Angiopoietin-2 in ischemic cardiac patients

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Abstract

Background: Coronary artery disease (CAD) is the most common cause of death globally according to WHO. Its known that ischemia and cardiac dysfunction promotes the angiogenesis and new vessel formation to compensate for the decreased blood supply through the diseased arteries.Angiopoietin-2(Ang-2) along with several other growth factors are responsible for the process of new vessel formation. Many patients have some degree of renal insufficiency post PCI mainly due to contrast media and are associated with rise in the serum Ang-2 level. Ang-2 is found to be decreased post PCI with the restoration of the normal blood flow. Many clinical trials relate the Ang-2 with the severity of CAD and renal function.

Objectives: Highlight the serum levels of Ang-2 pre and post PCI and its validity to be used to diagnose and predict severity of CAD.

Methods: We have searched literatures in PubMed, google scholar, Egyptian bank of knowledge and science direct.

Conclusion: In this review we emphasize that Ang-2 is found to be an important marker for diagnosis and prognosis of CAD and is closely related to renal functions in ischemic cardiac patients candidate for PCI.

Keywords: Percutaneous coronary intervention (PCI); contrast induced nephropathy (CIN); angiopoietin-2(Ang-2).

DOI: 10.21608/svuijm.2021.66008.1111

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Received: 4 February, 2021.
Revised: 1 March, 2021.
Accepted: 9 March, 2021.
Published: 4 July, 2023

Cite this article as: Ahmed Magdy Abdelazim, Mohammed Abdelrazek Elsenbsy, Mohammed H Hassaan, Mohammed AK. (2023). Angiopoietin-2 in ischemic cardiac patients. *SVU-International Journal of Medical Sciences*. Vol.6, Issue 2, pp: 482-488.

1. Introduction: Percutaneous coronary intervention (PCI)

It's a non-surgical procedure that been widely used nowadays to treat the narrowing lesions found in the coronary arteries. It's considered to be a replacement to coronary artery bypass graft **(Al-Lamee et al., 2019).**

This procedure concludes maily stent delivery through the catheter angioplastyafter balloon infaltion to oppose the media of the artery with the stent struts.

1.1. Indications

PCI is used mainly to open a blocked coronary artery and restore arterial blood flow to heart tissue and prevent the deterioration of the cardiac functions **(Oberhauser et al., 2009).**

Its used to releive chronic arterial stenosis with sebsequent improvement of chest pain in patients with stable angina.

Percutaeous coronary intervention is also used in non-ST-segment elevation myocardial infarction to improve the outcome and mortality shortly after cardiac ischemic event **(Kumar and Cannon, 2009).**

1.2. Complications

Although PCI is considered to be a non-surgical procedure,and also performed with a well-trained invasive cardiologist its carries a number of risks.

Bleednig : from the insertion point in the groin (femoral artery) or wrist (radial artery) is common, in part due to the use of antiplatelet drugs **(Dash, 2013).**

Infection at the skin puncture site on pre-formed hematoma.

Allergic reaction to the contrast dye used.

Deterioration of kidney function: Many patinets suffer from different degrees of nephropathy post PCI even with no element of chronicityof kidney disease .pre-existing nephropathy is believed to be main cause of deterioration due to diseased renal parenchyma and decreased renal filteration capacity **(Azzalini et al., 2019).**

The extent of nephropathy after the procedure depends on many factors including the amount of dye used, the duration of the procedure and pre-existing nephropathy.

Nephropathy is thought to be caused by renal ischemia and distubed hoemostasis of renal parenchyma which in turn promotes the process of angiogenesis **(Podkowińska and Formanowicz, 2020).**

Several growth factors are recognized to induce the angiogenesis as; Ang-1, Ang-2 (ANGS), tumor necrosis factor(TNF-α) and vascular endothelial groth factor(VEGF) **(Lee et al., 2004).**

Numerous strategies were discussed to reduce the risk of nephropathy after PCI along with multivariable adjustment, age, sex, diabetes, ejection fraction, periprocedural hypotension, presentation with acute coronary syndrome, and contrast volume.

Heart attack which is considered the most serious complication during the procedure and may eventually require ending of the procedure **(Pang et al., 2020).**

2. Contrast induced nephropathy (CIN)

It's a form of injury to the kidney tissues which occures during exposuring to contrast media during medical imaging.

2.1. Pathogenesis

Its ought to be certain that the contrast media is to some extent irriatant to renal

parenchyma and tend to accumulate in the renal tubules. This is believed to be the main pathogenesis in developing renal injury **(Andreucci et al., 2014).**

Renal ischemia and tubular necrosis thought to contribute in the pathogenesis of nephropathy post PCI.Its mainly associated with subclinical micro-albuminuria(30-300mg) ,although serum creatinine level may be within the normal range.Rare cases have been recognized to progress into acute renal failure requiring renal replacement therapy through heamodialysis **(Gounden, 2020).**

2.2. Risk factors

Many risk factors have been recognized to be invloved to increase the propability of CIN as shown in many previous studies.Age, diabetes, hypertension and reduced intravascular volume are good examples of these risk factors **(van der Molen et al., 2018).**

A) **Previous kidney disease:** Its been classified according the european guidelines that pre-existing renal parenchymal disease to be a major risk factor when estimated glomerular filteration rate (eGFR) < 45 ml/min/1.73 m2 of body surface area before intra-arterial administration of the dye **(Nyman et al., 2018).**

B) **Other factors :** Many other factors contribute to contarst induced nephropathy (CIN) other than the pathological condition of the renal parenchyma before the PCI procedure.These factor include the amount of dye injected during the procedure,the use of contrast media with high osmolarity,multiple contrast injections within 72 hours and co adminsteration of nephrotoxic drugs **(Sendeski, 2011).**

2.3. Prevention

Many precuations should be placed in mind in order to prevent and lower the risk of post PCI nephropathy.Patient examination and evaluation of the kidney condition before the procedure is crucial to avoid renal impairment and secure renal tissues against the harmful effect of the contrast **(Hossain et al., 2018).**

Adjustment of the radiocontrast dose,treating the risk factors and stopping any other nephrotoxic agents should be helpful to help protect the kidney **(Davenport et al., 2013).**

3. Angiopoietin-2

3.1 Background

Angiopoietin-2 is known as a growth factor that belongs to the tyrosine kinase sinaling pathway whih is involved in angiogenesis.

Along with other growth factors like tumor necrosis factor(TNF-α) and vascular endothelial growth factor(VEGF), its known to be apotent stimulator to angiogenesis and new vessel formation **(Akwii et al., 2019).**

Its triggered by inflamatory conditions, cancer and hypoxia.The process of new vessel formation is some how complicated and require many steps including, vascular wall disruption, increasing vascular permeability and then complete pericyte coverage of the vessel wall **(Thurston and Daly, 2012).**

Its found in numerous articles that angiopoietin-2 in particular is linked with coronary artery disease, renal impairment, pancreatitis, pneamonia and generalized

conditions of inflammation **(Schuldt et al.; Tsai et al., 2018).**

3.2 Mechanism of action

Ang-2 as a biochemical molecule has a wide variety of pathways to be activated and eventually enhance angiogenesis, known to be discussed in many reviews.

3.2.1 Tie-2 dependent signaling

Tie-2 receptor,is a tyrosine kinase receptor containing epidermal growth factor part in the membrane of the endothelial cells of the stem cells with a binding site for Aniopoietins **(Lee et al., 2004).**

Ang-2 induced Tie-2 phosphorylation leads to chemotaxis and migration of the pericytes to form a tube which later on become a well-formed vessel tube.Foxol and β1 integrin act as a negative regulator for the Angiopoietins mediated angiogenesis **(Felcht et al., 2012).**

3.2.2 Tie-2 independent signaling

Many studies reviewed another pathway of activation and mechanism of action of Ang-2.

Its found that integrins act as an alternative receptor for Ang-2 and subsequent phosphorylation leads to migration and chemotaxis of the endothelial cells enhancing angiogenesis **(Bogdanovic et al., 2006).**

Activation of either of both pathways represent a potent stimulator for induction of angiogenesis and new vessel formation.

3.3 Role of Ang-2 in physiological functions

Its shown that the Ang-2 has many important roles early during fetal life and is critical for embryonic survival.

Its believed that Ang-2 expression is increased in the developing placenta as its important for formation of neural crest and head shapening and patterning **(McKinney et al., 2016).**

These facts are confirmed by the low serum levels of angiopoietin-2 in cases of intra-uterine growth retardation(IUGR).

During adult life its important to explore the role of Ang-2 which is not yet completely understood, but many evidences are found supporting its role in ontroling the vascular permeability **(Bergers and Song, 2005).**

3.4 Role of Ang-2 in pathological conditions

In the last years there is a growing interest to explore and understand the role of Ang-2 in the various clinical conditions **(Fischer et al., 2005).**

3.4.1 Inflammation

So many overlapping is found in the process of inflammation and angiogenesis in which Ang-2 and other VEGFs are involved.Increased permeability of the vasculature seems to be the main pathogenesis in progression of inflammation and edema **(Claesson-Welsh, 2015).**

3.4.2 Pneamonia

Elevated serum levels of Ang-2 are observed in paients with hospital acquired pneamonia.Pneumolysin mediated activation of Ang-2 is thought to be the main mechnism involved **(Anderson et al., 2018)**

3.4.3 Chronic kidney disease

Nephropathy has been found to pass through many stages and Ang-2 is believed to have an essential role in the pathogenesis and progression of the disease.

Destruction of the renal glomeruli and proliferation of the glomerular basement

membrane is considered the main and leading pathology **(Kitching and Hutton, 2016).**

Renal ishcemia and alteration of the vascular structure is thought to play an important role in the pathogenesis of nephropathy and accordingly rising the need to angiogenesis and new vessel formation.

Serum Ang-2 level is found to be associated with the proggresion of CKD and subsequent rise in the renal function **(David et al., 2010).**

Diabetes mellitus, nephrotoxic drugs and intraveous contrast adminstration specally during PCI proedure are considered the main causes of nephropathy **(Faggioni and Mehran, 2014).**

3.4.4 Cardiovascular disease

Its ought to be certain that Ang-2 is involved in vessel remodeling and pathogenesis of cardiovascular diseases (CVD).(**Tsai et al., 2018).**

Most of CVD like coronary artery disease and congestive heart failure have elevated serum level of angiopoietin-2 which is believed to be involved in the angiogenesis as a result of confounding ischemia **(Yoshiji et al., 2005).**

In this review, inconsistency with many other reviews, we are emphasizing that serum Ang-2 level is associated the increased need to angiogenesis and in turn to the degree of arterial stenosis and cardiac ischemia.

In cardiac patients candidate for PCI its found that the levels of Ang-2 decreased significantly post PCI compared to its levels preprocedural which is consistent with the relieve of cardiac ischemia **(Jian et al.,2019).**

Conclusion

In this review we emphasize that Ang-2 is found to be an important marker for diagnosis and prognosis of the CAD and is closely related to renal functions in ischemic cardiac patients candidate for PCI.It ould have the potential to predit the extent and severity of ischemia in patients with CAD.

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