International Journal Publishing
INFLUENCE: International Journal of Science Review
Volume 5, No. 1, 2023
https://influence-journal.net/index.php/influence/index

Research Article

Ischemic Stroke, Aortic Stenosis, Heart Failure with Complications Anemia and Hyponatremia

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Academic Editor: Nguyen Ngoc Anh

Abstract. Ischemic stroke is a circulatory disorder in brain is caused by reduced or stopped blood flow in some areas of brain. Aortic stenosis is a heart valve disorder characterized by remodeling progressive fibro-calcification and thickening of the aortic valve leaflets over the years, evolves that occur in an early aortic valve (tricuspid) or an abnormal aortic valve (bicuspid) cause severe obstruction to cardiac outflow. Heart failure is a complex clinical syndrome that can occur as result of heart problem structural or functional impairment that impairs the ability of the ventricles to fill or secrete adequate amounts of blood to meet the metabolic demands of the tissues. The patient had a diagnosis of compensatory dyspnea et causa aortic stenosis, right hemiparesis, and repair aphasia delivered to the laboratory from neurorestoration room on January 9th, 2018 for a complete hematology and electrolyte examination (Na+,K+, Cl-).

Keywords: *Aortic, Failure, Heart, Ischemic, Stenosis, Stroke.*

A. INTRODUCTION

1. Aortic Stenosis

Aortic stenosis is a heart valve disorder characterized by remodeling progressive fibro-calcification and thickening of the aortic valve leaflets over the years, evolves that occur in an early aortic valve (tricuspid) or an abnormal aortic valve (bicuspid) cause severe obstruction to cardiac outflow. Aortic sclerosis is in the preclinical phase from calcified aortic valve disease, namely focal areas of calcified valves and leaf thickening valves without significant obstruction to cardiac blood flow [1].

Other risk factors, namely metabolic syndrome, diabetes mellitus, hypertension, smoking and increased plasma Lp (a).

Aortic valve consists of 3 cusps located at base of aorta, called based on its location, namely left coronary, right coronary, and non-coronary. Each valve leaf it consists of valvular interstitial cells, smooth muscle cells and endothelial cells. Calcification process preceded with endothelial damage. Occurrence of endothelial damage can be triggered by several factors, such as lipid-derived species, cytokines, mechanical stress, and radiation. Injured endothelium will undergo changes in the form of increased permeability to lipoproteins, especially low-density lipoprotein (LDL) and lipoprotein(a) (Lp(a)). Lipoprotein accumulation in fibrous layer and then will undergo oxidation due to uncoupling of nitric oxide synthase (NOS) triggers production of reactive oxygen species (ROS), which increases Lipid oxidation and cytokine secretion trigger the invasion of inflammatory cells into the aortic valve. On aortic valve lipoproteins (i.e., LDL and Lp(a)) are converted to lysophospholipid derivatives by lipoprotein

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phospholipase A2 (Lp-PLA2) and ectonucleotide pyrophosphatase/phosphodiesterase 2 (ENPP2; also known as autotaxin (ATX)). The next stage is mineralization and calcification. Autotaxins secreted by the interstitial cells of the valves also change lysophosphatidylcholine (lysoPC) to lysophosphatidic acid (lysoPA). Some of these factors, namely lysoPA, the receptor activator of the nuclear factor-ÿB ligand (RANKL; also known as TNFSF11) and WNT3a cause the transition from valve interstitial cells to osteogenic. Arachidonic acid (AA) is produced by the cytosol producing PLA2 eicosanoids (prostaglandins and leukotrienes) via the prostaglandin G/H synthase 2 (PTGS2; also known as COX2) and 5-lipoxygenase (5-LO). Eicosanoids promote inflammation and mineralization. Kimase and angiotensin-converting enzyme (ACE) increases the production of angiotensin II, which increases the synthesis and secretion of collagen by valve interstitial cells. Increased production of matrix metalloproteinases (MMPs) and decreased synthesis of tissue metalloproteinase inhibitors (TIMPs), causing tissue irregular fibrous deposits accumulate in the aortic valve. Microcalcification process is initiated by microvesicles secreted from valve interstitial cells and macrophages. Plus, expressions overexpression of ectonucleotidases (ENPP1, 5ÿ-nucleotidase ecto (NT5E)) and alkaline phosphatases (ALP) causes apoptosis and mineralization. Bone morphogenetic protein 2 (BMP2) cause osteogenic transdifferentiation, which is related to factor expression bone transcription factors (eg, runt-related transcription factor 2 (RUNX2) and protein homebox MSX2). Cells that resemble osteoblasts lead to the calcification process the aortic valve continues with the formation of skeletal bone. Matrix deposition mineralization is accompanied by fibrosis and neovascularization is supported by factors vascular endothelial growth (VEGF). Neovascularization increases recruitment of cells inflammatory and bone marrow-derived osteoprogenitor cells, as shown in Figure 1. A2AR, A2A adenosine receptor; sPLA2, PLA2 secretor; LPAR, acid receptor lysophosphatidate; Ox-PL, oxidized phospholipids; Ox-LDL, oxidized LDL; TGFÿ, transforming growth factor-ÿ; TNF, tumor necrosis factor [1].

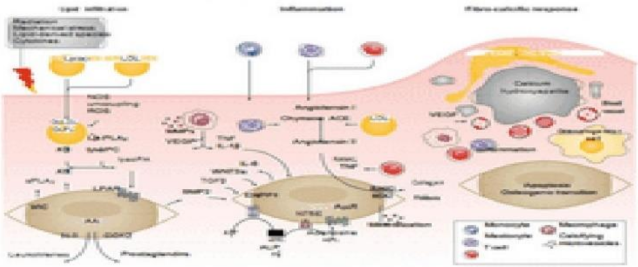

Figure 1. Pathogenesis of AS calcification
Source: Lindman BR, Clavel MA, Mathieu P, Lung B, Lancellotti P, Ptto CM, et all. Calcific Aortic Stenosis. www.nature.com/ndrp. Vol. 2. 2016. p.1-27.

Diagnosis of aortic stenosis is made by echocardiography demonstrates anatomy of heart valves and blood flow. The normal aortic valve has a gradient only a few mm Hg. The decreased valvular area causes an increased gradient pressure, and this parameter is used to classify and grade aortic stenosis as mild, moderate or severe, as shown in Table 1 [1,2].

Table 1. Gradient of aortic stenosis[1]

	Average (mmHg)	Aortic Valve Area (cm^2)
Light	< 25	>1.5
Moderate	25 – 40	1.0 - 1.5
Critical	> 40	<1.0
Awfully	> 70	<0.6

Gold standard for the diagnosis of aortic stenosis is a non-invasive examination with echocardiography. Doppler echocardiography is a cardiac chamber catheterization that provides a definitive diagnosis stenosis. Cardiac catheterization is used when there is a discrepancy between of clinical features and non-invasive examination. However, this invasive procedure increases the risk of bleeding and cerebral embolism.

Echocardiogram (Cardiac ultrasound) is the best non-invasive way to evaluate the anatomy and function of aortic valve.

Aortic stenosis is nonspecific on ECG. ECG pattern can show if there is left ventricular hypertrophy, disorders of the heart's electrical conduction system, such as left bundle branch block due to the calcification process in aortic stenosis [1,2].

X-ray chest can help in the diagnosis and determine the severity disease, degree of valvular calcification, and left ventricular condition [1,2].

Other imaging techniques, namely Positron emission tomography (PET) are combined with multiple detector computed tomography (MDCT) (PET-MDCT) with 18F marker sodium fluoride (18F-NaF), and Cardiac magnetic resonance (CMR) [1].

Blood biochemical markers are useful for detecting left ventricular dysfunction, namely the measurement of type B natriuretic peptide (BNP) levels.

Other blood biochemical markers, such as high sensitive cardiac troponin (hs-cardiac troponin), growth-differentiation factor 15 (GDF15), soluble IL-1 receptor-like1 (IL-1RL1; also known as ST2) and miRNAs$_{196\text{-}198}$ [1].

2. Ischemic Stroke

Stroke is a circulatory disorder in the brain characterized by neurological deficits that appear suddenly, occur for at least 24 hours.

Stroke can be classified based on the cause, duration of the attack, and the vascular system affected blood. Based on the cause, strokes are classified into two groups, ischemic stroke which is the cause of most cases of stroke (85%) and stroke bleeding occurs in 15% of cases. Ischemic stroke is a circulatory disorder in brain is caused by reduced or stopped blood flow in some areas of brain. It can be caused by thrombotic lesions resulting from atherosclerosis and by emboli that have detached from the lesions atherosclerosis in the heart or cerebral arteries. This circulatory disorder results in impaired brain function and if there is severe interference it can result death of some brain cells is called infarction [3,5-8].

Based on the duration of the attack, stroke is classified as transient ischemic attack (TIA) and stroke that is irreversible or completed stroke. TIA also known as transient brain attacks last less than 24 hours and resolve on their own. Stroke occurs when the neurological deficit continues [7,8].

Based on vascular system affected, stroke can affect anterior circulation, posterior circulation, and small vessels, which will show clinical signs different. The blood vessels included in the anterior circulation are the internal carotid arteries and its branches, while those included in the posterior circulation include arteries vertebral, basilar arteries, and posterior cerebral arteries.

Many factors can affect flow of blood in brain, including [3] :

1. State of pulse or arteries, arteries can be narrowed by the process of atherosclerosis or occluded by a thrombus or embolus. Blood vessels can also be compressed by movement and calcifications in cervical spine.
2. Blood conditions can also affect blood flow and oxygen supply. That blood increased viscous, increased blood viscosity, increased hematocrit (eg in polycythemia) can slow blood flow. In severe anemia, oxygen may also decrease.
3. Cardiac abnormalities can lead to brain ischemia. If the heart rate is irregular and inefficient then cardiac output will decrease and result in blood flow reduced in brain.

Stroke is caused by atherosclerosis. Ischemic stroke in the age group over 45 years, most often caused or present relation to atherosclerosis. Atherosclerosis means hardening of the arteries. It is used for a group of disorders that cause thickening of arteries reduced flexibility (elasticity) of arterial wall which is a process that occurs for 3 years.

Process of atherosclerosis is preceded by endothelial dysfunction, then which continues with formation of fatty streaks, fibrous plaques, advanced compound lesions (advanced, complicated lesion), until complications arise [12-15].

Cell death in cerebral infarction occurs by two different pathways, namely necrotic and apoptotic pathways. In the necrotic pathway, cytoskeletal damage occurs rapidly due to energy disturbances in the cell. Ischemia of a lesser degree, such as seen in ischemic penumbra, it is more likely cause cell death by apoptotic pathway that occurs within days or weeks.

Cell death by necrotic pathway is the result of a series of events such as those shown in Figure 3. Ischemia will cause a decrease in energy production so that the cell's need for energy is not met. As a result, damage occurs mitochondria accompanied by the formation of oxygen radicals. In addition, disruption of energy availability will cause interference with ionic pump function, resulting in an increase in ion levels intracellular sodium, chloride, and calcium. The increase in the levels of these three ions is also due to the activation of kainate receptor, alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA), and N-methyl-D-aspartate (NMDA) by glutamate and excitotoxin stimulation released during ischemia. An increase in intracellular ion level causes protease stimulation resulting in damage to the cytoskeleton and DNA as well as stimulation phospholipase resulting in the release of prostaglandins and leukotrienes. Various events This will cause damage to the cell membrane and release of cytosolic contents. Necrotic cell death is often accompanied by inflammation and detachment inflammatory mediators that can affect normal cells adjacent to injured area.

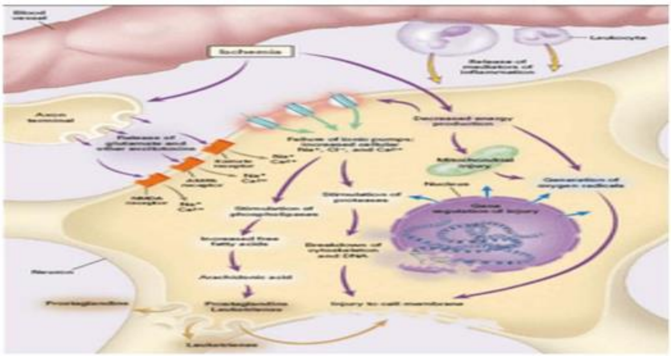

Figure 3. Mechanism of neuron damage due to acute cerebral ischemia
Source: Brott T, Bogousslavsky J. Treatment of acute ischemic stroke. N Eng J Med. 2000;343(10):710-22.

There are several important aspects in the diagnosis of stroke, namely determining whether symptom that arise due to stroke, TIA or other conditions that resemble a stroke (stroke mimics), determine whether the patient is having a haemorrhagic or ischemic stroke, as well as determine the etiology and risk factors in the patient, which will be useful for treatment patients and secondary prevention. In stroke, it is also necessary to assess the severity of the disease predict prognosis.

Diagnosis of stroke is established based on the results of clinical and radiological examinations. On clinical examination may reveal partial or complete loss of brain function. Partial loss of brain function can take the form of paralysis of the limbs or other muscles half of the body, aphasia, or other symptoms depending on the part of the brain that is affected. Complete loss of brain function can range from loss of consciousness to coma, on commonly occurs in hemorrhagic strokes. Stroke needs to be differentiated by various circumstances others with similar symptoms, such as hypoglycemia, brain tumor, brain abscess, head injury, migraine, epilepsy, and multiple sclerosis [9,15,19].

Radiological examination that is widely used for the diagnosis of stroke is computed tomography scans (CT scans) and magnetic resonance imaging (MRI). CT examination used to identify or rule out bleeding as a cause of stroke and can also identify tumors, abscesses, or other processes that mimic stroke. However, examinations carried out within the first few hours after infarction are usually show no abnormal features, and infarction may not be seen for up to 24 or 48 hours after the attack. MRI can reliably detect the location and extent of infarction throughout area of brain and it can detect bleeding. Constraints to the inspection include taking a long time, not being widely, available, and being expensive.

Ideal biochemical markers for diagnosis, monitoring, and prognosis of stroke must be met the following criteria: specific for the brain, can be detected in the blood of patients with acute stroke, presenting early within a few hours after the attack, reflect peak levels extent of brain damage, can differentiate between stroke and TIA, hemorrhagic and ischemic stroke, the area of the lesion and the penumbra, and can predict functional outcome biochemical markers of stroke that are directly related to central nervous system abnormalities, viz protein S-100B[23,28,29], neuron specific enolase (NSE)[28], fatty acid binding protein (FABP), glia fibrillary acid protein (GFAP)[30-32], myelin basic protein (MBP) [35], PARK7[36,37], and nucleoside diphosphate kinase A (NDKA) [37].

3. Heart Failure

Heart failure is a complex clinical syndrome that can occur as result of heart problem structural or functional impairment that impairs the ability of the ventricles to fill or secrete adequate amounts of blood to meet the metabolic demands of the tissues [39,42].

Based on the patient's functional capacity, *New York Heart Association* (NYHA) established the commonly used classification of heart failure. This classification is subjective and used to assess the severity of the disease [39-41,43,44].

Process occurrence of heart failure is associated with decreased cardiac output and increased cardiac filling pressure. In the acute setting, a low cardiac output will stimulate the baroreceptor reflex resulting in neurohormonal activation, namely activation sympathetic system, the renin-angiotensin-aldosterone system (RAAS), which will maintain arterial perfusion to vital organs. Sympathetic system activation will increase contractility myocardium, pulse and peripheral vasoconstriction to maintain cardiac output. Meanwhile, activation of the renin-angiotensin-aldosterone system causes vasoconstriction (angiotensin) and increase blood volume by retention of salt and water (aldosterone). There was also an increase in vasopressin and natriuretic peptides. Further circumstances will lead to progressive dilatation of the heart and changes in the structure of the heart called remodeling [39-41,46].

In addition to the classification according to the NYHA, the classification of heart failure is also determined according to American College of Cardiology / American Heart Association (ACC / AHA) for complement the NYHA classification system. This classification assigns risk factors to occurrence of heart failure and intervention therapy as reduce mortality and morbidity of heart failure [39-41,43,45].

Remodeling is a process that starts at the cellular level which is marked by myocyte hypertrophy, imbalance between proliferation and degradation of extracellular matrix, apoptosis and changes in myocyte function.

This process will cause a change in geometry and the structure of the left ventricle in the form of ventricular dilatation and hypertrophy so that shape of the ventricles become more spherical changes in the size and structure of the ventricles will increase the stress hemodynamics on the ventricular wall and increases regurgitant flow through the valve mitral. This situation will lead to a decrease in heart function either decrease contractility and cardiac output [39,46].

The diagnosis of heart failure is based on clinical signs and symptoms, and is supported by appropriate examinations such as ECG, X-rays of the lungs, biomarkers and echocardiography, as seen in Figure 5 [39-41]. The patient should be classified according to the dysfunction criteria systolic or diastolic and in left or right heart failure class.

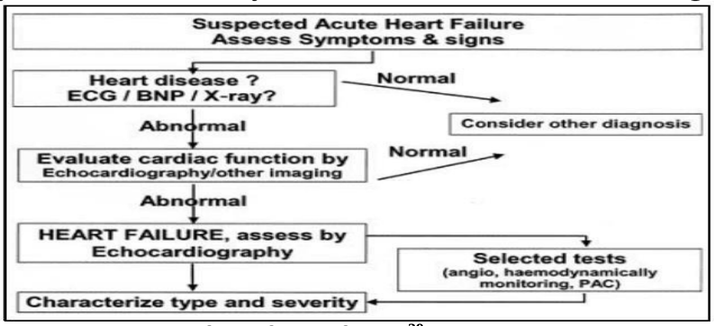

Figure 5. Diagnostic flow of heart failure[39]

Source: Immanuel S. The role of MR pro ADM and MR pro ANP as markers of heart failure. Osman F, editor. In: Clinical Pathology Continuing Education; 2010. p.215-37.

BNP is a hormone that belongs to the natriuretic peptide group.Natriuretic peptide reflects neurohormonal activation. Another natriuretic peptide is a type A (atrial) natriuretic peptide produced primarily by the atria. Natriuretic peptide type B (brain) is generated primarily by the ventricles. C-type natriuretic peptide is produced by vascular endothelium.

Natriuretic peptide levels were increased in conditions including stretching of the heart wall, the addition of excessive fluid volume (i.e. in: heart failure, renal failure, primary hyperaldosteronism), and decreased peptide clearance (renal failure) [43,47].

BNP and NT-proBNP are secreted into the circulation in equivalent amounts an increase in BNP levels also reflects an increase in NT-proBNP levels in the blood. Theoretically, the NT-proBNP examination is superior to BNP because of the NT content proBNP is higher and more stable [43].

Heart failure causes the release of other biologic markers, including adrenomedulin. Adrenomedulin is a peptide with 52 amino acids that belongs to the superfamily calcitonin gene related peptide (CGRP). Adrenomedulin is increased in heart failure and after myocardial infarction. Mid-regional proADM (MR-proADM) fragment is more stable in circulation and can be a marker of cardiac status. Compared to NT-proBNP,

Fragment MR-proADM has similar sensitivity but less specificity. Rather, as superior prognostic markers even in patients with mild clinical symptoms. ANP is a hormone whose secretion is triggered by cardiac dilation but has time half-life of 2.5 minutes making it difficult to measure. Mid-regional proANP is the result of a breakdown proANP, namely amino acids 31-67 which are more stable in circulation. Compared with NT-proBNP, MR-proANP assays provide equivalent performance for diagnosis of heart failure, but it has a better prognostic value. Check use MR-proADM and MR-proANP add diagnostic and prognostic power in failure heart [39].

Other biochemical markers of heart failure, namely growth stimulation expressed gene 2 (ST2). ST2 is a protein that is part of the interleukin-1 (IL-1) receptor family. It has two isoforms, namely the transmembrane receptor form (ST2L) and the soluble ST2 (sST2). In heart failure, ST2 levels will increase in the presence of a stretch stimulus cardiomyocytes. Initially interleukin-33 (IL-33) which binds to the ST2L receptor will protect heart muscle against right ventricular hypertrophic changes when the heart gets excessive pressure. Conversely, high levels of sST2 in the circulation cause blockade of the anti-hypertrophic effect. Superiority of the sST2 marker over NT-proBNP is that this examination is not influenced by various conditions such as gender, hypoxemia, renal dysfunction, metabolic risk factors, cirrhosis of the liver with ascites, and sepsis. Various studies state ST2 as a strong predictor for assessing heart failure progression and prognosis, associated with increased mortality as well can be used as monitoring to monitor improvement in heart failure after treatment[40]. Another new biochemical marker for heart failure is copeptin. Copeptin or C terminal part of provasopressin is a neurohormone that is secreted together with origin of vasopressin (AVP) from the hypothalamus in response to hypovolemia and increased plasma osmolality. Increased copeptin in heart failure is associated with increased mortality, risk of hospitalization, and severity of heart failure. Copeptin can add prognostic value to predictors that are currently being used ie clinical variables and natriuretic peptides [41]. Biochemical markers of heart failure development are important in detecting abnormalities from the outset as a preventive aspect. One of the biochemical markers for remodeling extracellular matrix is galectin-3 (Gal-3). Galectin-3 is ÿ-galectoside-binding lectins that mediate cell-to-cell and cell-to-extracellular matrix interactions, and act as a new chemoattractant against monocytes and macrophages. He plays an important role in Fibrosis conditions including those of the heart. Cardiac fibrosis can cause myocyte abnormalities, heterogenesity and tissue dyssynchrony, ventricular dilatation, and contractile dysfunction. Fibrosis Myocardial infarction can cause great arterial stiffness which can lead to dysfunction diastolic and heart failure. High levels of Gal-3 are associated with onset of atrial fibrillation (AF). Elevated Gal-3 levels are also considered an important activator and marker of inflammation atherosclerosis in coronary artery disease. Gal-3 can be considered as a marker for clinical assessment of the prognosis of chronic heart failure [42].

4. Anemia in Heart Disorder

Anemia is common in aortic stenosis and its prevalence increases with age severity of aortic stenosis. Anemia will result in decreased tissue perfusion, hypertrophy left ventricle and increased interstitial fibrosis. Untreated anemia will occur heart failure. If anemia is accompanied by aortic stenosis, the failure will worsen heart, due to decreased myocardial perfusion, increased oxygen demand and myocardial ischemia occurs. The risk of death from aortic stenosis with anemia is two times that without anemia.

It is known that anemia is associated with heart failure, but the target of treatment for anemia in heart failure is not yet accurate. Heart failure with more anemia found in old age, NYHA functional class III and IV, more drug consumption and with more co-morbidities, such as diabetes mellitus, kidney disease chronic disease and hypertension, as well as more frequent and longer hospital stays [49].

Renal hypoxia becomes a stimulus to secrete erythropoietin. Blood pressure drop mean arterial will activate the sympathetic nerves that trigger systemic vasoconstriction and activates the renin-angiotensin-aldosterone system (RAAS) resulting in fluid retention which causes hemodilution. Eventually there is a decrease in renal flow and filtration rate glomerulus. The presence of hemodilution causes a poor prognosis because it is associated with more severe decompensation, and reduced distribution of oxygen in the tissues. Anemia cause remodeling of the heart due to cardiomyocyte apoptosis. Ischemia myocardium will secrete cytokines such as TNF-ÿ. Cytokines interfere with erythropoiesis several ways, including inhibiting the production of erythropoietin (EPO), interfering with function EPO and affect the success of treatment. From a study found linear relationship between death rate and hemoglobin level. Reported each 1g/dL increase in hemoglobin in anemia reduces the risk of death within 1 year by 40% and reduces the risk of hospital admission with heart failure by 21% [49].

Several causes of anemia in heart failure, including nutritional deficiencies such as iron deficiency iron, pro-inflammatory cytokines and angiotensin converting enzyme inhibitors (ACE) drugs inhibitors), angiotensin receptor blockers (ARBs) and cyclooxygenase inhibitors (COX inhibitors), as shown in Figure 7 [49]:

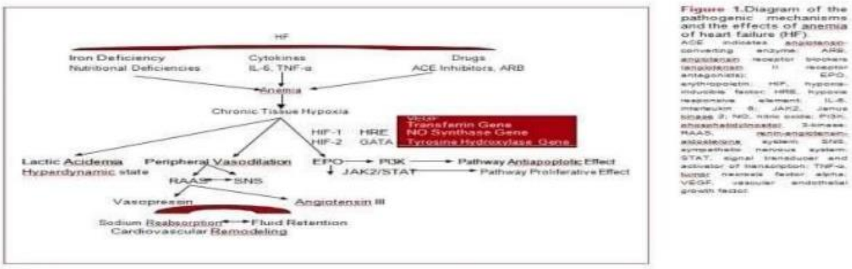

Figure 6. Pathogenesis of anemia in heart failure

Caramelo C, Just S, Gil P. Anemia in Heart Failure: Pathophysiology, Pathogenesis, Treatment, and Incognitae. Rev Esp Cardiol 60(8); 2007.p. 848-60.

There are two types of iron deficiency anemia, namely marked absolute iron deficiency anemia by iron deficiency with a normal erythropoietin response and iron deficiency anemia functional, namely anemia of chronic disease (ACD) and ACD with iron deficiency which characterized by iron deficiency with suboptimal response to EPO. Response to Suboptimal EPO can be caused by increased cytokines such as IL-1ÿ, TNF-ÿ, IL-6; production reduced endogenous EPO; and reduced sensitivity of the erythrocyte precursor response to endogenous or exogenous EPO [50].

Iron deficiency anemia needs to be differentiated from thalassemia ÿ trait based on saturation transferrin, serum ferritin level, body iron stores, and hemoglobin electrophoresis [50].

Diagnosis of ACD with iron deficiency is very difficult to enforce because of the backup ACD iron increases while iron deficiency iron stores decrease. To know in the presence of ACD with iron deficiency, the sTfR (mg/L) / log ferritin (ÿg/L) ratio was used. Ratio >2 is found in chronic iron deficiency anemia and latent deficiency anemia. Ratio <2 found in functional deficiency anemia. Based on Thomas criteria, then in case with ACD given Epo treatment, where as in iron deficiency anemia with ACD given Epo and iron. In latent and chronic iron deficiency anemia [50].

The result of Ret-He, serum iron (SI) and ferritin can be included in the plot stated by Thomas, et al. The plot is used to help establish anemia iron deficiency and anemia of chronic disease and follow the results of treatment. In a state of normal limit value of iron deficiency if Ret-He <25.0 pg [51].

Mechanism by which ACE inhibitors and ARBs induce anemia is by decreasing EPO synthesis endogenous, decreased response to EPO, inhibition of erythroid precursor growth, changes in response to treatment with recombinant human EPO (rHuEPO), decreased levels of IGF-1 and inhibition of catabolism of N-acetyl-seryl-aspartyl-proline, namely peptides that reduce the proliferation of series precursor erythrocytes [49].

Hyponatremia is a condition where there is a relative excess of fluid. it happens when (1) Amount of water intake exceeds the ability to excrete and (2) Inability to suppress secretion of anti-diuretic hormone (ADH), for example in the loss of water through the gastrointestinal tract, heart failure and cirrhosis of the liver or in inappropriate antidiuretic hormone (SIADH) syndrome.

5. Hyponatremia in Heart Failure

Hyponatremia makes it difficult to treat heart failure, causing prolonged hospitalization and death. Hyponatremia must be differentiated from depletion or dilution [52].

Hyponatremia induced by administration diuretic drugs, which increase sodium excretion, often concomitant with loss potassium/magnesium. Treatment is given isotonic saline and potassium/magnesium if the levels are low. Meanwhile, dilutional hyponatremia is caused by excess water excretion impaired, resulting in dilutional hyponatremia. If isotonic saline is given, reduce serum sodium concentration. Free water excretion is achieved by sodium reabsorption in distal nephron segment with low water permeability, mechanism-damaging diuretic drugs. This is thiazide class and a mineralocorticoid receptor antagonist so it should be avoided. it is advisable to give drugs that work proximally, such as acetazolamide and loop diuretics agents. Vasopressin antagonists, which promote low water permeability in the duct coligentes, free water excretion occurs, but is still under investigation for the treatment of dilutional hyponatremia in heart failure [53].

B. RESULT AND DISCUSSION

A 59-years-old male patient was brought to the laboratory from the neurorestoration room on January 9th, 2018 for a complete hematology and electrolyte examination (Na+, K+ Cl-) with clinical description of compensatory dyspnea et causa aortic stenosis, right hemiparesis, and repair aphasia.

Laboratory Examination Results January 9th, 2018

Check Type	Flag	Results	Unit	Reference value
Complete hematology				
Hemoglobin (Hgb)	*	11,4	g/dL	13-16
Hematocrit	*	32	%	40-48
Erythrocyte	*	3.7	10^6 /uL	4.5-5.5
Relative Reticulocyte	*	2.2	%	0.5-2.0
Absolute Reticulocyte		8.2	10^3 /uL	2.4-11
MCV		87	fL	82-92
MCH		31	Pg	27-31
MCHC		36	g/dL	31-36
RDW-CV	*	12,1	%	12.2 - 14.6
Leukocytes		7.0	10^3 /uL	5.0-10.0
Basophils		0	%	0-1
Eosinophils	*	0	%	1-3
Stem Neutrophils	*	0	%	2-6
Segment Neutrophils	*	84	%	50-70
Lymphocytes	*	11	%	20-40

1. Before Additional Data

On January 9th, 2018, Mr TP, 59 years old, received blood test materials from the room Neurorestoration for complete hematological examination and electrolytes (Na+, K+, Cl-) with clinical description of compensatory dyspnoea et causa aortic stenosis, right hemiparesis and aphasia repair. The results showed that Hb, Ht and erythrocyte levels were reduced with relative neutrophilia and low sodium levels. Based on clinical description and the results of laboratory tests, it is suspected patient had cardio-cerebrovascular disorders complicated by anemia and hyponatremia. Anemia in aortic stenosis aggravates and causes heart failure, whereas hyponatremia with aortic stenosis exacerbates heart failure as well as both increase the risk of death.

In patients with aortic stenosis anemia complications can occur because aortic stenosis occurs Obstruction of cardiac blood flow results in decreased myocardial perfusion resulting in myocardial ischemia which will secrete pro-inflammatory cytokines such as TNF-ÿ. Enhancement pro-inflammatory cytokines cause suboptimal response to EPO. Interfering cytokines erythropoiesis in several ways, including inhibiting EPO production, interfering with EPO function and affect the success of treatment. Cause of anemia in aortic stenosis others occur due to the release of the pro-inflammatory cytokine hepcidin. Hepcidin is produced by liver cells in the inflammatory process, one of which functions to inhibit iron release by macrophages so that iron cannot be used to form hemoglobin.

Hyponatremia is likely to occur when aortic stenosis progresses to heart failure. Hyponatremia in heart failure is due to dilution due to water retention due to discharge arginine vasopressin (AVP) and reduced distal tubule flow. There are 2 mechanism of hyponatremia in heart failure. The first mechanism, in heart failure occurs increased expression of aquaforin-2 which has an impact on increasing permeability and reabsorption water in the collecting ducts of the nephrons, both of which cause excessive reabsorption of free water resulting in hyponatremia. The second mechanism, in heart failure, is activation baroreceptors increase the sympathetic system and stimulate angiotensin II, eventually the circulatory effectiveness decreases due to increased AVP sensitivity, increase AVP release, and increased thirst. Glomerular filtration failure or increase water reabsorption in the proximal tubule causes decreased flow in the distal nephron. Under normal circumstances, water reabsorption in the proximal tubule and sodium reabsorption in the distal nephron. In heart failure, there is an increase in water reabsorption beyond capacity maximum in the proximal tubule so that the distal nephron lacks water. As a result, sodium reabsorption fails because there is no dilution of urine in that section.

2. After Additional Data

From additional data the patient entered the Bandung Adventist Hospital on December 17, 2017 with recurrent ischemic stroke and history of pro AVR aortic stenosis.

On December 20th, 2017 the patient was referred to the National Brain Center Hospital with clinical repair of recurrent stroke and aortic stenosis who are planning to wait in line for Aortic valve replacement was performed at the Harapan Heart and Vascular Hospital. So, from the emergency room, the patient entered the Neurorestoration room.

On December 21st, 2017 a head CT scan was carried out without contrast obtained acute infarction in the left lobe in accordance with the clinical patient there is a side hemiparese right.

On December 22nd, 2017 a Doppler echocardiography examination was obtained aortic stenosis and left ventricular hypertrophy, according to the clinical description of aortic stenosis pro AVR. On January 9th, 2018 an ECG examination was carried out and found hypertrophy left ventricle. The presence of left ventricular hypertrophy causes increased hemodynamic stress on the ventricular wall and increases regurgitant flow through the mitral valve cause a decrease in cardiac function both decreased contractility and cardiac output. This condition is a cause of heart failure.

This patient had a history of hypertension with medication. Hypertension is a factor risk of aortic stenosis, stroke and heart failure. Known from the drug data given There are anti-hypertensive drugs, including Concor which is a beta blocker and Tenace which is a class of ACE inhibitors. ACE antihypertensive drugs. Inhibitors are known to affect the erythropoietin response leading to anemia.

From the laboratory results at the RSAB on December 17th, 2019, Hb levels and sodium is still within normal limits. Whereas on December 21st, 2019 it was obtained Sodium levels start to decrease with chloride increasing slightly. Chloride content increased possibly due to compensatory mechanisms of acid-base disorders, blood gas analysis should be done to determine the acid-base status patient remembers that there is dyspnea and disturbances in the central nervous system. Besides that, Hyperchloremia may be caused in stroke by impaired function of ionic pumps and due to the activation of the kainate receptor, alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) and N-methyl-d-aspartate (NMDA).

The cause of hyponatremia in this patient is likely due to dilutional hyponatremia heart failure leading to fluid retention due to AVP release and decrease flow in the distal tubule and known from the drug data given was not found administration of diuretic drugs. It should be to distinguish depletion or hyponatremia dilution was carried out by checking the osmolality of the urine.

From the complete hematology results on January 9th, 2018, anemia was found on February 11st, 2018, the result of a peripheral blood picture of normocytic anemia was obtained normochromic according to bleeding. The presence of bleeding is supported by urinalysis results complete with hemoglobinuria and hematuria.

Anemia in this patient is probably anemia of chronic disease because of CRP results on December 21st, 2019 found an increase although it is not known CRP levels on February 11st 2018, but complete urinalysis results were found urinary tract infection indicates an inflammatory process. Urinary tract infection occurs This may be due to the use of a urinary catheter. There is a urinary tract infection must be confirmed by urine culture.

Ret-He was used to determine the presence of anemia of chronic disease with iron deficiency. The results of the Ret-He measurement on February 11 2019 were > 25 pg, possibly iron deficiency can be ruled out.

On December 21st, 2017, PT was found to be prolonged due to drug administration simarc which is an oral anticoagulant with an INR according to the therapeutic target.

An increase in D-dimer levels was found which is a marker of coagulation activation accompanied by clot lysis. Coagulation activation in these patients is due to stenosis Aortic stasis occurs which will lead to the formation of thrombus and emboli. From the patient's medical history, he denied diabetes mellitus, but from the results of the examination HbA1C on December 21st, 2018 was obtained in the prediabetes category according to PERKENI, it is recommended to do an Oral Glucose Tolerance Test, but in this patient not possible to do. It is recommended to do level monitoring blood glucose by checking HbA1C every 3 months.

From the results of the lipid profile, it was found that HDL cholesterol levels were low with low LDL levels in target in patients who have 2 risk factors (hypertension and HDL cholesterol level low) according to category from NCEP ATP III. LDL cholesterol levels are still in the range possible target of therapy because the patient is given the drug Atorvastatin to reduce LDL cholesterol levels.

From the results of total calcium levels on February 19th, 2018 it was found to be reduced, possibly due to insufficient albumin levels as evidenced by the results of albumin levels on the same date and ionic calcium levels are still within normal limits.

On December 21st, 2018 an increase in CK was obtained. CK increase can find in several conditions, including muscle damage and treatment of statin groups. Increased CK activity with

CKMB is within the reference range, likely muscle injury not from the heart muscle, this patient had a stroke, possibly the increase was also due to a brain injury resulting in an increase in CKBB.

C. CONCLUSIONS

Aortic stenosis in this patient is probably related to age and other risk factors, namely hypertension, low HDL cholesterol levels and prediabetes. Inspection is recommended Lp(a) to support other aortic stenosis risk factors, NT pro BNP as a marker left ventricular dysfunction in aortic stenosis.

Ischemic stroke in this patient is likely due to a heart defect causes brain ischemia due to decreased cardiac output so that blood flow in the brain reduced and possibly due to embolism due to aortic stenosis causing flow stasis blood, thereby facilitating the formation of thrombus and emboli.

Heart failure in this patient was classified as left systolic heart failure based on clinical signs and echocardiography and ECG examination found inability of the left ventricle to pumping, low contractility, decreased EF, CO and SV, no pulmonary obstruction, and no oedema. To confirm the diagnosis of heart failure it is recommended together with NT pro BNP levels and creatinine clearance to determine class and stage of failure heart.

Possible causes of anemia in this patient are anemia of chronic disease and bleeding without iron deficiency. Hyponatremia as a complication still needs to be checked for urine osmolality determine the cause.

ACKNOWLEDGEMENT

Special thanks to Mahar Mardjono National Brain Center Hospital for their continuos support and encouragement for my pursuit

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