE inhibitors, Aldosterone antagonists, Amiloride, Loop diuretics, Methyldopa, Amlodipine,	Amiodarone, lorcainide, Propafenone, Theophylline, Terlipressin, Unfractionated Heparin (aldosterone antagonist)	Cyclophosphamide, Vincristine, Vinblastine Cisplatin, Hydroxyurea, Melphalan Tacrolimus, Methotrexate, interferon a and y, levamisole,	Azithromycin Trimethoprim-sulfamethoxazole, ciprofloxacin, cefoperazone/ Sulbactam,


Serum Sodium <135mEq/L
280-295 mOsm/kg
Plasma osmolality
>295 mOsm/kg
Isotonic hyponatremia
<280 mOsm/kg
Hypertonic hyponatremia
Hypotonic hyponatremia
<100 mOsm/kg
Urine osmolality
>100 mOsm/kg
Excess water intake
Impaired renal Concentrating ability
Hypovolemic hyponatremia
Extracellular fluid
Hypervolemic hyponatremia
Urine sodium
>20 mEq/L
<10 mEq/L
Renal solute loss
Extrarenal solute loss
Urine sodium
>20 mEq/L
<10 mEq/L
Renal failure
Edematous disorders
•Heart failure
•Cirrhosis
•Nephrotic syndrome
Urine sodium >20 mEq/L
Euvolemic hyponatremia
SIADH
Reset osmostat
Endocrinopathies
• Hypothyroidism
• Glucocorticoid deficiency
Potassium depletion
• Diuretic use
SIADH = Syndrome of inappropriate antidiuretic hormone secretion

Clinical features of hyponatraemia

Most patients with hyponatremia may appear asymptomatic, severe symptomatic hyponatremia is a medical emergency that needs immediate treatment. Clinical features depend on several factors and vary between individual. The rate of reduction in serum sodium concentration, age of the patient, and the volume of extra cellular fluid (ECF) all alter the clinical presentation.

CNS symptom

Most of the clinical features are related to dysfunction of the central nervous system and are more evident when the decline of serum sodium concentration is more or rapid. Non-neurologic features of hyponatremia are fatigue, thirst, weakness, cramping, nausea, vomiting, bloating, swelling, and tightness of the hands and feet. Most patients with a serum sodium level more than 125 mEq/L or with chronic hyponatremia do not present with neurologic symptoms, because of volume adaptation by the brain.

Gastro intestinal features, such as nausea and vomiting, are most common in patients with serum sodium concentration between 125 and 130 mEq/L. Acute hyponatremia (<2 days in duration) in a previously asymptomatic young adult can cause severe central nervous system symptoms even at serum sodium concentration between 125 and 130 mEq/L. Once the sodium concentration falls below 125 mEq/L, neurologic symptoms predominate. Headache, muscle cramps,

reversible ataxia, psychosis, lethargy, restlessness, disorientation, anorexia, and agitation are symptoms seen in patients with serum sodium concentration below 125 mEq/L.

Clinical signs include abnormal sensorium hypothermia, depressed deep tendon reflexes, pseudobulbar palsy, and Cheyne-Stokes respiration.

Complications of severe hyponatremia

If hyponatremia develops rapidly, it cause seizures, coma, brainstem herniation, respiratory depression, permanent brain damage, and death. These complications primarily due to hyponatremia induced cerebral edema, which is most commonly seen in patients undergone surgery or in patient with primary polydipsia. Menstruating women are also at increased risk of severe neurologic features associated with hyponatremia.

Clinically important hyponatremia is a particular challenge in patients with acute neurologic symptoms such as cerebral salt-wasting syndrome, syndrome of inappropriate antidiuretic hormone secretion (SIADH), anoxic or traumatic brain injury, or subarachnoid hemorrhage, since the presentations can overlap significantly.

Difference between acute and chronic hyponatraemia is clinically essential because chronic hyponatraemia is extraordinarily well-tolerated, even at very low concentration of serum sodium, and overly aggressive therapy can cause serious

neurological problem. Aggressive initial management is essential in patients with acute severe symptomatic hyponatraemia, which may potentially leads to irreversible neurological disease and death.

Hyponatraemia is refered as acute when it develops within 48 h of prior normal plasma sodium concentration. Acute hyponatraemia occurs in patient with intake of large amount of hypotonic fluids (postoperative patients, marathon runners) and also in patient using 'ecstasy' (3,4-memylene dioxy meth amphetamine, MDMA). As a result of osmotic effect, water enters intracellularly and results in cerebral oedema. Eventually, the extracellular water is moved into the cerebrospinal fluid, and cerebral edema gradually decreases by extruding sodium and potassium salts and certain organic solutes called osmolytes.

Hyponatraemia is refered as chronic if it develops gradualy and persists for greater than 48 h. Patients with chronic slow onset hyponatraemia are typically symptoms free because of adaptation of brain to changes in osmolality. This adaptation happens at the expense of loss of intracellular osmolytes, which normally protect the brain from a rapid increase in osmolality of the ECF. In these patients, sudden increase in plasma osmolality results in water moving out of neurons, leading to shrinkage of cerebral tissue. This is the possible reason for central myelinolysis, which was first described in the pons, but can occur diffusely throughout the brain.

Neurological deterioration typically occurs over several days with fluctuating level of consciousness, seizures, respiratory depression and hypotension. Ultimately, patients may present with pseudobulbar palsy with dysphagia, inability to speak and use all four limbs. Recovery from this syndrome is variable, and many neurological problems are permanent. The magnetic resonance imaging (MRI) imaging demonstrate the demyelinated lesions 3-4 weeks after the treatment of hyponatraemia.

Hyponatraemic encephalopathy is most likely to occur in patients who suffer a hypoxic incident and have underlying severe liver disease, and in premenopausal females. As there is no effective treatment after the occurance of central demyelination, prevention is of primary mode of treatment.

Neurological deterioration typically develops over several days with fluctuating consciousness, convulsions, hypoventilation and hypotension. Eventually, patients may develop pseudobulbar palsy with difficulty in swallowing, inability to speak and quadriparesis. Recovery from this syndrome is variable, and many neurological complications are permanent. The magnetic resonance imaging (MRI) scans demonstrate the demyelinated lesions 3-4 weeks after the correction of hyponatraemia.

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TREATMENT OF HYPONATREMIA

Therapy for hyponatremia should be individualized. Patients with the risk of hyponatremia-associated complications should be balanced against the risk of serum sodium correction. Several important factors should be taken before deciding treatment, including the following:

- The rapidity of onset of hyponatremia
- The degree, duration, and clinical features of hyponatremia
- The presence or absence of risk factors for neurologic problems

ACUTE SYMPTOMATIC HYPONATREMIA

Acute symptomatic hyponatremia occurs in less than 48 hours. Clinical features are mainly related to cerebral dysfunction resulting from brain cell edema. Once the serum sodium concentration falls below 125 mEq/L, neurologic features predominate. In acute severe and rapidly developing hyponatremia, the risk of complications of cerebral edema more than the risk of osmotic demyelination. so treatment should begin promptly.

Prompt monitoring of correction of the serum sodium concentration is indicated for patients with acute severe symptomatic hyponatremia. The primary aim is to increase the serum sodium concentration by 1.5 to 2 mEq/L/hour until symptoms decreases. The main focus being to decrease the risk of seizures. Even in symptomatic patients, the sodium concentration should not be increased by more than 12 mEq/L in the first 24 hours and by more than 18 mEq/L in the first 48 hours, in order to avoid central pontine myelinolysis .

Infusion of hypertonic fluid (3% Nacl) at a rate of 1 to 2 mL/kg/hour and addition of a loop diuretic, to increase the water excretion, are commonly used to achieve this aim. Hypertonic fluid may be given at a rate of 4 to 6mL/kg/hour if patient presented with severe neurologic symptoms, particularly seizures, are present. Once a patient is symptoms free and sodium concentyation are greater than 118 mEq/L, correction should be gradualy reduced to no more than 8 mEq/L in 24 hours to attain a target concentration of 125 mEq/L. In all patients, aggresive monitoring of serum sodium and electrolytes levels is mandatory until sodium levels increase and symptoms subside.

A recent alternative management to saline administration in the treatment of hyponatraemia is the use of ADH receptor antagonists. The most particular management for SIADH is to block the V2 receptors in the renal tubules that mediate the diuretic effect of ADH. Vasopressin antagonists are recently indicated

for the management of euvolaemic and hypervolaemic hyponatraemia, and these agents are commonly used if SIADH or ADH is the cause.

Currently, an orally active vasopressin receptor antagonist tolvaptan is available. The usefulness of oral tolvaptan in ambulatory patients with SIADH, heart failure and cirrhosis is recently demonstrated. V2-receptor antagonist is not useful for particular causes of hyponatraemia, such as Cerebral salt wasting syndrome, psychogenic polydipsia and beer potomania.

While SIADH is commonly a transient problem, a chronic phase may occur in patients with ectopic ADH secreting tumours and in patients is useing antipsychotic drugs . If water restriction and salt tablet therapy are not useful in these patients, the following drug therapy is useful to antagonise the effect of ADH ,administration of loop diuretic along with salt tablets;

- demeclocycline;
- lithium carbonate;
- orally active vasopressin antagonists such as tolvaptan.

Infusion of loop diuretic (20 mg furosemide orally twice a day) along with salt tablets will antagonise the effect of ADH but also decreases the oedema formation by the latter.

Oral Demeclocycline (300-600 mg twice a day) inhibits the effect of ADH in the renal collecting tubule. It requires 7 days to act in renal tubules, and urinary

concentrating effect is always impaired, causing in nephrogenic diabetes insipidus and even hypernatraemia. Demeclocycline is nephrotoxic drug in patients having cirrhosis and is contraindicated in children because some side effects like bone development problems and teeth discoloration.

Oral Lithium carbonate (300 mg ,twice a day) also inhibits the action of ADH. It is less useful than demeclocycline and when used in long duration, it can induce interstitial nephritis and acure renal failure. So, lithium should be used for only in patients where demeclocycline is contraindicated, such as children and cases with liver disorders.

Treatment options for hyponatremia

treatment	mechanism	Limitation
Fluidrestriction	Induces negative water balance Increases plasma osmolality and serum sodium	No direct inhibition of excess hormone No inhibition of hormone on kidney nonadherence

Treatment	mechanism	Limitation
Demeclocycline	Impairs AVP action at renal tubules Induce nephrogenic DI	Nephrotoxicity (cirrhosis patients) Hypersensitivity Drug interactions Unsafe in pregnancy
Urea	Decreases sodium excretion	Unsafe in pregnancy Azotemia Liver failure Can reduce effects of lithium
Lithium	Impairs AVP at renal tubules	Inconsistent results Lithium toxicity Anti-anabolic effects in cirrhosis and congestive heart failure
Diuretics (loop/thiazide)	Increase water excretion by inhibiting sodium and chloride reabsorption in loop of Henle and distal tubule	Hypersensitivity Hepatic coma Anuria Severe electrolyte depletion

COMPLICATION OF TREATMENT

Central pontine myelinolysis is the important complication after rapid correction with sodium.

CLINICAL PRESENTATION

The clinical presentation may be different, may present with a rapidly evolving paraparesis or quadriparesis and pseudobulbar palsy. They may present as locked in syndrome, in which intellectual activitys are preserved but cannot be expressed. Less often it can present as ataxia and other movement disorders or behavioural symptoms.

DIAGNOSIS

Diagnosis is mainly based on clinical suspicion and is confirmed by imaging . MRI is the primary method for diagnosis and is superior to CT.

MANAGEMENT

The most critical step in the management of CPM is recognizing the patient at risk and preventing rapid correction of hyponatremia-especially chronic severe hyponatremia. Once a diagnosis is confirmed, the treatment of CPM is usually supportive.

HEART FAILURE

DEFINITION

The current American College of Cardiology Foundation (ACCF)/American Heart Association (AHA) guidelines define HF as a complex clinical syndrome that results from structural or functional impairment of ventricular filling or ejection of blood, which leads to the chief clinical symptoms of dyspnea and fatigue and signs of HF, namely edema and rales

Some patients present without sign and symptoms.

The prevalence of HF is thought to be increasing, in part because current recent treatment for cardiac disease , such as acute myocardial infarction (MI), structural

heart disease, and arrhythmias, are allowing patients to survive longer duration with variable clinical manifestation.

HF patients are now broadly classified into HF with a reduced EF (HFrEF; previously known as systolic failure) or HF with a preserved EF (HRpEF; previously known as diastolic failure) .

Any condition that leads to an alteration in LV structure or function can predispose a patient to developing HF.

Most common causes of heart failure are

1.coronary heart disease

2.hypertension

Both of these condition interact with each other leads to worsening of heart faiure. Although the contribution of diabetes mellitus to HF is not well known, diabetes hastens atherosclerosis and often is associated with hypertension.

In 20–30% of the patients with HF with a reduced EF, the exact causes is not known. These patients are referred to as having non ischemic, dilated, or idiopathic cardiomyopathy .

Other causes of heart failure

1.viral infection

2.toxin exposure like alcohol and chemotheraphy drugs

3. Genetic defects in the cytoskeleton like desmin , cardia myocin, virculin and laminin in patients with duchenne's, becker's , limb girdle muscular dystyophy

PATHOGENESIS

Heart failure is the progressive disorder.It is initiated after index event.this event may damage the cardiac musculature resulting loss of function and disrups the ability to produce adequate force. This index event may be acute like myocardial infarction and gradual causes like pressure or volume overload status. All causes leads to left ventricular dysfuction.

Some patients with LV dysfunction may remain asymptomatic for some duration of illness, one probable explanation is that a number of

compensatory mechanisms become triggered in the presence of cardiac injury and/or LV dysfunction .These factors allow the patient with symtoms free for some duration.

CAUSES OF HEART FAILURE

HFrEF	HFpEF
Myocardial infarction/ischemia Hypertension Obstructive/regurgitant valvular disease Intracardiac/extra shunting Corpulmonale Pulmonary vascular disorder Genetic disorder Metabolic disorder Viral Chagas disease Bradyarrhythmias Tachyarrhythmias	Hypertrophic cardiomyopathy Secondary hypertension Aging Amyloidosis Sarcoidosis Fibrosis Endomyocardial disorder

COMPENSATORY MECHANISMS

- activation of the renin-angiotensin-aldosterone (RAA) and adrenergic nervous systems, which are responsible for maintaining cardiac output through increased retention of salt and water
- increased myocardial contractility
- There is activation of a family of compensating vasodilatory molecules like the atrial and brain natriuretic peptides (ANP and BNP), prostaglandins (PGE2 and PGI2), and nitric oxide (NO), that offsets the excessive peripheral vascular constriction.

These factors maintains the patient in asymptomatic status and minimally symptomatic. At some point patients become symptomatic, with a resultant striking increase in morbidity and mortality rates. Although the exact mechanisms that are responsible for this transition are not known .During transition period ,there is increasing activation of neurohormonal, adrenergic and cytokine systems that lead to a series of adaptive changes within the myocardium collectively known as LV remodeling.

NEUROHUMORAL ACTIVATION IN HEART FAILURE

The decreased cadriac output in HF patient causes unloading of high pressure baroreceptor present in the left ventricle , carotid sinus and aortic arch receptors , leads to loss of inhibitory parasympathetic stimuli to the ce nervous

system (CNS), with a resultant generalized activation of efferent sympathetic tone, and nonosmotic secretion of arginine vasopressin (AVP) from the pituitary. . AVP (or antidiuretic hormone [ADH]) is a potent vasoconstrictor that increases the permeability of collecting ducts in kidney, leading to the reabsorption of free water. Sympathetic nervous system stimulation of the heart, kidney, peripheral vasculature, and skeletal muscles leads to volume overload.

Sympathetic stimulation of the kidney leads to the secretion of renin, with increase in the circulating levels of angiotensin II and aldosterone. The activation of the renin-angiotensin-aldosterone system encourages salt and water retention and leads to vasoconstriction of the peripheral vasculature, cardiac hypertrophy,cardiac cell death, and myocardial fibrosis. These neurohormonal mechanisms assist short-term alteration by maintaining blood pressure, and hence perfusion to important organs, the same neurohormonal mechanisms are supposed to contribute to end-organ changes.

CELLULAR AND MOLECULAR CHANGES

1. Cardiac myocyte hypertrophy
2. changes in the contractile properties of the cardiac musculature
3. gradual loss of myocytes through necrosis, apoptosis, and autophagic cell death
4. β-adrenergic desensitization;

5. changes myocardial energetics and metabolism;

restructuring of the extracellular matrix with disbanding of the organized structural collagen, followed by replacement of structural collagen by non structural interstitial collagen which not give support to the musculature

.**BIOLOGIC STIMULI FOR CELLULAR CHANGES**

1. mechanical stretch of the cardiac myocyte
2. circulating neurohormones (e.g., noradrenaline, angiotensin II),
3. inflammatory markers (e.g., tumor necrosis factor [TNF]),
4. peptides and growth factors (e.g., endothelin), and
5. reactive oxygen species (e.g., superoxide).

Continuous neurohormonal activation and mechanical overload cause in transcriptional and posttranscriptional modification in the genes and proteins that control excitation-contraction coupling and cross-bridge interaction.

The changes in the excitation-contraction are

1.decreased function of sarcoplasmic reticulum Ca2+ adenosine triphosphatase (SERCA2A), causing decreased calcium uptake into the sarcoplasmic reticulum

2. hyperphosphorylation of the ryanodine receptor, causing calcium leakage from the SR.

The changes occur in the cross-bridges are

1. decreased appearance of α-myosin heavy chain

2. increased appearance of β-myosin heavy chain,

3.myocytolysis, and disturbance of the cytoskeletal links between the sarcomeres and the extracellular matrix.

All these modification impairs the ability of the cardiac myocyte to contract normaly and therefore contribute to the reduced left ventricular systolic function noted in patients with HF.

ATP is the important molecule for myocardial relaxation.during myocardial ischemia consentration of ATP is decreased , leads to impairment in relaxation and increased stiffness secondary to hypertrophy. In addition to distrubed myocardial relaxation, increased myocardial stiffness and increased myocardial nonstructural collagen content may contribute to diastolic failure. Importantly, diastolic failure can occur alone or in combined with systolic failure in patients with HF.

LEFT VENTRICULAR REMODELING

It is refered as changes in Left Ventricular mass, volume, and shape and the composition of the heart that occur after index event and/or abnormal hemodynamic changes. LV remodeling independently leads to progression of

heart failure.left ventricular wall became thin and get dilated due to increased LV end diastolic volume.

High end diastolic stress cause

(1) .hypoperfusion of subendocardium causing worsening of failure

(2) increased oxidative stress with activation of genes that are sensitive to free radical generation (e.g., TNF and interleukin 1β) leads to myocardial injury

(3) continuous activation of stretch-activated genes (angiotensin II, endothelin, and TNF) and stretch activation of hypertrophic signaling pathways.

CLINICAL FEATURES

The main symptoms of HF are fatigue and breathlessness. Fatigue is due to the low cardiac output in patient HF, skeletal-muscle abnormalities and other noncardiac condition like anemia . In the early stages of HF, breathlesness is witnessed only during exercise; once disease progresses, dyspnea occurs with less vigorous activity, and it may occur even at rest. The causes of dyspnea in HF is multifactorial. The most principal mechanism is congestion of pulmonary vascylature with accumulation of in the interstitial or intra-alveolar space, which stimulates juxtacapillary J receptors, which in turn stimulate the rapid, shallow breathing . Other causes of dyspnea on exertion are decreased pulmonary compliance, increased resistance in airways , fatiquability of respiratory muscle

and/or diaphragm and anemia. Dyspnea become less when right ventricular (RV) failure and tricuspid regurgitation develops.

Orthopnea is defined as dyspnea occurring in the recumbent posture, is commonly a later symptoms of HF . It occurs due to redistribution of fluid from the splanchnic circulation and lower extremities into the central circulation during recumbent posture, which leads to increase in pulmonary capillary pressure.

Nocturnal cough is most common clinical manifestation of this process. Orthopnea usually is relieved by sitting upright posture or sleeping with extra pillows. Orthopnea is a relatively specific feature of HF, it may also occur in patients ascites and pulmonary disease .

PAROXYSMAL NOCTURNAL DYSPNEA (PND) refered as acute episodes of severe dyspnea and coughing that occur at night and awaken the patient from sleep, usually 1–3 h after the patient retires. PND may present as coughing or wheezing, possibly due to increased bronchial arteries pressure leading to compression in the airways, along with interstitial pulmonary edema that leads to increased resistance in the airways. Cardiac asthma is commonly related to PND, is characterized by wheezing secondary to bronchospasm, and must be differentiated from primary pulmonary causes of wheezing.

CHEYNE-STOKES RESPIRATION Also known as periodic or cyclic respiration, It is present in 35%-40% of patients with severe HF and commonly

associated with low cardiac output. It occurs due to increased sensitivity of the respiratory center to arterial PCO2. It is characterised by apneic phase, during which arterial PO2 decreases and arterial PCO2 increases. These modification in the arterial blood gas stimulate respiratory center in the brain resulting in hyperventilation and hypocapnia, followed by recurrent apnea.

It may present as acute pulmonary edema.

Other clinical features HF are present with anorexia, nausea, and early satiety with abdominal pain and fullness . It may be due to edema of the bowel wall and a congestion of liver. Congested liver and stretching of its capsule may lead to right upper-quadrant pain. Cerebral features like confusion, disorientation, and sleep and mood disturbances are observed in patients with advanced HF, usually elderly patients with cerebral arteriosclerosis and decreased cerebral perfusion. Nocturia is common clinical feature of HF and may leads to insomnia.

PHYSICAL EXAMINATION

In mild to moderately severe HF, the patient feels no distress at rest except uncomfortable when lying on supine position for more than a few minutes. In advanced HF, the patient must sit in upright posture, may have labored breathing, and may not be able to complete a sentence because of dyepnea. Systolic blood pressure may be normal or high in early stage of HF, but it usually is reduced in late stage of HF because of severe LV systolic dysfunction. The pulse pressure is

diminished, reflecting reduced in stroke volume. Sinus tachycardia is a commom clinical finding. It is a nonspecific sign caused by increased adrenergic activity which leads toPeripheral vasoconstriction(cool peripheral extremities) and cyanosis of the lips and nail beds.

In the mild stages of HF, the jugular venous pressure may be normal at rest but positive abdominojugular reflux is present. Giant v waves is usually seen in tricuspid regurgitation.

PULMONARY EXAMINATION

Pulmonary crackles (crepitations) usually due to transudation of fluid from the intravascular space to the alveolar space. In pulmonary edema, patient present with rales over both lung fields and expiratory wheezing . Rales are specific when it is present without lung disease. Rales are commonly absent in patients with chronic HF because of adequate lymphatic drainage of alveolar fluid. Pleural effusions occur usually with biventricular failure. Pleural effusion is often bilateral in HF, when they are unilateral, they occur commonly in the right pleural space.

CARDIAC EXAMINATION

1.apical impulse shifted to downwards and lateraly due to cadiomegaly

2. Third heart sound (S3)is palpable and audible

3.tachycardia and tachypenea

4,Fourth heart sound(S4) is not a specific indicator of HF but is commonly present in patients with diastolic LV dysfunction. The mitral and tricuspid regurgitation murmurs are often present in patients with severe HF.

ABDOMINAL EXAMINATION

Tender hepatomegaly , pulsate liver (if tricuspid regurgitation) are present. Ascites and jaundice are usually late clinical finding in advanced HF.Both direct and indirect bilirubin are elevated.Peripheral edema is a common manifestation of HF, but it is nonspecific and usually not present in patients who are treated with diuretics. Peripheral edema is always symmetric and dependent in HF and presen in ankles and the pretibial region in ambulatory cases. In bedridden patients, edema is found in the sacral area and the scrotum. Long-standing edema leads to induration and pigmentation of skin.

CARDIAC CACHEXIA

With severe advanced HF, patient present with weight loss and cachexia. It is probably due to multifactorial and includes elevation of the resting metabolic rate; anorexia, nausea, and vomiting due to congestion of liver and abdominal fullness; elevation of circulating levels cytokines like TNF; and decreased intestinal absorption is due to congestion of veins present in the intestinal wall. When present, it indicate poor prognosis.

INVESTIGATION

- complete blood count
- a panel of electrolytes
- blood urea nitrogen
- serum creatinine hepatic enzymes
- urinalysis.
- Selected patients need fasting serum glucose(DM)
- fasting lipid panel (dyslipidemia)
- thyroid function test
- ECG (to assess rhythm disturbance LV hypertrophy and prior MI)
- chest x-raye
- Two-dimensional (2-D) echocardiogram/ Doppler/EF%
- B-type natriuretic peptide (BNP) and N-terminal pro-BNP (NT-proBNP)

HF should be differentiated from (1) disease causing circulatory congestion due to salt and water retention(e.g., renal failure), and (2) noncardiac causes of pulmonary edema (e.g., acute respiratory distress syndrome).

HYPONATREMIA AND ACUTE DECOMPENSATED HEART FAILURE

Like most other causes of hyponatremia,HF impairs the ability to excrete ingested water by increasing antidiuretic hormone levels.when cardiac output and SBP are reduced,hypovolemic hormones, such as renin,ADH and norepinephrine respond. Although edematous cases with HF have increased plasma and extracellular fluid volume, the body perceives volume depletion since the low CO decreases the pressure perfusing the baroreceptors in the carotid sinus and renal afferent arteriole.

The degree of neurohumoral activation is generally related to the severity of cardiac dysfunction,as assessed by left ventricular EF of functional class. The neurohumoral changes limit both sodium and water excretion in an attempt to return perfusion pressure to normal. ADH release directly enhances water reabsorption in the collecting tubules whereas angiotensin II and norepinephrine limit distal water delivery by lowering the glomerular filtration rate and by increasing proximal sodium and water reabsorption.In addition, both the low CO and high angiotensin II level are stimuli to thirst, leading to enhanced water intake.

CARDIORENAL SYNDROME

Cardiorenal Syndrome (CRS) Definition:

A pathophysiologic disorder of the heart and kidneys whereby acute or chronic dysfunction in one organ may induce acute or chronic dysfunction in the other organ

CRS Type I (Acute Cardiorenal Syndrome):

Abrupt worsening of cardiac function (e.g., acute cardiogenic shock or decompensated congestive heart failure) leading to acute kidney injury

CRS Type II (Chronic Cardiorenal Syndrome):

Chronic abnormalities in cardiac function (e.g., chronic congestive heart failure) causing progressive and permanent chronic kidney disease

CRS Type III (Acute Renocardiac Syndrome):

Abrupt worsening of renal function (e.g., acute kidney ischemia or glomerulonephritis) causing acute cardiac disorder (e.g., heart failure, arrhythmia, ischemia)

CRS Type IV (Chronic Renocardiac Syndrome):

Chronic kidney disease (e.g., chronic glomerular disease) contributing to decreased cardiac function, cardiac hypertrophy, and/or increased risk of adverse cardiovascular events

CRS Type V (Secondary Cardiorenal Syndrome):

Systemic condition (e.g., diabetes mellitus, sepsis) causing both cardiac and renal dysfunction

TYPE 1 CARDIORENAL SYNDROME

Type 1 CRS (acute CRS) occurs in approximately 25% to 33% of patients admitted with ADHF. There are direct and indirect effects of HF that can be identified as the primers for AKI and dysfunction. Factors beyond the classic hemodynamic mechanisms appear to play a role in the pathogenesis of renal injury. Venous congestion, sympathetic nervous system dysfunction, anemia, activation of the renin-angiotensin aldosterone system (RAAS), disruption of the hypothalamic-pituitary axis, and a marked alteration of immune and somatic cell signaling have all been implicated. The complexity of this syndrome presents a key challenge for singular diagnostic or treatment approaches.

there are 4 subtypes of type 1 CRS:

1) de novo cardiac injury leads to de novo kidney injury;

2) de novo cardiac injury leads to acute-on-chronic kidney injury;

3) acute-on-chronic cardiac decompensation leads to de novo kidney injury; and

4) acute-on-chronic cardiac decompensation leads to acute-on-chronic kidney injury.

Type 1 CRS is characterized by an acute heart disorder leading to AKI and occurs in ~25% of patients admitted with ADHF . Among these patients, pre-morbid chronic kidney disease (CKD) is common and predisposes to AKI in nearly 60% of cases. AKI is an independent risk factor for 1-year mortality in ADHF patients, including patients with myocardial infarction who develop HF or have a reduced left ventricular EF . This independent effect might be due to an associated acceleration in cardiovascular pathobiology due to kidney dysfunction through the activation of neurohormonal, cell signaling, oxidative stress, or exuberant repair (fibrosis) pathways.

Upon initial recognition, AKI induced by primary cardiac impairment implies inadequate renal perfusion until proven otherwise . This should prompt clinicians to consider the diagnosis of a low CO state and/or marked increase in venous pressure leading to kidney congestion. It is important to remember that central venous pressure transmitted to the renal veins is a product of right heart function, blood volume, and venous capacitance, which is largely regulated by neurohormonal systems.

PREDISPOSITION FOR CARDIORENAL SYNDROMES

Obesity and cardiometabolic changes

Obesity leads to type 2 diabetes mellitus (DM), hypertension, obstructive sleep apnea, atrial fibrillation, HF, hyperuricemia, and CKD, all directly or indirectly related to excess adiposity. The adipocytes secrete cytokines which cause cardiac and renal injury by (IL)-6 and TNF alpha. The IL-6 release high-sensitivity C-reactive protein. Thus, hs CRP levels are increased in obese individuals .Changes in the leve lof lipid content within cardiomyocytes are playing a pathological role in cardiac remodeling. Obesity-related glomerulopathy is described as a condition of hyperfiltration in obese individuals without DM that ultimately predisposes to CRS type 1 .cardiometabolic syndrome in the absence of DM has been associated with 3- to 7-fold increased risk of CRS type 1

Cachexia

Cachexia and nutritional deficiencies associated with either HF or CKD may contribute to further damage and fibrosis of the other organ and leads to infection or death.

Hypertension and diabetes

Hypertension directly related to augmented loss of nephrons and reductions in GFR. Diabetes leads to glomerular dysfunction, damage, and ultimate loss of function and contributes to kidney failure.

Proteinuria

Albuminuria and gross proteinuria are associated with the risk of AKI . Albuminuria is predictive of the development of HF. In established HF, microalbuminuria is a risk marker for cardiovascular disease.

Uremic solute retention

Uremia causes myocyte dysfunction manifested by impaired movement of calcium in the cytosol leads to impaired contraction of myocyte elements. Uremia directly contributes to accelerated fibrosis and adverse cardiac remodeling after MI.

Anemia

Anemia in HF is multifactorial, encompassing hemodilution due to water retention, blockade of normal iron transport, inflammation/cytokine-induced erythropoietin deficiency, and tissue resistance, malnutrition, cachexia, vitamin deficiency, all amplified in the presence of pre-existing CKD .

Repeated episodes of subclinical AKI

some individuals undergo repeated episodes of either subclinical or unrecognized episodes of AKI over the course of a lifetime develop CRS in the setting of ADHF.

Cardiac and Renal Fibrosis

Increased stress or injury to the myocardium, glomeruli, and renal tubular cells, due to uncontrolled hypertension, DM can involve recruitment of immune cells, production of cell signaling proteins from local pericytes, mast cells, and macrophages, resulting in activation of resident fibroblasts and myofibroblasts, and in the final common pathway, the deposition of procollagen into the extracellular matrix, which is irreversibly crosslinked to collagen-generating cardiac and renal fibrosis .In the myocardium and the kidney, angiotensin II and aldosterone are major stimuli for macrophages to secrete galectin-3, which in turn works as a paracrine signal on fibroblasts to help translate the signal of transforming growth factor β (T GFβ) to increase cell cycle (cyclin D1) and direct both the proliferation of pericytes and fibroblasts, and the deposition of procollagen 1 leads to progression of CKD and HF

The Acute Pathways of CRS Type 1

Hemodynamics and congestion

The increase in blood pressure is likely a reflection of sodium retention and sympathetic activation. A dysfunctioning left ventricle is particularly sensitive to afterload variations, and therefore, an increase in blood pressure can abruptly worsen left ventricular filling pressures, leading to pulmonary congestion irrespective of total intravascular volume. Subsequently, a vicious cycle arises in

which cardiac remodeling leads to functional mitral regurgitation, further increase in left atrial pressure, and pulmonary hypertension. Chronic passive congestion of the kidneys results in attenuated vascular reflexes over time. As with the heart, venous congestion is one of the most important hemodynamic determinants of CRS and has been associated with the development of renal dysfunction in the setting of ADHF . It is commonly observed that coexisting renal dysfunction may complicate the treatment course of HF and that the use of intravenous loop diuretics often alleviate congestion at the cost of worsening renal function within days of hospitalization and is a strong, independent predictor of adverse outcomes . Although loop diuretics provide prompt diuresis and relief of congestive symptoms, they provoke a marked activation of the sympathetic and RAAS, resulting in renovascular reflexes and sodium retention, and thus are considered a primary precipitant of CRS.

Volume and Blood Pressure Management Window

Patients at risk for cardiorenal syndrome type 1 have a narrow window for management of both blood pressure and volume; extremes in either parameter can be associated with worsened renal function.

Neurohormonal activation

The RAAS has an important role in the initiation and maintenance of vascular, myocardial, and renal dysfunction leading to edema in HF (55). Increased renin

secretion occurs early in biventricular failure, which leads to stimulation of angiotensin II. Angiotensin II has direct trophic effects on cardiomyocytes and renal tubular cells that promotes cellular hypertrophy, apoptosis, and fibrosis .In normal subjects, an “escape” from renal salt-retaining effects of aldosterone usually occurs after 3 days, thus avoiding edema formation. This aldosterone escape phenomenon, however, does not occur in HF patients, and the continued sodium retention contributes to the pulmonary congestion and edema, .Aldosterone stimulates macrophages in heart and kidney tissue to secrete galectin-3, which in turn stimulates fibroblasts to secrete procollagen I and III that is crosslinked to collagen, resulting in fibrosis. As a result of sympathetic activation, catecholamines play a vital role in the pathogenesis and progression of HF . It is well known that elevated plasma norepinephrine levels in patients with HF correlate with increased mortality

Hypothalamic-pituitary stress reaction

Activation of corticotrophin releasing factor neurons in the paraventricular nucleus of the hypothalamus is necessary for establishing the classic endocrine response to stress for example, ADHF. Any stressor that activates the hypothalamus-pituitary-adrenal axis leads to an increase in concentrations of the adrenal stress hormone cortisol and arginine vasopressin. Arginine vasopressin stimulates the V1a receptors of the vasculature and increases systemic vascular

resistance, while stimulation of the V2 receptors in the principal cells of the collecting duct increases water reabsorption and leads to hyponatremia. Arginine vasopressin also enhances urea transport in collecting ducts of the nephron, thereby increasing the serum blood urea nitrogen. The clinical consequences of these changes include sodium and water retention, pulmonary congestion, and hyponatremia, which occurs both in low-output and high-output cardiac failure. It is important to recognize that hyponatremia is a relatively late sign of arginine vasopressin overstimulation, and thus, earlier modulation of this system is an important consideration in treatment. The arterial underfilling occurs secondary to a decrease in cardiac output in low-output HF and arterial vasodilatation in high-output HF, both of which decrease the inhibitory effect of the arterial stretch baroreceptors on the sympathetic and RAAS. Thus, a vicious cycle of worsening HF and edema formation occurs.

Inflammation and immune cell signaling

Inflammation classically has 4 components: 1) cells; 2) cytokines; 3) antibodies; and 4) complement. Thus, the term inflammation in CRS has been termed “low-grade” or better described as an imbalance between the immune system cell signaling pathways promoting and inhibiting inflammation. Over the past 30 years, there has been increasing evidence on the role of activation of the inflammatory response in the pathogenesis of different types of heart disease,

including HF. An early work of Levine et al. (63) showed that in patients with severe HF, circulating levels of tumor necrosis factor-alpha were much higher than normal. Numerous studies showed activation of inflammation at various levels in HF patients. Further support for the inflammatory etiology of HF came from the demonstration that inflammatory cytokines may also be produced by cardiomyocytes, following ischemic or mechanical stimuli, but also by the innate immune response, represented by Toll-like receptors, pentraxin-like C-reactive protein, and pentraxin 3 (64–69). These findings suggest that in HF, an immune dysregulation may exist; cytokines not only could produce distant organ damage such as AKI, but they also may play a role in further damaging myocytes. There is evidence supporting the prognostic value of various circulating markers of inflammation, particularly C-reactive protein, pentraxin 3, tumor necrosis factor-alpha, IL-1, and IL-6.

Excessive elevations of cytokines and markers of inflammation have been consistently documented in ADHF (75). Inflammatory activation may have a role in HF by contributing to both vascular dysfunction and fluid overload in the extravascular space (76). The amount of fluid in the pulmonary interstitium and alveoli is tightly controlled by an active process of reabsorption. Recent studies have shown that inflammation interferes with this process and thus leads to pulmonary fluid overload despite no increase in total body fluid (77,78). This

mechanism could be a cause for inadequate renal perfusion pressures, peritubular edema, pathological reduction of glomerular filtration, and finally, mixed inflammatory and ischemic tubular damage.

The role of the gut and endotoxemia

Underperfusion of the intestine and the hematogenous release of endotoxin in patients with HF has been proposed as a mechanism for progression of HF and CRS type 1, particularly in patients with cachexia

Superimposed infection

Superimposed infection, often pneumonia, is a common precipitating or complicating factor in ADHF.

Iatrogenesis

Among the mechanisms involved in organ crosstalk between the heart and kidney, we must consider iatrogenesis. In several clinical conditions, drugs required to treat DM, oncological diseases, infections, HF itself, or fluid overload may affect the delicate balance between the heart and the kidney, leading to progressive deterioration of both. Metformin is an antidiabetic drug that can result in lactic acid accumulation and worsening heart function due to a negative inotropic effect. Chemotherapeutic agents used in solid tumor treatments may induce a tumor lysis syndrome, with a sudden increase in circulating uric acid levels. Such an effect, although less dramatic, may also be induced by diuretic

therapy. Uric acid, as discussed in the preceding text, is potentially toxic to the myocardium as well as for the tubulointerstitial component of the kidney. Antibiotics may cause interstitial nephritis and tubular dysfunction, and contribution to progressive renal insufficiency, especially when glomerular filtration is stressed by a low cardiac output and activation of the RAAS . Iodinated contrast causes a much different form of AKI characterized by transient vasoconstriction and decreased perfusion followed by direct tubular toxicity as the contrast is taken up by proximal tubular cells and transported into the interstitium in the kidney. Contrast-induced nephropathy can be an important cause of negative feedback on the heart with progressive worsening of cardiac disease due to uremic complications . Cardiac surgery is a well-recognized antecedent to type 1 CRS and AKI, particularly if the patient has received contrast in the days before the operation. Because this is one of the timed forms of AKI, there has been considerable effort in demonstrating the novel markers of AKI (neutrophil gelatinase-associated lipocalin, kidney injury molecule [KIM]-1, L-type fatty acid binding protein [LFABP], N-acetyl-β-D-glucosaminidase [NAG], and others) serve as both baseline risk predictors and diagnostic indicators of kidney damage after cardiac surgery .

Progressive salt and water retention alter intraglomerular hemodynamics and thereby influence physiological tubular-glomerular feedback . Patients may already

be undergoing treatment with angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, direct renin inhibitors, and/or aldosterone blockers, all of which may negatively impact tubuloglomerular feedback. However, holding these agents, while temporarily causing less creatinine retention in the blood pool, has been associated with worsening of HF over the longer term. Combinations of angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, direct renin inhibitors, and especially aldosterone blockers when glomerular filtration rate is reduced below 45 ml/min, may lead to secondary hyperkalemia. Nonsteroidal inflammatory agents reversibly inhibit cyclooxygenases 1 and 2, impair prostaglandin synthesis, and result in sodium and fluid retention, as well as tissue edema, which consistently worsen HF outcomes . In the kidney, edema may result in impaired oxygenation and metabolite diffusion, distorted tissue architecture, obstruction of capillary blood flow and lymphatic drainage, and disturbed cell–cell interactions that may then contribute to progressive organ dysfunction.

The cornerstone of treatment for ADHF is the use of oral and intravenous loop diuretics. These agents represent a double-edged sword as they may resolve congestion but worsen renal perfusion by arterial underfilling and heightened activation of the sympathetic and RAAS leading to type 1 CRS .

Although registry data have demonstrated that earlier diuretic use decreases mortality in severe ADHF, there is an overall relationship between increased loop diuretic dosing and mortality Felker et al. , in a small randomized trial of ADHF, demonstrated that higher doses and continuous infusions of furosemide resulted in more patients developing AKI (rise in creatine >0.3 mg/dl) with no improvement in hospitalization or death. These arguments suggest the clinician needs better guidance on the use of loop diuretics in ADHF. Two such sources of guidance include the use of bioimpedance to estimate body water levels as well as novel biomarkers of AKI such as neutrophil gelatinase-associated lipocalin, which rises in the setting of diuretic-induced AKI .

Oxidative Stress: Final Common Pathway of Injury

Oxidative stress is a final common pathway for cellular dysfunction, tissue injury, and organ failure. The most widely recognized chemical reactions generating reactive oxygen species are the Haber-Weiss and Fenton equations. These equations require oxygen, water, hydrogen, and a metal catalyst in the form of iron, copper, and so on. Since iron is the most abundant metal element in cells, it is believed that labile iron is the major stimulus for oxidative stress that results in tissue injury . The release of poorly liganded labile iron that remains unbound in a fraction has been implicated in both acute ischemic cardiac models and a variety of injury models in the kidney. Importantly, labile iron transitioning from Fe2+ to

Fe3+ facilitates the production of hydrogen peroxide and the dangerous hydroxyl radical, which overwhelm the homeostatic antioxidant defense mechanisms in cells . Attempts to slow these reactions may have benefit, particularly for the kidney, and include alkalinization, cooling, and binding the iron catalyst. It is important to recognize in probably every case of CRS that oxidative stress and injury to both the heart and kidneys is playing a potentially reversible role and that these mechanisms represent a final common pathway for tissue damage and organ failure.

Failure of Counter-Regulatory Mechanisms

In response to wall tension, the cardiomyocyte produces large quantities of natriuretic peptides that work to reduce wall tension, vasodilate, and promote natriuresis and diuresis .Ischemia is also recognized as a stimulus for natriuretic peptide production. Natriuretic peptides, working via natriuretic peptide receptors in the glomerulus and the renal tubules, activate cCMP and reduce sodium reabsorption. When given in supraphysiological doses, B-type natriuretic peptide reduces levels of catecholamines, angiotensin II, and aldosterone . However, this counter-regulatory set of functions appears to be overwhelmed in CRS type 1, and thus, the patient worsens clinically and develops oliguria in the setting of markedly elevated levels of natriuretic peptides.

MATERIALS AND METHODS :

STUDY POPULATION:

source of data:

The study will be conducted on 100 patients admitted to Government Rajaji Hospital & Madurai Medical College during the study period from april 2017 to september 2017.

Inclusion criteria:

All patients with acute decompenstated heart failure of any etiology with a duration of hospital stay more than 24 hours with or without renal dysfunction

Exclusion criteria:

1.Patients with documented renal artery stenosis

2.Patient with diabetic nephropathy(proteinuria >300mg.24 hours

3.Patients with chronic kidney disease (Sr.creatinine >5mg/dl)

4.Patients with history of NSAID abuse

5.Patients not satisfying above criteria(hospital stay <24 hours)

ANTICIPATED OUTCOME:

Hyponatremia as an independent risk factor for acute decompenstated heart failure and important factor contributing to the development of WRF .

DATA COLLECTION:

Informed consent will be obtained from all patients to be enrolled for the study. In all the patients relevant information will be collected in a predesigned proforma.

The patients are selected based on clinical examinations, biochemical tests and echocardiogram. The patients are followed over a period of six months with serum sodium and creatinine levels measured at regular intervals.

LABORATORY INVESTIGATIONS

a)Complete blood count,

b)Renal function test,

c)Urine routine,

d)Serum electrolyte,

e)Electrocardiogram,

f)Echo

g)USG abdomen

STUDY PROTOCOL

- Patients with clinical and radiological evidence of acute decompensated heart failure are to be included in the study.
- Then they are classified into structural, ischemic and electrical abnormalities by clinical , radiological and biochemical evaluation

- In all the patients above investigation are done to classify them as mild hyponatremia , moderate hyponatremia and severe hyponatremia
- Above patients are further classified as having worsening renal function by correlating with creatinine levels

DESIGN OF STUDY:

Prospective study.

PERIOD OF STUDY:

6 MONTHS (april 2017 to September 2017)

COLLABORATING DEPARTMENTS:

DEPARTMENT OF CARDIOLOGY

DEPARTMENT OF NEPHROLOGY

DEPARTMENT OF BIOCHEMISTRY

CONSENT: Individual written and informed consent.

ANALYSIS: Statistical analysis will be performed using appropriate tests as required according to data.

CONFLICT OF INTEREST: NIL

PARTICIPANTS:

100 acute decompensated heart failure at Government Rajaji hospital, Madurai

METHOD OF STUDY

This study was conducted in Govt. Rajaji Hospital, Madurai which is allied to Madurai Medical College. This study subjects were choosen from the patients admitted in Department of Medicine and Department of cardiology , Govt. Rajaji Hospital madurai.

The study was conducted in 100 patients with acute decompensated heart failure of any cause without chronic renal failure with clinical background of diabetes mellitus ,hypertension ,coronary artery disease , valvular heart disease and arrthythmia.

Clinical criteria to classify patients having acute decompensated heart failure worsening renal function

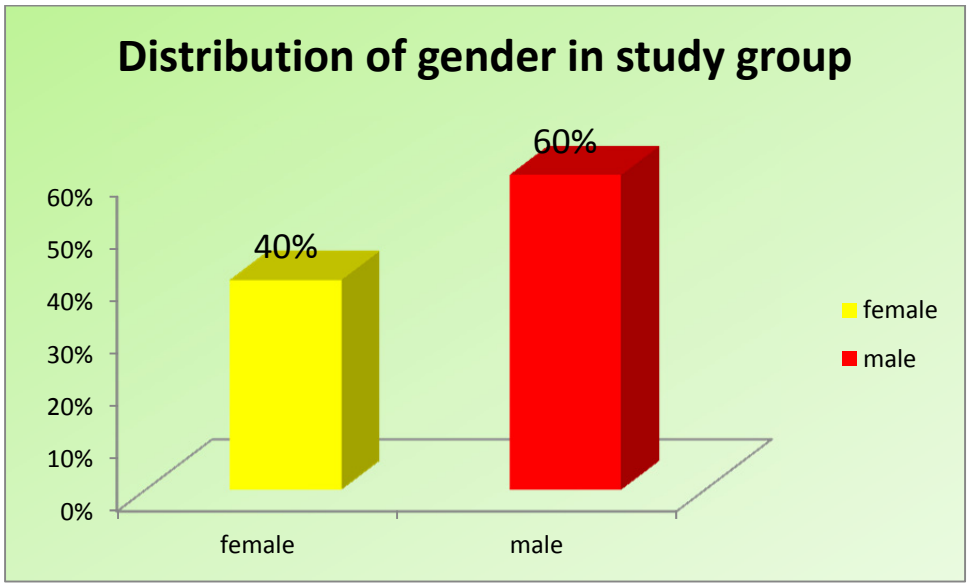
If the patient had oedema legs, ascites, cardiac enlargement, radiological evidence of congested lungs and responded to treatment for congestive cardiac failure , then the diagnosis of congestive cardiac failure was made.

When there were raised serum urea and creatinine levels when compared with previous levels along with signs and symptoms with excluding chronic kidney disease .

Classification	Hyponatremia(mEq/l)	Worsening renal function(mg/dl)
Mild	130-135	1.2- 2
Moderate	125-129	2-3
Severe	Less than 125	More than 4

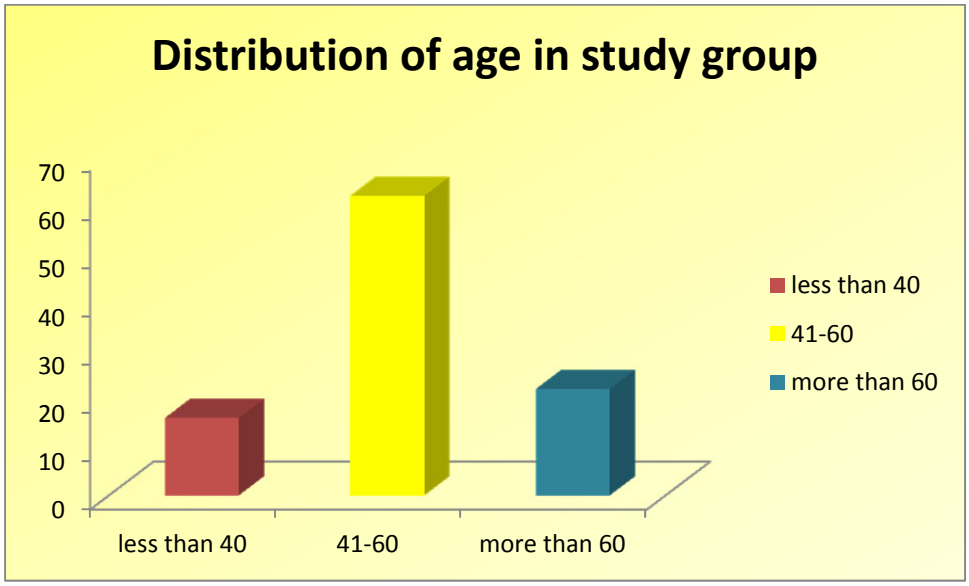
RESULTS AND INTERPRETATION

GENDER DISTRIBUTION



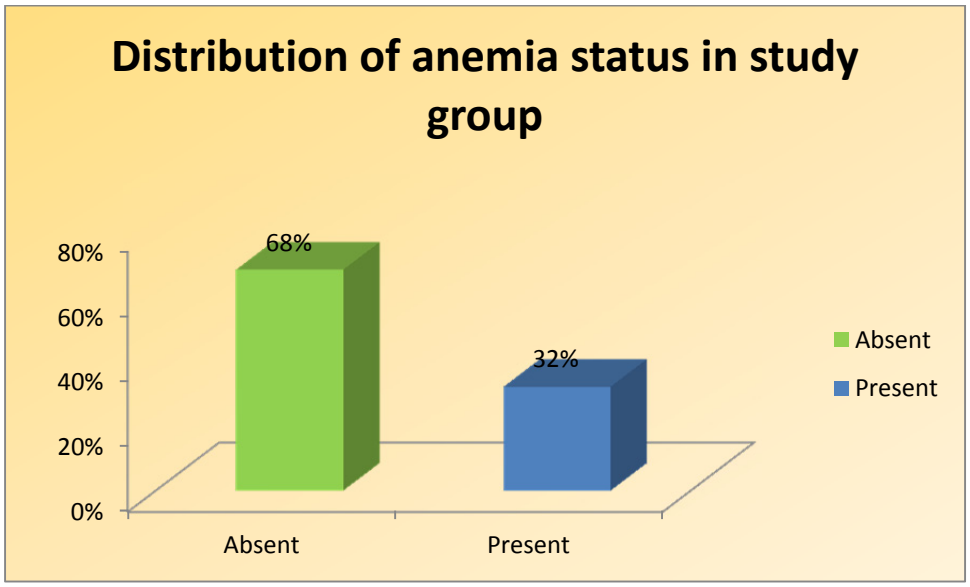
GENDER	frequency	Valid persent
female	40	40
male	60	60
total	100	100

AGE DISTRIBUTION



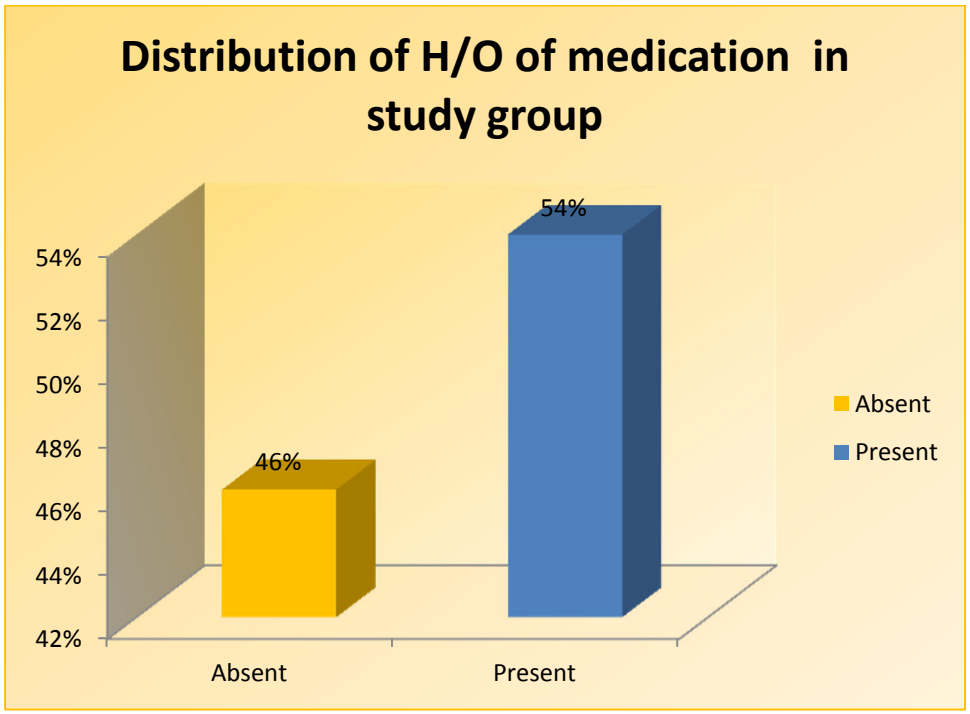
Age group	frequency	
<40	16	16
40-60	62	62
>60	22	22
total	100	100

DISTRIBUTION OF ANEMIA



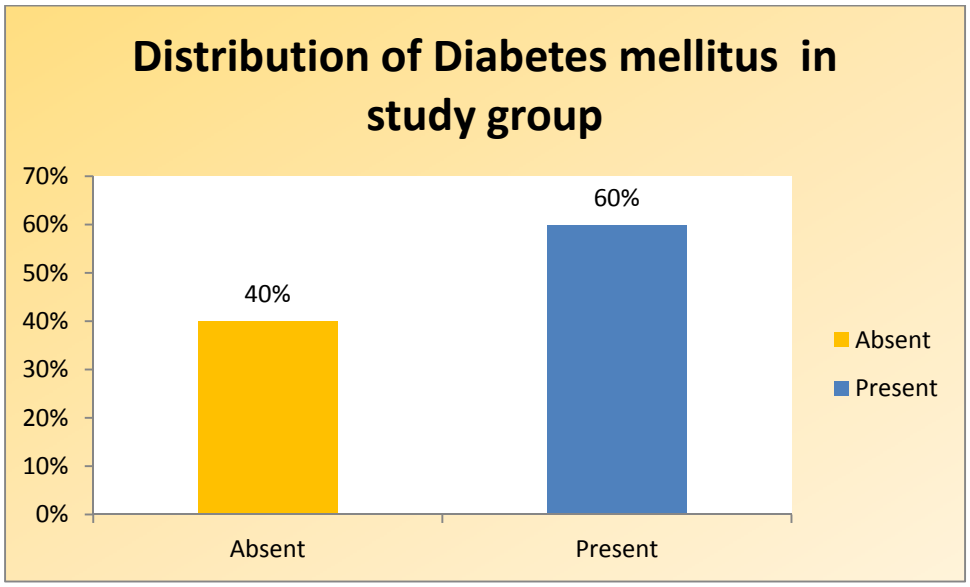
anemia	frequency	Valid persent
absent	68	68
present	32	32
total	100	100

DISTRIBUTION OF DRUG USAGE



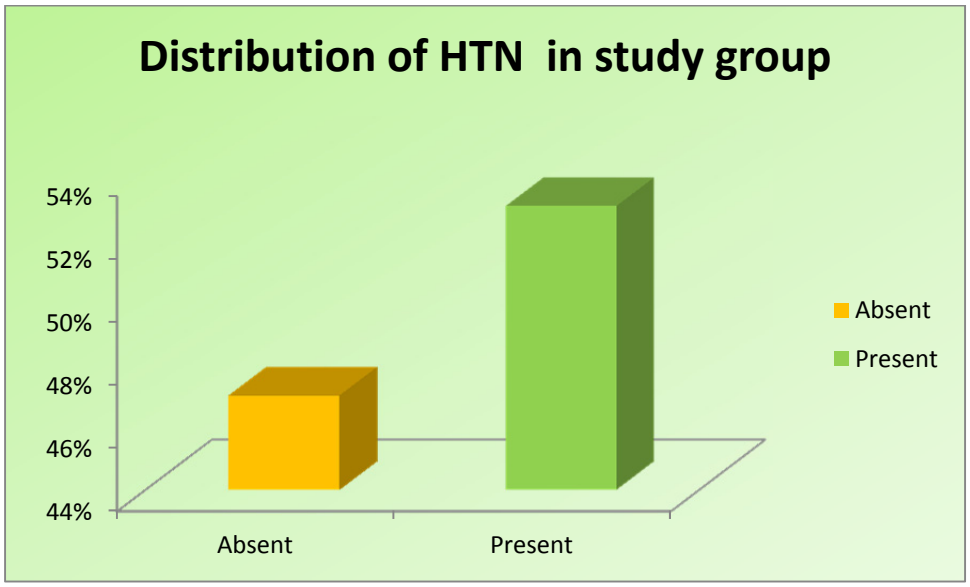
medication	frequency	Valid percent
absent	46	46
present	54	54
total	100	100

DISTRIBUTION OF DM



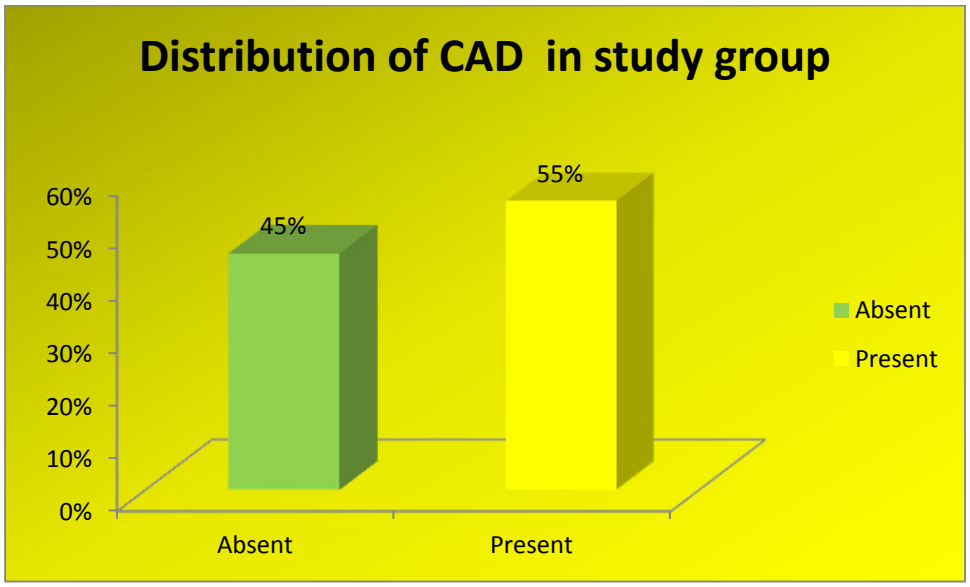
Diabetes mellitus	frequency	Valid persent
absent	40	40
present	60	60
total	100	100

DISTRIBUTION OF HYPERTENSION



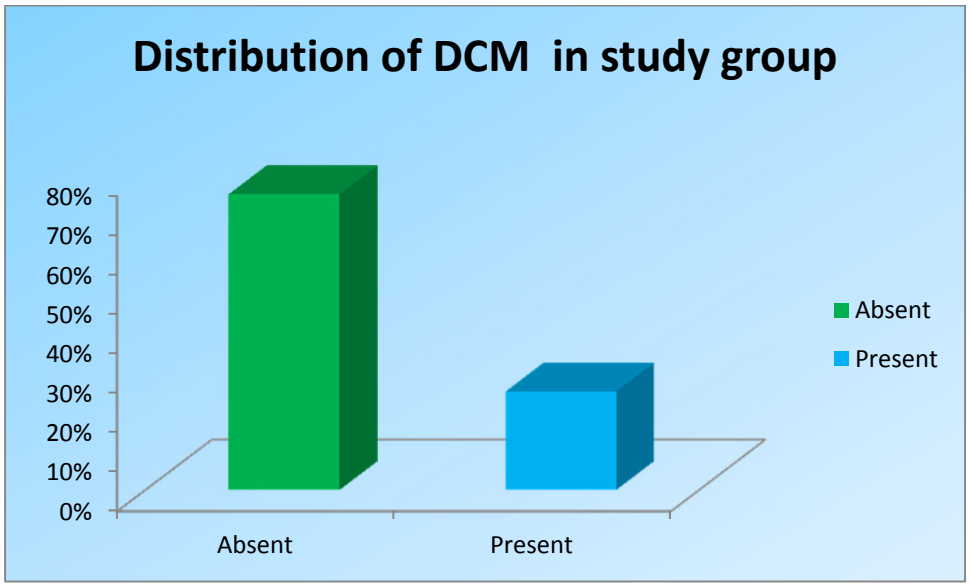
hypertension	frequency	Valid percent
Absent	49	49
present	51	51
total	100	100

DISTRIBUTION OF CAD



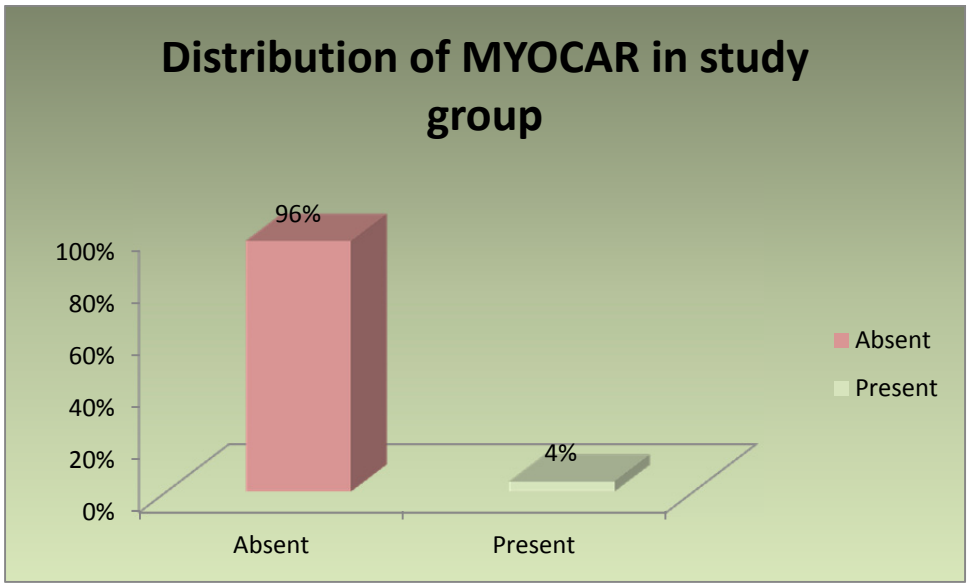
cad	frequency	Valid persent
absent	45	45
present	55	55
total	100	100

DISTRIBUTION OF DCM



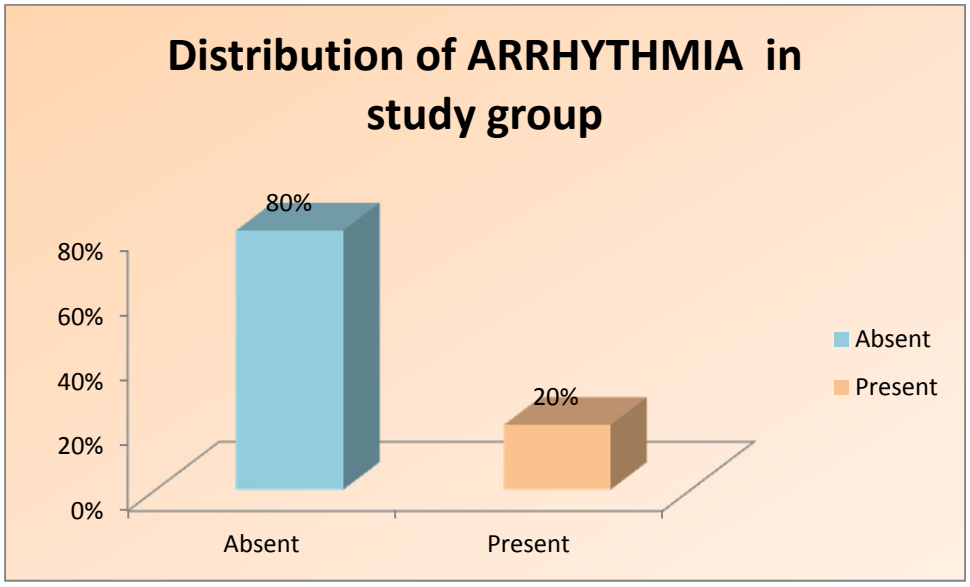
DCM	frequency	Valid present
absent	75	75
present	25	25
total	100	100

DISTRIBUTION OF MYOCARDITIS



myocarditis	frequency	Valid percent
absent	96	96
present	04	04
total	100	100

DISTRIBUTION OF ARRHYTHMIA



arrthythmia	frequency	Valid percent
absent	80	80
Present	20	20
total	100	100

WEIGHT DISTRIBUTION AMONG MALES

Weight(male)	frequency	Valid persent
<60	25	41.66
>60	35	58.33
total	60	100

WEIGHT DISTRIBUTION AMONG FEMALES

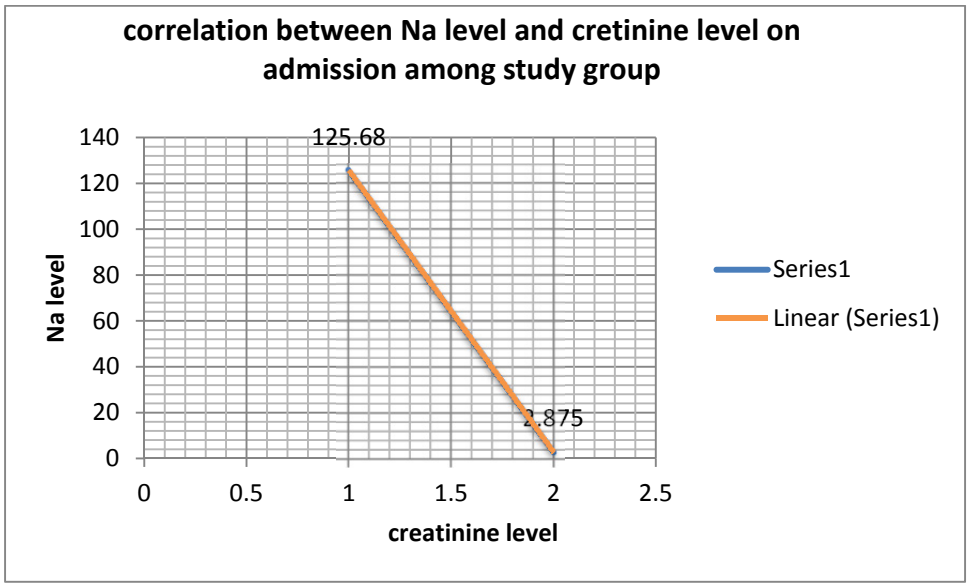
Weight(female)	frequency	Valid persent
<55	16	40
>55	24	60
total	40	100

DISTRIBUTION OF HEART DISEASE

Valvular disease	frequency	Valid persent
absent	86	86
present	14	14
total	100	100

CORRELATION BETWEEN SODIUM AND CREATININE LEVELS ON ADMISSION

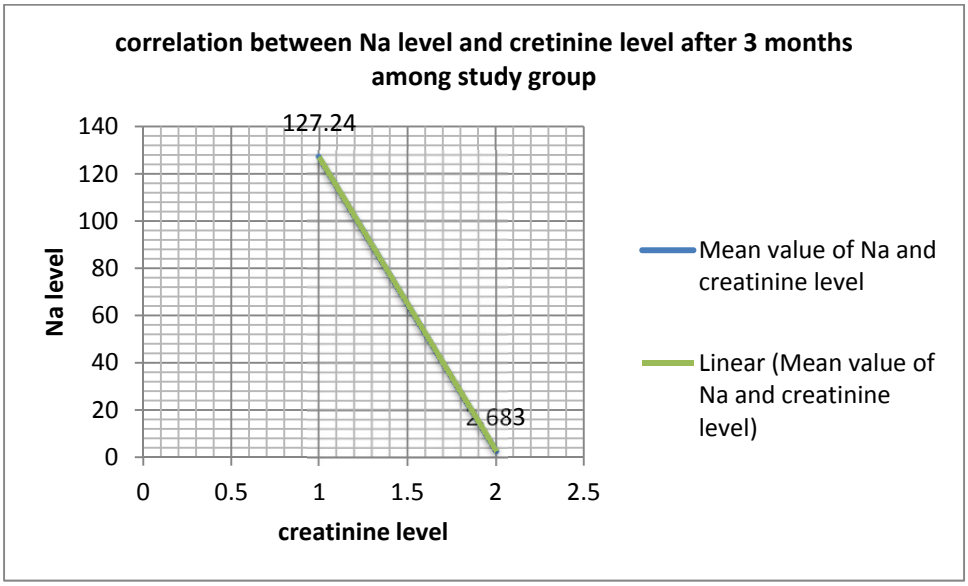
Na mEq/l	freq	Valid %	ON	Cr mg%	freq	Valid %
130-135	30	30	ADMIS	<2	1	1
125-129	34	34	SION	2-3	60	60
<125	36	36		>3	39	39
Total	100	100		total	100	100



CORRELATION BETWEEN SODIUM AND CREATININE LEVELS

AFTER THREE MONTHS

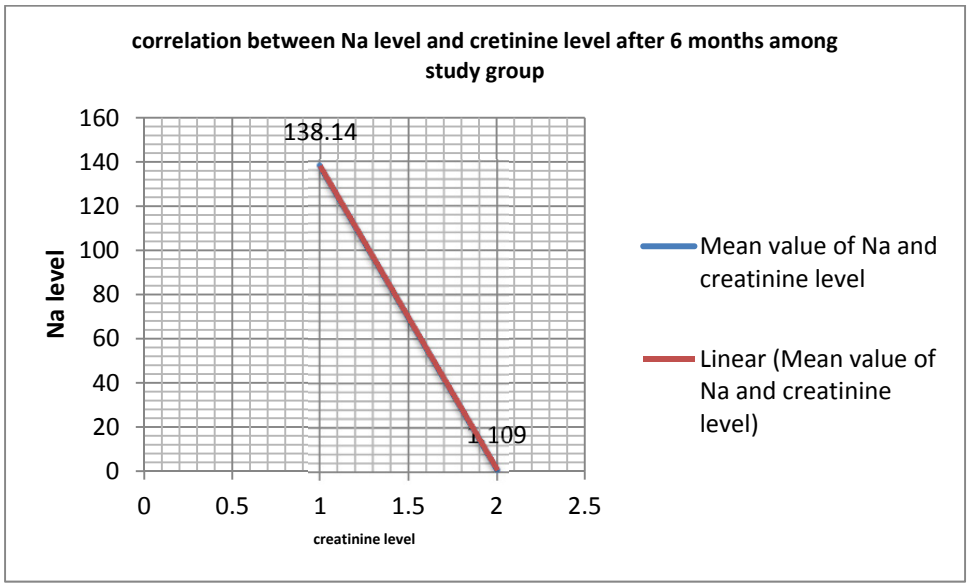
Na mEq/l	freq	Valid %	After 3 Months	Cr mg%	freq	Valid%
130-135	36	36		<2	04	04
125-129	42	42		2-3	81	81
<125	22	22		>3	15	15
Total	100	100			100	100



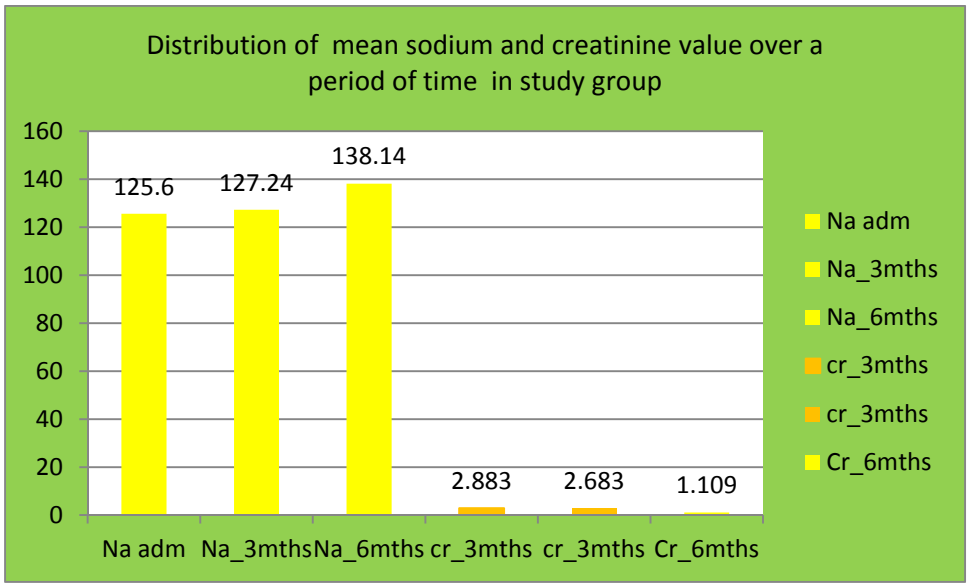
CORRELATION BETWEEN SODIUM AND CREATININE LEVELS

AFTER SIX MONTHS

Na mEg/l	freq	Vaild%	At 6 months	Cr mg/dl	freq	Valid%
130-135	100	100		100	100	100
125-129	0	0		0	0	0
<125	0	0		0	0	0
Total	100	100		100	100	100



STATISTICAL CORRELATION BETWEEN SODIUM AND CREATININE



period		Mean	Std deviation	correlation value(r value)		Pearson correlation test p value
Admission	na	125.68	4.900794	-0.583	Negative correlation	0.0001□
	Cr	2.875	0.46349			
At 3 month	Na	127.24	4.1854	-0.34	Negative correlation	0.001□
	Cr	2.683	0.387704			
At 6 months	Na	138.14	2.778053	-0.301	Negative correlation	0.002□
	Cr	1.109	0.241667			
□ significant p value						

DISCUSSION

This study was undertaken keeping in view of frequent occurrence of htponatremia in acute decompensated heart failure patient who are at highest risk of developing electrolyte disturbance and acute renal failure.

In the present study totally 100 patients are included. Out of 100 patients ,40% (40) were female, 60%(60) were male.

In this study, 16%(16) of patients were presented below 40 years, 62% (62)patients between 40-60 years and 22% (22) patients above 60 years.

In the present study,32% had anemia,54% had history of drug intake,60% had diabetes mellitus,51% had hypertension,55% had coronary artery disease,25% had dilated cardiomyopathy,4% had myocarditis, 14% had valvular heart disease and 20% had arrhythmia.

Some patients had more than one risk factors.hypertension,diabetes mellitus, drug intake and anemia are the most important risk factors associated with acute decompensated heart failure.

At the time of admission in hospital, patient with ADHF had different levels of sodium concentration and different serum creatinine level. patient with severe hyponatremia had more serum creatinine when compared with moderate and mild hyponatremia.

After three months of treatment, some patient became severe hyponatremia with more serum creatinine and some patiend had corrected sodium levels winh minimal cretinine changes. After six months ,maximum number of patient had acceptable variation in serum sodium and creatinine concentration. During six months of observation, patient with severe hyponatremia had repeated attack of dyspnea when compared with mild hyponatremia. The main observation is sodium concentration in patient with ADHF is inversely related to serum creatinine concentration

CONCLUSION

Heart failure is the most common chronic heart related conditions in the developed countrys. It is characterized by specific neurohormonal activation of multiple interrelated systems that can lead to clinical worsening and significant morbidity and mortality. In this regard, hyponatremia occurs due to inappropriate and continued activity of vasopressin despite hypoosmolality and volume overload. Hyponatremia is also due to diuretic use in an attempt to treat volume overload. When hyponatremia occurs, it is a marker of heart failure severity and identifies patients with increased mortality. When the patient with presented with rish factors for CRS 1, renal failure develops.so, hyponatremia leads to CRS 1 .

The recent introduction of specific vasopressin-receptor antagonists o□ers a targeted treatment to these pathophysiological derangements. Some clinical trials with AVP-receptor antagonists have demonstrated an increase in free-water excretion, improvement in serum sodium, modest improvements in dyspnea . So,frequent monitoring of eletrolytes is the important step in the management of heart failure.

SUMMARY

Hyponatraemia is the most common electrolyte disturbance in hospitalized patients in different clinical settings, and is commonly observed in patient with ADHF. It is more common in hospitalized patients with worsening heart failure than in outpatients. .Heartfailure-associated hyponatraemia is frequently hypervolaemic with both body sodium and water are in excess, but the water exeeds sodium.Therefore,hypervolaemic hyponatraemia is a marker of congestion.

The volume overload can predispose to WRF, via several mechanisms such as tissue oedema and intra-abdominal hypertension. Another explanation is general neurohumoral activation including non-osmotic release of vasopressin, and increased levels of plasma renin, angiotensin II, aldosterone, and catecholamines and directly affect renal haemodynamics.

The treatment is mainly based on

- optimization of cardiac function by using beta blockers, ACE inhibitors or ARBs,
- preservation of renal function by blood pressure control, avoiding nephrotoxic drugs,contrast dye and excessive diuresis,
- maintaining appropriate fluid intake by frequent monitoring of eletrolytes
- using vasopressin antagonists.

This study support the concept that hyponatremia is the important risk factor for cardiorenal syndrome type 1 in patients with ADHF.

LIMITATION OF STUDY

- Hyponatremia is independent risk ractor for all system failures.
- This study was conducted in only in tertiary level hospital
- Smaller study group
- The study population involved patients seeking medical care in a tertiary care centre and hence may not represent the general population
- Patient observation was done only for six months
- This study only tell about morbidity of the patient not mortality.

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PROFORMA

Name:

Age / Sex:

Occupation:

Presenting complaints:

Past History:

H/o DM, HT, CKD, CVD, NSAID INTAKE, CAD

Clinical Examination:

General Examination:

Consciousness,

Pallor,

Jaundice,

Clubbing,

Lymphadenopathy,

Hydration status,

Pedal edema

Vitals:

PR

BP

RR

SpO2

Systemic examination:

CVS:

RS:

ABDOMEN:

CNS:

Laboratory investigations:

a)Complete blood count,

b)Renal function test

c)Urine routine,

d)Serum electrolyte,

e)Electrocardiogram,

f)Echo

g)USG abdomen

KEY TO MASTER CHART

ARR--- Arrthythmia

AN---anemia

CA---coronary artery disease

CR---creatinine

DCM---dilated cardiomyopathy

DM---diabetes mellitus

EF---ejection fraction

GFR---estimated glomerular filtration rate

GEN---gender

HE---height

HT---hypertension

ME---medication

MYO---myocarditis

NA---sodium

VHD---valvular heart disease

WT ---weight

																ADMISSION			3 MONTHS			6 MONTHS		
S.N	NAME	HE	WT	AG	GEN	AN	ME	DM	HT	CA	VHD	DCM	MYO	ARR	EF%	NA	CR	GFR	NA	CR	GFR	NA	CR	GFR
1	ganesan	142	55	52	m	A	P	P	P	P	A	A	A	A	42	128	2.2	36.5	133	1.8	44.6	139	1.1	73
2	danapalan	155	63	67	m	A	P	A	A	P	A	P	A	A	35	125	2.9	26.3	129	2.5	30.5	140	0.9	84.8
3	jeyaraman	172	61	68	m	P	P	P	A	P	A	A	A	A	47	130	2.3	31.7	133	2.1	34.7	141	0.8	91.1
4	saroja	165	59	58	f	A	P	A	P	P	A	P	A	A	47	131	2.2	31	128	2.8	24.3	139	1.1	62.06
5	maniselvi	140	43	39	f	P	P	A	A	A	P	A	A	P	41	127	3.1	19.8	130	2.8	21.89	140	1.2	51.07
6	raja	148	51	51	m	A	P	P	P	A	A	P	A	A	49	125	2.9	26.1	130	2.7	27.98	137	0.8	94.43
7	muthu	168	67	48	m	A	A	A	P	A	A	A	A	A	50	134	2.6	39.5	128	3.4	30.17	138	0.9	113.99
8	mani	145	47	35	m	A	A	P	A	A	A	A	P	A	49	133	2.7	30.4	130	3.1	26.5	141	0.9	91.3
9	ramasamy	150	57	61	m	A	P	P	P	P	A	A	A	A	29	130	2.8	26.8	122	3.5	21.4	135	1.1	68.13
10	kandhasamy	157	65	71	m	P	P	A	P	P	A	P	A	A	33	131	2.5	29.9	122	3.2	23.33	136	1.4	53.3
11	saraswathy	140	45	35	f	P	P	A	A	A	P	A	A	P	38	131	2.8	23.9	124	3.3	20.3	137	1.3	51.42
12	lakshmi	131	40	27	f	P	A	A	A	A	P	A	A	A	55	130	2.7	23.7	125	3.2	20	139	1.1	58.13
13	raman	151	49	61	m	P	P	P	P	A	A	A	A	A	49	131	2.6	24.9	128	3.1	20.8	137	1.1	58.73
14	saradha	140	45	54	f	A	P	P	A	A	P	A	A	A	39	129	3.1	17.7	125	3.6	15.3	135	1.1	49.9
15	radha	135	41	21	f	P	P	A	A	A	P	A	A	A	42	128	3.4	20.4	134	2.5	27.7	139	1.4	49.43
16	sankar	164	71	56	m	A	A	P	P	A	A	P	A	A	54	130	3.3	30.2	128	2.9	34.32	136	1.2	82.94
17	kannan	157	58	61	m	P	A	P	P	P	A	A	A	A	46	124	3.4	22.5	133	2.8	27.3	137	1.3	58.8
18	karupayee	152	62	45	f	P	A	A	A	P	A	A	A	A	37	120	3.6	23.2	128	3.1	27	135	1.4	59.68
19	mathi	170	68	58	m	A	P	P	P	A	A	P	A	P	44	119	3.5	26.6	127	2.9	32.1	134	1.3	71.6
20	arivuselvi	155	61	53	f	P	A	A	P	A	A	A	A	P	50	118	3.6	20.9	125	2.8	26.9	143	1.1	68.4
21	gokul	151	49	68	m	A	P	P	A	P	A	A	A	A	41	125	3.3	17.8	130	2.9	20.3	136	0.9	65.4
22	arunachalam	149	61	53	m	A	P	P	P	P	A	A	A	A	39	132	2.1	42.1	128	2.5	35.4	140	0.9	98.4
23	sumathy	157	59	46	f	A	P	P	A	A	A	A	A	A	49	119	2.7	29.1	125	2.1	37.5	142	0.8	98.3
24	samy	153	65	57	m	P	A	P	P	P	A	A	A	P	37	128	2.4	37.5	116	2.8	32.1	139	0.9	100.03
25	vinitha	142	40	18	f	A	A	A	A	A	P	A	A	A	50	126	2.5	27.7	132	2.2	31.5	139	1.1	62.9

26	vijay	156	47	24	m	A	P	A	A	A	P	A	A	A	42	125	2.9	31.4	129	2.5	36.4	140	1.3	70
27	sethupathy	158	69	53	m	A	A	A	P	P	A	A	A	A	35	131	2.2	45.5	128	2.8	35.8	137	1.3	77.06
28	ramkumar	142	43	57	m	A	P	P	P	A	A	P	A	A	48	127	3.1	19.2	130	2.7	22.06	140	1.2	49.63
29	monisha	149	42	21	f	P	A	A	A	A	P	A	A	P	47	130	3.3	21.5	128	2.9	24.5	136	1.2	59.1
30	nithya	157	35	35	f	A	P	A	A	A	A	A	P	A	37	124	3.4	15.3	133	2.8	18.6	137	1.1	47.4
31	ajith	158	43	21	m	A	A	A	A	A	P	A	A	A	41	121	2.9	30.1	130	2.5	34.9	140	1.1	79.5
32	kamala	165	60	68	f	A	P	P	P	A	A	P	A	A	45	120	3.3	18.6	125	2.8	21.9	139	1.3	47.1
33	kumar	158	45	57	m	A	A	A	P	P	A	A	A	A	48	123	3.3	18.9	131	2.9	21.5	136	0.9	69.3
34	gurusamy	164	46	51	m	A	P	P	A	A	A	A	A	P	50	123	2.9	23.6	129	2.5	27.3	140	1.2	56.9
35	perumal	153	58	43	m	A	P	P	P	P	A	A	A	A	44	127	3.3	28.5	118	2.9	32.4	138	1.4	67.1
36	gunasekar	158	62	41	m	A	P	A	A	A	A	P	A	A	49	124	3.1	33	133	2.8	36.6	137	1.4	73.2
37	tamil	169	68	58	f	P	P	P	P	A	P	A	A	A	33	125	2.9	27.3	129	2.5	31.6	140	1.2	65.9
38	meenatchi	157	62	53	f	A	A	P	A	P	A	A	A	A	49	121	2.7	28.3	125	2.1	36.4	142	0.8	95.6
39	dharani	159	45	29	f	A	A	P	A	A	A	A	A	A	48	129	2.4	29.5	116	2.8	25.3	139	0.9	78.7
40	jaiganesh	164	70	54	m	P	A	A	P	P	A	A	A	A	29	125	2.9	34.6	130	2.5	40.2	140	1.1	91.3
41	balaji	157	58	58	m	A	P	P	P	P	A	P	A	A	25	123	2.1	37.8	130	2.5	31.8	140	0.9	88.2
42	balasudharam	154	49	52	m	A	A	P	A	P	A	A	A	A	50	120	2.7	26.7	124	2.1	34.3	142	0.8	89.95
43	anantd	168	61	54	m	A	P	A	P	A	A	A	A	A	49	130	2.4	36.5	116	2.8	31.3	139	0.9	97.3
44	rani	168	67	56	f	P	A	A	P	P	A	P	A	P	40	126	2.5	31.9	132	2.1	38.01	139	1.1	72.6
45	prabakar	148	55	64	m	P	P	P	P	A	A	P	A	A	32	125	2.8	24.9	129	2.5	27.9	140	1.1	63.4
46	marimuthu	156	69	67	m	P	A	P	A	P	A	A	A	A	48	116	3.3	25.5	125	2.8	30	133	1.3	64.7
47	ramalakshmi	148	58	62	f	P	P	A	P	A	A	A	A	A	47	126	3.3	19.5	130	2.9	22.1	136	0.9	71.3
48	balakumar	165	70	61	m	A	A	P	A	P	A	A	A	P	50	125	2.9	31.8	129	2.5	36.9	148	1.3	71
49	sudha	155	59	49	f	A	P	P	P	A	A	P	A	A	35	131	2.2	34.6	128	2.8	27.2	135	1.3	58.6
50	sudhasan	144	52	46	m	A	A	P	A	P	A	A	A	A	40	127	3.1	26.3	130	2.5	32.6	142	0.9	90.6

51	lokesh	171	65	48	m	A	P	P	P	P	A	A	A	A	44	130	3.3	24.5	128	2.9	27.9	136	1.5	53.9
52	kannagi	175	70	57	f	A	A	P	A	A	A	P	A	A	46	124	3.4	19.7	133	2.8	23.9	137	1.5	44.5
53	selvam	145	65	49	m	A	P	A	P	P	A	A	A	A	39	120	3.6	22.2	125	2.8	28.6	136	1.1	72.74
54	yasodha	165	61	68	f	P	A	A	A	A	A	A	P	A	48	127	3.4	14.9	134	2.4	21	139	1.1	45.9
55	begam	149	55	48	f	P	P	P	A	P	A	A	A	A	30	121	2.9	20.1	125	2.7	21.6	136	1.1	52.9
56	ramesh	158	67	57	m	A	A	A	P	A	A	A	A	A	32	129	3.3	22.8	130	2.9	25.9	136	0.9	83.6
57	amutha	157	60	68	f	A	P	P	P	P	A	A	A	A	30	118	3.6	13.8	125	2.6	19.1	133	1.1	45.2
58	ramprabhahar	159	64	49	m	A	P	P	P	A	A	A	A	P	32	131	2.7	29.2	126	2.1	37.5	142	0.8	98.5
59	srinivasan	167	69	51	m	A	A	A	A	P	A	P	A	A	47	129	2.4	34.6	125	2.8	29.7	139	0.9	92.3
60	marisevi	166	59	53	f	A	A	P	P	A	A	A	A	P	44	121	3.6	16.4	128	2.8	26.6	136	1.5	39.4
61	murali	165	65	65	m	A	P	P	P	P	A	P	A	A	30	130	3.3	20	133	2.9	28.7	136	1.5	43.96
62	manokar	158	62	58	m	A	P	P	A	P	A	A	A	A	36	124	3.4	20.2	130	2.8	31.1	137	1.5	45.9
63	praveen	168	70	53	m	P	P	P	A	P	A	A	A	A	46	125	2.9	28.4	132	2.5	41.6	140	1.1	74.9
64	sugadev	149	55	52	m	A	P	A	P	A	A	A	A	A	49	120	3.6	18.2	127	2.8	29.5	133	1.1	59.5
65	manoj	158	60	68	m	A	A	P	A	P	A	A	A	P	42	134	2.6	22.5	130	3.4	21.7	138	1.9	30.8
66	karuppasamy	157	68	69	m	A	P	P	P	A	A	A	A	A	49	133	2.7	24.2	127	3.1	26.6	141	0.9	72.6
67	leela	169	55	64	f	A	P	A	P	P	A	P	A	A	39	130	2.8	17.2	129	3.5	17.4	135	1.3	37
68	nirmala	159	60	48	f	P	P	P	A	P	A	A	A	A	44	118	3.3	19.2	124	2.8	28.6	133	1.2	52.9
69	devi	157	58	49	f	A	A	P	P	P	A	P	A	P	36	132	2.1	29	121	2.5	30.7	140	0.9	67.4
70	priya	145	53	43	f	P	A	P	P	A	P	A	A	A	34	119	2.7	21.9	130	2.1	35.5	142	0.8	73.9
71	hemalatha	158	57	47	f	A	A	A	A	P	A	P	A	P	35	128	2.4	25.4	122	2.8	27.5	139	0.9	67.7
72	natarajan	168	69	58	m	P	P	P	P	P	A	A	A	A	31	128	2.5	30.6	133	2.2	43.9	139	1.1	69.6
73	nagarajan	168	67	51	m	A	A	A	P	P	A	P	A	P	38	125	2.7	29.9	128	2.5	40.7	140	1.3	62.1

74	nathiya	162	64	53	f	P	A	P	P	P	A	A	A	P	28	118	3.6	17.8	125	2.7	29.9	133	0.9	71.1
75	yamuna	163	62	67	f	A	P	P	A	P	A	A	A	A	46	118	3.3	15.8	123	2.8	23.5	133	0.6	86.7
76	krishnan	152	59	60	m	A	A	P	P	P	A	A	A	A	37	125	2.8	22.8	131	1.9	42.4	136	0.9	70.9
77	subbulakshmi	153	60	50	f	P	P	A	P	P	A	A	A	A	49	118	3.2	19.4	124	2.8	28.1	133	1.1	56.5
78	ramamoorthy	157	64	50	m	A	A	P	P	A	A	P	A	A	50	131	2.2	35.4	120	2.8	35.2	135	1.5	51.9
79	bramman	166	70	55	m	P	A	P	A	P	A	A	A	A	45	127	3.1	26	130	2.7	37.6	139	1.3	61.9
80	sathyan	170	74	44	m	A	A	P	P	P	A	A	A	A	25	132	2.1	45.8	127	2.4	50.6	140	0.9	106.7
81	jeyaprakash	158	60	58	m	A	P	P	A	P	A	A	A	A	48	119	2.7	24.7	127	2.1	40.2	142	0.8	83.2
82	pothiraj	158	68	54	m	A	P	A	A	P	A	A	A	A	48	128	2.4	33	119	2.8	35.7	139	0.9	87.9
83	lavanya	147	58	53	f	A	P	P	P	P	A	P	A	P	32	126	2.5	23.2	131	1.8	40.7	139	1.1	52.8
84	sugumar	168	65	51	m	A	A	P	A	P	A	P	A	A	40	118	3.2	24.5	124	2.8	35.2	137	1.1	71.1
85	saravanan	168	63	68	m	P	A	A	A	P	A	A	A	A	42	132	2.1	30	125	2.5	30.9	140	0.9	70
86	maya	150	45	20	f	A	A	A	A	A	P	A	A	A	50	119	2.4	26.6	130	2.1	37.3	142	0.8	79.7
87	rajakumari	155	50	29	f	P	A	A	A	A	P	A	A	P	40	118	3.6	18.2	127	2.8	28.8	133	1.1	59.5
88	muthukrishnan	155	54	49	m	A	A	A	P	A	A	A	A	A	35	125	3.3	20.7	132	1.9	44.2	136	0.9	75.8
89	kannusamy	144	50	68	m	A	A	A	P	P	A	A	A	A	39	118	2.9	17.2	124	2.5	24.6	136	1.5	33.3
90	sundhari	162	60	57	f	P	A	P	A	P	A	A	A	A	37	134	2.6	22.6	122	3.4	21.3	138	1.9	30.9
91	kumari	153	68	58	f	A	P	P	A	A	A	P	A	A	34	133	1.7	38.7	121	3.1	26.1	141	0.9	73.1
92	divya	150	72	31	f	A	A	A	A	A	A	A	P	A	50	130	2.8	33.1	123	3.5	32.5	139	1.1	84.2
93	prabu	177	75	66	m	A	P	P	P	P	A	A	A	A	47	125	2.9	26.6	132	2.5	37.9	140	1.3	59.3
94	sathyan	166	65	55	m	A	P	P	P	P	A	A	A	A	25	118	3.6	21.3	125	2.8	33.7	138	1.1	69.7
95	hema	158	55	28	f	P	P	A	A	A	P	A	A	P	45	133	2.1	34.6	121	2.5	35.7	140	0.9	80.8
96	rajasekar	148	50	40	m	A	A	P	P	P	A	A	A	A	29	119	2.7	25.7	129	2.1	40.7	142	0.8	86.8

97	rajesh	153	51	49	m	A	P	A	P	A	A	A	A	A	30	130	2.4	26.9	120	2.8	28.3	139	0.9	71.6
98	rajathi	146	48	48	f	P	P	P	A	P	A	P	A	A	31	126	2.5	20.9	131	2.1	30.5	139	1.1	47.4
99	senthil	169	68	60	m	A	A	P	P	A	A	A	A	A	32	120	3.6	21	125	2.8	33.2	133	1.5	50.4
100	ramajeyam	175	74	57	m	A	P	P	A	P	A	A	A	P	25	124	2.9	29.4	131	2.5	41.9	140	1.1	77.5

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Name of the Candidate	:	Dr.V.Nareshkumar
Course	:	PG in MD., General Medicine
Period of Study	:	2015-2018
College	:	MADURAI MEDICAL COLLEGE
Research Topic	:	A study of Hyponatremia in acute heart failure patients in predicting the acute cardio-renal syndrome type 1
Ethical Committee as on	:	27.07.2017

The Ethics Committee, Madurai Medical College has decided to inform that your Research proposal is accepted.

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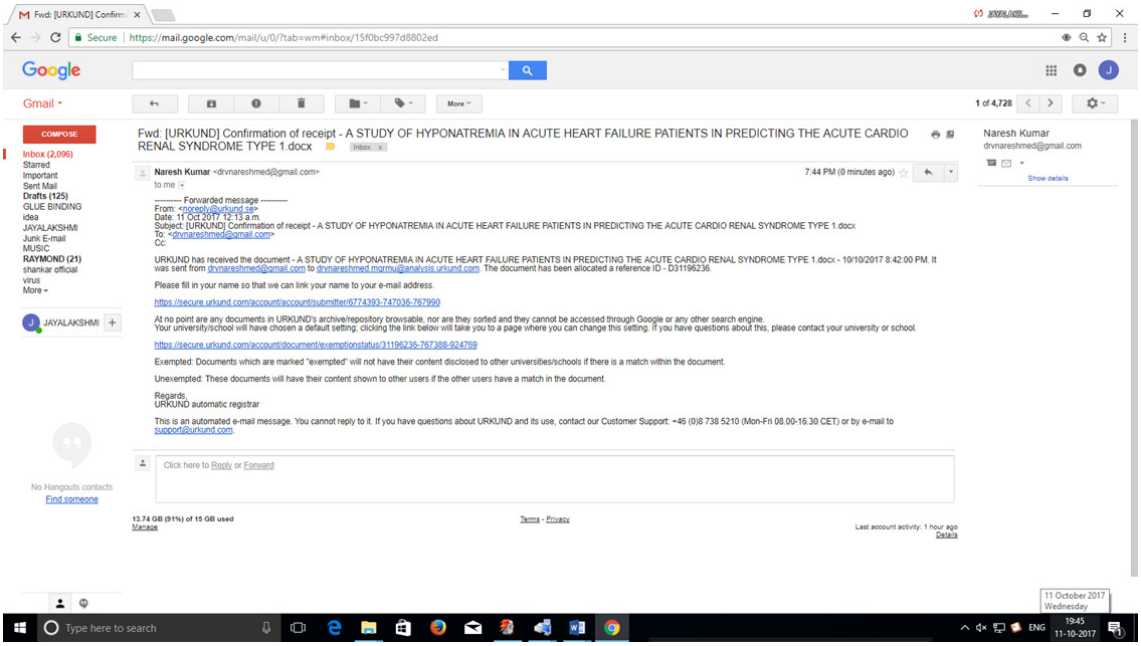
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