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β2-Microglobulin Relationship with Congenital Heart Disease and Heart Failure

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Abstract:

Congenital heart disease (CHD) is a common condition in infants and can lead to chronic heart failure, which is associated with poor prognosis. The levels of β2-MG have been found to be elevated in various cardiovascular diseases and are associated with disease severity and prognosis. However, the diagnostic value of β2-MG in infants with CHD combined with chronic heart failure has not been well studied. Understanding the diagnostic value of this biomarker can help in the early diagnosis of congestive heart failure associated with CHD and improve clinical management and prognosis.

Keywords: β2-Microglobulin, Congenital Heart Disease, Heart Failure.

Introduction:

Several pathophysiological mechanisms could explain the elevation of β2-MG in heart failure. Inflammation has been suggested as a potential mechanism linking B2M and CVD. Evidence proposed that increased B2M levels were positively associated with inflammatory markers **(1).**

On other hand, in patients with heart failure, kidney function is a strong independent predictor of future hospitalization and death **(2)** and reduced kidney perfusion common in advanced HF**.** Also B2M has been recognized as a marker of renal function, asit can be freely filtered by the glomerulus, reabsorbed and metabolized by the proximal tubule during normal kidney condition, and its circulating level elevates when GFR decreases **(3).**

Also, HF triggers myocardial remodeling, apoptosis, and fibrosis, processes associated with heightened cellular turnover. β2-MG is released during cell death and tissue repair, reflecting increased turnover in cardiomyocytes and vascular smooth muscle cells. Ventricular hypertrophy and fibrosis in HF also contribute to β2-MG elevation, as these processes involve active inflammation and extracellular matrix remodeling (**4).**

Effect of the inflammation in heart failure on B2M:

Heart failure is defined as an inflammatory disease in immunology and immunopathology research **(5)**.

In response to the tissue injury that happen in heart failure, the heart begins tissue repair mechanisms by engaging the innate immune system (**6)**. Immune activation and tissue damage, often lead to elevated B2M levels due to increased cellular turnover and immune system activation, consistent with the engagement of innate immunity, significant increase in the level of pro-inflammatory cytokines is observed after cardiac insult (**7**).

Studies have shown corelationship between severity of heart failure and levels of proinflammatory cytokine TNFα and one of its secondary mediator interleukin-6 (IL-6) reveiling their potency as biomarkers (**6).**

Cytokines have important role in the control of beta-2 microglobulin release from multiple haemopoietic cells, that cytokines not only control the static expression of beta-2 microglobulin on the surface of haemopoietic cells but also hugely affect their shedding **(8).**

Effect of heart failure on renal function and B2M:

B2M is a sensitivity indicator mirroring the function of proximal renal tubules **(9).** It is filtered by the kidneys, and reduced kidney perfusion common in advanced HF leads to its accumulation.

Cardiac and kidney function are strongly interconnected and the communication between the two organs happens through different pathways, including perfusion, filling pressures and neurohormonal activity **(10).**

Patients with heart failure often show renal dysfunction, which is a predictor of poor outcome. The cardiorenal syndrome is common and has been reported in 63% of all patients hospitalized with congestive heart failure **(11)**.

Renal dysfunction is one of the most powerfull predictors of outcome in heart failure. Several studies have revealed that both reduced perfusion and increased congestion (and central venous pressure) leading to worsening renal function in heart failure **(12).**

Heart failure affect renal function as follow:

1-Increased Intracapsular Pressure:

Increased pressure within the renal parenchyma can result from increased volume in the kidney caused by increased interstitial fluid in HF, in the status of an organ (the kidney) that can't expand in volume. interstitial congestion of the kidney, combined with the faliure of the interstitium to expand because of the renal capsule, compresses intrarenal structures such as veins, glomeruli, and tubules, diminishing their function (**12).**

2-Increased Perirenal Pressure:

Increased volume of adipose tissue within the perirenal fascia may cause an increase in perirenal pressure. Perirenal adipose tissue compressing the renal vasculature, leading to pathologic activation of the renin-angiotensin-aldosterone system (RAAS) and reduced renal perfusion perirenal adipose tissue can lead to RAAS activation through its inflammatory properties and increased local levels of TNF-α (**13)**.

3-Increased Intra-Abdominal Pressure:

In patients with severe HF, increase of intra-abdominal pressure (IAP) may be due to ascites or increased fluid in the splanchnic system in the absence of ascites. The presence of ascites and its severity have been associated with impaired renal function in HF**(14).**

4-Renal Tamponade:

There is impairment in renal function when central venous pressures increase in patients with HF. The renal capsule surrounding the kidney is very rigid and will not permit expansion when pressures increase. Increased central venous pressures lead to an increase in renal interstitial pressures, compressing renal structures such as the tubules, intrarenal veins, and glomeruli in the encapsulated kidney **(12).**

Effect of CHD on B2M:

CHD is not only a cardiovascular disease, renal arterioles may also be implicated in it, causing an increase of concentrations in serum β2-MG, which changes as the disease progresses **(15).**

Increase survival in the patients with CHD is associated with increase the risk of secondary renal damage. There is a three-fold increase in mortality of the patients with CHD when Glomerular Filtration Rate (GFR) decreased moderately or severely. Therefore, early diagnosis of renal impairment can lead to better management and improvement of the life styles of such patients **(16).**

Elevated urine B2M is the result of renal exposure to harmful substances which can cause renal damage **(17).** Therefore, evaluation of B2M is one suitable method in predictive renal involvement.

CHD affect renal function as follow:

1-Polycythemia:

Polycythemia is responsible for cyanotic nephropathy compared to hypoxia, and the severity of polycythemia was not proportional to elevated erythropoietin **(18).**

2-Proteinuria:

Duration of cyanotic disease is a risk factor for glomerular injury. Hyper viscosity following prolonged cyanotic disease causes a decrease in peritubular capillary blood flow that is responsible for proteinuria following increased glomerular hydrostatic pressure. This phenomenon together with pedocyte dysfunction leads to proteinuria. Eventually, prolonged proteinuria causes interstitial renal fibrosis which leads to a decrease in GFR and creatinine clearance **(18)**.

3- Nephropathy:

Nephropathy is one of the complications of CHD, specially the cyanotic form, and tubular damage develops during the first decade of life in the patients with cyanotic heart disease **(19**). Also demonstrated that in the patients with cyanotic heart disease, nephropathy is marked with renal tubular dysfunction similar to glomerular dysfunction. They also reported that measurement of urine N-acetyl-β_2 glucosaminidase (NAG) and urine β_2 M is helpful for the early diagnosis of either tubular or glomerular dysfunction in the patients with cyanotic heart disease **(20).**

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