The Egyptian Journal of Hospital Medicine (January 2025) Vol. 98, Page 297- 303

Evaluation of the Relation between Insulin- Like Growth Factor 2 and Ventricular Septal Defect in Outpatient Pediatric Cardiology Clinic Patients of Suez Canal University Hospitals: Review Article

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ABSTRACT

Background: Ventricular septal defect (VSD) is among the most prevalent congenital heart defects, resulting from an abnormal opening between the heart's ventricles. This defect causes blood shunting between the left and right ventricles, leading to complications such as pulmonary hypertension, heart failure, recurrent respiratory infections, and growth delays. The severity of symptoms and the need for intervention depend on the size of the defect and its physiological impact. Diagnosis typically involves advanced imaging techniques such as echocardiography, electrocardiograms, and cardiac catheterization, which are essential for accurate evaluation and management. Recent advancements in proteomics have significantly enhanced our understanding of congenital heart disease, offering detailed insights into cardiac development at the molecular level. Proteomic approaches help identify biomarkers, improve diagnostic accuracy, and facilitate the discovery of new therapeutic strategies. The insulin-like growth factor-2 (IGF-2) pathway plays a critical role in cardiac growth, development, and regeneration. This pathway influences processes such as cardiomyocyte proliferation and differentiation, making it a potential target for novel treatments aimed at repairing or regenerating damaged heart tissue.

Objective: This review article aimed to throw the light on the relation between Insulin- like Growth Factor 2 and Ventricular Septal Defect in pediatrics.

Materials and methods: We searched Google Scholar, Science Direct, PubMed and other online databases for VSD, IGF-2, Congenital heart defects and Pediatric cardiology. The authors also reviewed references from pertinent literature, however only the most recent or comprehensive studies from 1996 to 2021 were included. Documents in languages other than English were disqualified due to lack of translation-related sources. Papers such as unpublished manuscripts, oral presentations, conference abstracts, and dissertations that were not part of larger scientific studies were excluded.

Conclusion: Integrating advanced diagnostic technologies with molecular and proteomic research provides a promising avenue for improving outcomes in congenital heart defects. These approaches not only enhance early detection and precise management but also open doors to innovative therapies for pediatric patients with complex cardiac conditions.

Keywords: VSD, IGF-2, Congenital heart defects, Pediatric cardiology.

INTRODUCTION

Congenital cardiac defects rank as the 2nd primary cause of mortality in infancy & kids. Cardiac anomalies rank among the most prevalent congenital defects in babies and kids. A congenital heart defect (CHD) is an anatomical deformity of the heart or major vessels that arises throughout the development of intrauterine, regardless of the age at which it presents. The prevalence of congenital heart abnormalities is estimated to be 4-8 per one thousand newborns. Ventricular septal defect (VSD) is the predominant kind of congenital heart disease [(1)].

Congenital heart disease

Classification: Congenital cardiac problems can be categorized as cyanotic or acyanotic based on the clinical presence of cyanosis in cases. Cyanotic anomalies can be further categorized as left-to-right shunts & obstructive lesions. Cyanotic defects, by definition, involve a right-to-left shunt. The relative frequency of these problem categories & the predominant defects within each category are presented [(2)].

Complications:

Congenital heart disorders can also lead to a variety of additional complications, including growth and development problems in adults & kids. Recurrent respiratory tract infections (RTIs) are characterized by infections of the sinuses, larynx, airways, or lungs, as well as pulmonary hypertension, endocarditis, & heart failure.

Diagnosis:

Congenital cardiac disorders are often identified in a fetus throughout pregnancy. Nonetheless, an assessment may occasionally be validated only following delivery [(1)].

Diagnosis throughout pregnancy: Congenital cardiac anomalies may be initially identified throughout a regular fetal ultrasound examination. A specialized ultrasound, known as a fetal echocardiogram, will be conducted between eighteen and twenty-two weeks of gestation to identify the precise diagnosis. This can be conducted if there is a familial history of congenital cardiac anomalies or a high-risk factor [(1)].

Received: 01/08/2024
Accepted: 01/10/2024

Diagnosis following the birth: Diagnosis of congenital cardiac defects in neonates may occur quickly following birth if diagnostic symptoms or signs, like cyanosis, are evident [(1)].

Echocardiography: An echocardiography is frequently utilized to examine the inside of the heart. Cardiac anomalies missed throughout fetal echocardiography may occasionally be identified as the kid grows [(3)].

Electrocardiogram: An electrocardiogram (ECG) is an examination that assesses the electrical activity of the heart. Adhesive sensors known as electrodes have been attached to the legs, arms, & chest. These are linked by wires to an electrocardiogram recording apparatus. The device exhibits the electrical impulses generated by the heart & indicates its beating efficiency [(4)].

Chest X-ray: A chest X-ray of the lungs & heart can assess pulmonary congestion or cardiomegaly. Both could indicate cardiac issues [(5)].

Pulse oximetry: Pulse oximetry is an assessment that quantifies concentration of oxygen in bloodstream. The examination includes placing a specialized sensor on the ear, fingertip, or toe that emits light waves. A computer is linked to the sensor & quantifies the absorption of light wavelengths. Oxygen influences the absorption of light waves, hence by examining the findings, the computer may rapidly discover the quantity of oxygen in the blood [(1)].

Cardiac catheterization: Cardiac catheterization is an effective method for acquiring detailed information regarding the blood flow via the heart. A catheter, a flexible & small tube, is introduced into a blood vessel, typically via an artery and/or vein located in the neck, groin, or arm throughout the treatment. The catheter is advanced into the heart, directed by X-rays or occasionally an MRI (**Magnetic resonance imaging**) scanner, facilitating pressure readings in various regions of the heart or lungs [(1)].

Ventricular septal defect

Anatomy:

Embryology: Between four and eight gestation weeks, the one chamber of the ventricle is successfully partitioned into 2 chambers. The division is attained through the fusion of the segment of the membrane interventricular septum, the bulbous cordis & the endocardial cushions, which is the proximal section of the truncus arteriosus. The muscular interventricular septum segment ascends as each ventricular chamber expands, ultimately converging with the left & right ridges of the bulbous cordis. The pulmonary valve is distinguished from the TV by the right ridge, which merges with the TV & the endocardial cushions. The left ridge merges with an interventricular septum ridge, maintaining continuity between the aortic ring & the mitral ring [(6)].

Structure of interventricular septum: The interventricular septum is a curvilinear structure that can be categorized into four zones based on anatomical markers in the right ventricle [(7)].

Pathophysiology: The extent of the shunt is contingent upon the defect size & the downstream resistance, namely pulmonary vascular resistance & pulmonary outflow tract obstruction. The pressure among the left & right ventricles is balanced and there is a significant left-to-right shunt in nonrestrictive ventricular septal defects. Blood can travel readily across the larger defects. In the absence of pulmonic stenosis, a significant shunt over time resulted in increased pulmonary artery pressure, right ventricular pressure overload, enhanced pulmonary artery vascular resistance, along with right ventricular hypertrophy. The elevated pulmonary vascular resistance results in a reversal of shunt direction (from the right ventricle to the left), resulting in Eisenmenger syndrome [(1)].

Clinical manifestations:

History: The case with a minor VSD is asymptomatic & exhibits normal development & growth. In cases of moderate ventricular septal defect, delayed development and growth, reduced activity, repeated respiratory infections, & congestive heart failure are particularly prevalent throughout infancy. Chronic pulmonary hypertension may be accompanied by a history of cyanosis & reduced activity levels [(1)].

Physical examination: Infants with minor ventricular septal defects are well-developed & exhibit cyanosis. Infants with significant ventricular septal defects may exhibit inadequate weight gain or symptoms of congestive heart failure prior to two or three months of age. Cyanosis and clubbing may occur in people with pulmonary vascular obstructive disorders. A systolic thrill might be detected at the lower left sternal border. Precordial bulge & hyperactivity are observed in the existence of a significant ventricular septal defect [(8)].

Diagnosis: VSD is typically identified postnatally. The dimensions of the VSD will determine the presence of symptoms, if any & whether a physician detects a heart murmur throughout an examination of the body. Indicators of a VSD may manifest at birth or may not become evident until somewhat later. A minor ventricular septal defect typically resolves naturally, and the infant may exhibit no indications of the problem [(8)].

Treatments: The management of a VSD is contingent upon the dimensions of the VSD & the complications it may induce. Several ventricular septal defects are minor & resolve spontaneously; if the ventricular septal defect is small & asymptomatic, the physician will monitor the infant routinely to approve the absence of heart failure indicators & to ensure the VSD resolves independently. If the ventricular septal defect fails to close spontaneously or is of significant size, additional treatment may be required.

Complications of ventricular septal defect operation: Infection, valve injury, AV block & residual ventricular septal defect.

PROTEOMICS

Introduction: The term proteome denotes the entirety of proteins synthesized or altered by an organism (such as an animal, human, bacteria, or plant) or biological system (such as cell culture, organ, or complex community from an environmental sample). In 1994, **Wilkins *et al.*** [(9)] invented the term "proteome" & established the 1st specialized proteomics laboratory to characterize proteins as a supplement to genetic information. Nonetheless, the complete proteome of a certain tissue, cell, organism, or organ remains unidentified [(9)].

Types of proteomics: Proteomics comprises 3 primary categories: structural proteomics, functional proteomics & expression proteomics [(10)].

Applications of proteomics in medicine: Proteomics is an innovative approach utilized in medicine, particularly in drug & biomarker development. Proteomics can detect & monitor biomarkers through the analysis of proteins in bodily fluids, involving serum, urine, cerebrospinal fluid & exhaled breath. Proteomics could enhance medication development by offering a detailed map of protein interactions correlated to illnesses [(11)].

Proteomics-based approach to cardiac developmental diseases

Introduction: Given that the onset of most congenital heart defects occurs throughout the early progress of the heart of humans, research aimed at understanding congenital heart defects has predominantly utilized vertebrate model systems, particularly the mouse [(12)].

Proteomic-dependent approaches in tissue of embryonic heart: Identifying & characterizing protein complexes & endogenic proteins in vivo under healthy environments is crucial for understanding normal cardiac development & the pathophysiology of congenital heart disorder. The application of these methods has been constrained by the absence of efficient mass spectrometry techniques & workflows for analyzing small samples in early-stage embryos & tissues. To uncover endogenous interactomes using directed mass spectrometry, strategies have concentrated on optimizing cell/tissue lysis conditions & protein extraction buffers, along with enhancing the effectiveness of immuno-isolation [(13)].

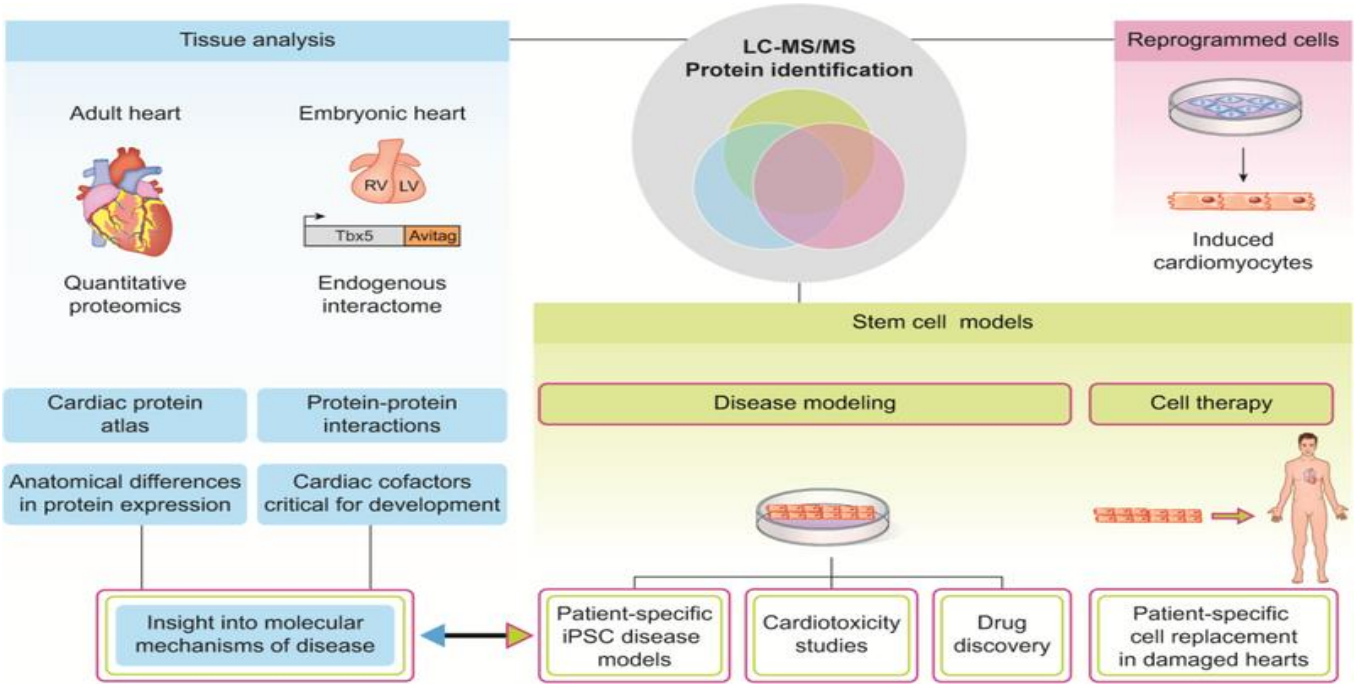

Figure (1): Proteomic-dependent approaches Schematic of cardiac cells & tissue [(13)].

Stem cells of embryonic differentiate into cardiomyocytes:
In vivo developing biology systems have clarified several molecular processes that contribute to congenital heart disease. The efficacy of these systems for the proteome analysis is constrained by the tissue amount that can be obtained from a specific species at a specific stage of progress [(14)].

Induced pluripotent stem cells differentiation into cardiomyocytes: Using the technology of induced pluripotent stem cells, a fully grown somatic cell, which is often produced from dermal fibroblasts, can be reprogrammed into a pluripotent stem cell that maintains the genetic features of its host, which could be a human case. The production of pluripotent stem cells that are induced requires the expression of four distinct transcription factors through the process of transduction. This is c-Myc, Sox2, Oct3/4, & Klf4 [(15)].

Fibroblasts Direct Reprogramming into Induced Cardiomyocytes: The method of changing fibroblasts into cells that are like cardiomyocytes is known as direct reprogramming. The procedure involves a direct cell type change in mouse fibroblasts through retroviral overexpression of three cardiac lineage-specific transcription factors, Gata4, Mef2C, & Tbx5 [(16)].

IGF-2
Introduction: In 1957, Salmon and Daughaday originally hypothesized the presence of insulin-like growth factors (IGFs) or somatomedins, suggesting that pituitary growth hormone influences skeletal growth through an intermediary class of growth-promoting peptides. Subsequent analysis identified two distinct compounds that demonstrated growth hormone-like actions on in vitro cartilage explants **[(17)]**.

Gene structure: The IGF2 gene in mice is located on the seventh chromosome & has six exons, with the coding region limited to three exons. The gene of insulin-like growth factors-2 consists of several alternatively spliced transcripts originating from various promoters. The human insulin-like growth factor-2 gene is situated on chromosome 11p15.5 & spans around thirty kilobases of DNA. Four promoters & ten exons yield various transcripts based on the originating promoter [(17)].

Genomic imprinting: Genomic imprinting, a mechanism for embryonic gene control, expresses a single paternal allele, with sequences arranged into chromosomal domains becoming more apparent with more gene examples. This finding gives weight to the hypothesis that imprinting may be managed on a regional level. The insulin-like growth factors-2 gene was among the initial genes identified as imprinted, with clear evidence indicating that the male insulin-like growth factors-2 allele is transcribed while the maternal allele remains inactive. Notably, the silencing of the paternal allele led to a decreased progeny size, which remained otherwise normal & viable [(18)].

Posttranslational processing: Typically, IGF2 is initially generated as a prohormone with 180 amino acids, which is later processed to provide the sixty-seven-amino-acid bioactive IGF2 protein. A signal peptide of twenty-four amino acids is initially excised from the N-terminus, resulting in proinsulin-like growth factors-2 (156 amino acids). The subsequent cleavage of proinsulin-like growth factors-2 yields a peptide product consisting of 104 amino acids, designated as insulin-like growth factors-2 (1-104). End proteolysis produces insulin-like growth factors-2 (1-87), resulting in a mature IGF2 peptide with sixty-seven amino a`. Both precursor forms of insulin-like growth factors-2, specifically insulin-like growth factors-2 (1-104) & IGF2 (1-87), collectively referred to as 'large IGFs,' were identified in human & bovine serum [(19)].

The mature peptide: Insulin-like growth factors-2 is a polypeptide with a composition akin to that of insulin-like growth factors-1, relaxin, & insulin. Insulin-like growth factors-2 consists of the C, B, A, & D domains, arranged sequentially from the N terminus to the C-terminus. These domains contain 3 α-helices. Three links maintain the structural integrity [(20)].

IGF-binding proteins (IGFBPs): Circulating IGFs are fragile and prone to breakdown. To attain functional stability, they need IGFBPs for trafficking in the bloodstream. Six classical IGFBPs exhibit high-affinity binding to IGFs & share a significant portion of their amino acid sequences. A recent discovery identified a set of proteins that bind insulin-like growth factors with reduced affinity. Despite their structural relation to classical IGFBPs & classification under the IGFBP (Insulin-like Growth Factor Binding Proteins) superfamily, their low binding affinity leads to their designation as IGFBP-related proteins [(21)].

IGF signaling pathway in cardiac regeneration & development: The heart is the initial functioning organ to mature. The heart begins to beat & circulate blood approximately twenty-one to twenty-two days during human fetal development and eight days in mouse embryogenesis. The heart has quick growth to satisfy the rising metabolic requirements of the growing embryo. Through embryonic & fetal development, this growth primarily occurs via hyperplasia, characterized by a rise in the quantity of cardiac cells. Following birth, cardiac

cells rapidly lose their capacity for proliferation. Consequently, the postnatal development of the heart results from cardiomyocyte hypertrophy & the increase of cardiac non-myocytes. Hypertrophic development results in a thirty- to forty-fold enhancement in the volume of individual cardiac cells [22].

Insulin-like growth factors in cardiac progress: There are seventy residues that make up insulin-like growth factor-1, which is a polypeptide that is organized into four domains that are called A–D. Proinsulin is made up of the A-C domains, but mature insulin is only made up of the B & A domains as its constituents. Circulating IGF-1 is predominantly released by the liver & controlled by hormones of growth. However, other organs can express insulin-like growth factor-1 in an autocrine or paracrine fashion. The dysfunction of the IGFG (insulin-like growth factor gene) induces perinatal mortality & growth retardation. Embryonic pericardial cells express insulin-like growth factor 1 receptor & respond to exogenous IGF stimulation. Pharmacological suppression of IGF receptors reduces FAK (Focal Adhesion Kinase) phosphorylation and pericardial growth [23].

MicroRNA regulation of the insulin-like growth factor signaling pathway

MicroRNAs can modulate the insulin-like growth factor pathway throughout heart progress. Mice deficient in miR-1 have significant cardiac abnormalities & heightened mortality by weaning. Fifty percent of the embryos demonstrated VSD, while the surviving adults displayed electrocardiographic abnormalities. IGF-1 receptor & IGF-1 are both targets of miR-1. IGF-1 receptor is moreover a target of another highly abundant miRNA in postnatal cardiomyocytes, miR-378. IGF-1 receptor is downregulated postnatally as miR-378 levels rise. Notably, IGF1 suppresses the expression of miR-378. The outcomes indicate a connection among miR-378, insulin-like growth factors-1 receptor, & IGF-1 that may have a role in the postnatal remodeling of the heart [24].

The insulin-like growth factors-binding proteins family

Insulin circulates freely in the blood, whereas insulin-like growth factors are transported attached to IGFBPs. The half-life of free insulin-like growth factors in circulation is brief, ranging from between ten and twelve minutes. Insulin-like growth factor binding proteins extend the half-life of insulin-like growth factor & modulate their transport into tissues and biological activity. Seven insulin-like growth factor-binding proteins were identified in mammals. They exhibit varying binding affinities & distinct geographical & tissue expression temporal patterns. They can either stimulate or inhibit the function of insulin-like growth factor, contingent upon the degree of expression & the cellular environment. IGFBP3 serves as the primary transporter of IGFs in the bloodstream, enhancing their activity while blocking them when overexpressed. IGFBP4 is consistently inhibitory, while IGF-binding proteins-6 selectively bind to IGF2, hence inhibiting its activity [25].

The insulin receptor substrate (IRS) family:

The insulin receptor substrate proteins function as adaptor proteins that arrange signaling complexes & begin intracellular signaling pathways. They participate in the signaling transmission from the insulin & insulin-like growth factor-1 receptors. They are universally conveyed & facilitate insulin-dependent mitogenesis & control of digestion of glucose in a lot of types of cells. Insulin receptor substrate-1 is a phosphoprotein that contains a domain of phosphotyrosine binding. The active insulin receptor also phosphorylates IRS2. Other family members have more limited expressions of tissue or are limited to humans & rodents. The dual loss of function of IRS1-2 in cardiomyocytes results in cardiac dilation, fibrosis, & continuing cardiac failure, ending in the mortality of the mice among six to eight months [26].

Alternative IGF1R ligands:

Alternative ligands can stimulate the insulin-like growth factor signaling pathway. The Dipk2a gene produces a molecule known as HASF. This paracrine factor promotes the proliferation of cardiomyocytes by activating the phosphatidylinositol 3-kinase/Akt signaling pathway. Management of 1ry adult mice cardiomyocytes with hypoxia & Akt-induced stem cell factor decreases apoptosis in vitro & direct injection of hypoxia & Akt-induced stem cell factor protein into the heart post-myocardial infarction exerts a protective influence, diminishing fibrosis & enhancing cardiac function relative to controls [27].

IGF signaling in cardiomyocytes from stem cells differentiation:

Management of mouse stem cells of embryo with insulin, insulin-like growth factors-1, or insulin-like growth factors-2 promotes mesoderm development & elevates the quantity of Nkx2.5-expressing cardiac progenitor cells (CPC). In contrast to cardiomyocytes produced from mouse embryonic stem cells, cardiomyocytes obtained from human embryonic stem cells exhibit significant proliferation in serum-free medium, which is contingent upon the PI3K/Akt signaling pathway. The inhibition of insulin-like growth factor receptor-1 with blocking antibodies reduces proliferation, but the administration of insulin-like growth factor-1 or insulin-like growth factor-2 enhances growth in a dose-dependent manner. Consequently, the insulin-like growth

factor/phosphatidylinositol 3-kinase/Akt pathway appears to be significant for the cardiomyocyte proliferation produced from human embryonic stem cells (HESC) [28].

IGF signaling in cardiac regeneration:

In contrast to the adult heart of a mammal, the adult heart of a zebrafish is capable of healing after being injured. When it comes to the regenerative process, which involves the proliferation of cardiomyocytes, IGF signaling is necessary [29].

Ethical considerations: All the procedures of the research were permitted by The Ethics Committee of Faculty of Medicine, Pediatric Cardiology Department, Suez Canal University. Administrative consents required have been taken. The objective of this research was to conduct research on humans in accordance with the Declaration of Helsinki, the ethical norm established by the World Medical Association.

- **Consent for publication:** I certify that each author has granted permission for the work to be submitted.
- **Funding:** No fund.
- **Availability of data and material:** Available.
- **Conflicts of interest:** None.
- **Competing interests:** None.

REFERENCES

1. **Desai K, Rabinowitz E, Epstein S (2019)**: Physiologic diagnosis of congenital heart disease in cyanotic neonates. Current opinion in pediatrics, 31 (2): 274–283.
2. **Hopkins M, Goldstein S, Ward C, Kuller J (2018)**: Evaluation and Management of Maternal Congenital Heart Disease: A Review. Obstetrical & gynecological survey, 73 (2): 116–124. https://doi.org/10.1097/OGX.0000000000000536
3. **Carapetis J, Beaton A, Cunningham M *et al.* (2016)**: Acute rheumatic fever and rheumatic heart disease. Nature reviews. Disease primers, 2: 15084. https://doi.org/10.1038/nrdp.2015.84
4. **Goldberger A, Goldberger Z, Shvilkin A (2017)**: Clinical Electrocardiography: A Simplified Approach E-Book: Clinical Electrocardiography: A Simplified Approach E-Book. Elsevier Health Sciences;. from https://www.researchgate.net/publication/322492475_Goldberger's_Clinical_Electrocardiography_A_Simplified_Approach_Ninth_Edition
5. **Sun R, Liu M, Lu L *et al.* (2015)**: Congenital Heart Disease: Causes, Diagnosis, Symptoms, and Treatments. Cell biochemistry and biophysics, 72 (3): 857–860. https://doi.org/10.1007/s12013-015-0551-6
6. **Kenny D (2018)**: Interventional Cardiology for Congenital Heart Disease. Korean circulation journal, 48 (5): 350–364. https://doi.org/10.4070/kcj.2018.0064
7. **Durden R, Turek J, Reinking B *et al.* (2018)**: Acquired ventricular septal defect due to infective endocarditis. Annals of pediatric cardiology, 11 (1): 100–102. https://doi.org/10.4103/apc.APC_130_17
8. **Garg N, Nayyar M, Khouzam R *et al.* (2018):** Peri-procedural antibiotic prophylaxis in ventricular septal defect: a case study to re-visit guidelines. Annals of translational medicine, 6 (1): 18. https://doi.org/10.21037/atm.2017.11.11
9. **Wilkins M, Sanchez J, Gooley A *et al.* (1996)**: Progress with proteome projects: why all proteins expressed by a genome should be identified and how to do it. Biotechnology & genetic engineering reviews, 13: 19–50. https://doi.org/10.1080/02648725.1996.10647923
10. **Rabilloud T, Lelong C (2011)**: Two-dimensional gel electrophoresis in proteomics: a tutorial. Journal of proteomics, 74 (10): 1829–1841. https://doi.org/10.1016/j.jprot.2011.05.040
11. **Chen Z, Liang Z, Zhu X (2015)**: A Review: Proteomics in Nasopharyngeal Carcinoma. International journal of molecular sciences, 16 (7): 15497–15530. https://doi.org/10.3390/ijms160715497
12. **Mirzaei H, Di Biase S , Longo V (2016):** Dietary Interventions, Cardiovascular Aging, and Disease: Animal Models and Human Studies. Circulation research, 118 (10): 1612–1625. https://doi.org/10.1161/CIRCRESAHA.116.307473
13. **Chick J, Munger S, Simecek P *et al.* (2016):** Defining the consequences of genetic variation on a proteome-wide scale. Nature, 534 (7608): 500–505. https://doi.org/10.1038/nature18270
14. **Shaukat A, Tajti P, Sandoval Y *et al.* (2019):** Incidence, predictors, management and outcomes of coronary perforations. Catheterization and cardiovascular interventions : official journal of the Society for Cardiac Angiography & Interventions, 93 (1): 48–56. https://doi.org/10.1002/ccd.27706.
15. **Kennedy L, Kaltenbrun E, Greco T *et al.* (2017)**: Formation of a TBX20-CASZ1 protein complex is protective against dilated cardiomyopathy and critical for cardiac homeostasis. PLoS genetics, 13 (9): e1007011. https://doi.org/10.1371/journal.pgen.1007011
16. **Ahn K, Lee J , Cho G *et al.* (2017)**: Placental thickness-to-estimated foetal weight ratios and small-for-gestational-age infants at delivery. Journal of obstetrics and gynaecology : the journal of the Institute of Obstetrics and Gynaecology, 37 (7): 883–887. https://doi.org/10.1080/01443615.2017.1312306
17. **De Meyts P, Whittaker J (2002)**: Structural biology of insulin and IGF1 receptors: implications for drug design. Nature reviews. Drug discovery, 1 (10): 769–783. https://doi.org/10.1038/nrd917
18. **Chao W, D'Amore P (2008)**: IGF2: epigenetic regulation and role in development and disease. Cytokine & growth factor reviews, 19 (2): 111–120. https://doi.org/10.1016/j.cytogfr.2008.01.005
19. **Senthil D, Choudhury G, Abboud H *et al.* (2002)**: Regulation of protein synthesis by IGF-I in proximal tubular epithelial cells. American journal of physiology.

Renal physiology, 283 (6): F1226–F1236. https://doi.org/10.1152/ajprenal.00109.2002

20. **Zheng H, Worrall C, Shen H *et al.* (2012)**: Selective recruitment of G protein-coupled receptor kinases (GRKs) controls signaling of the insulin-like growth factor 1 receptor. Proceedings of the National Academy of Sciences of the United States of America, 109 (18): 7055–7060. https://doi.org/10.1073/pnas.1118359109
21. **Cerrato F, Sparago A , Verde G *et al.* (2008)**: Different mechanisms cause imprinting defects at the IGF2/H19 locus in Beckwith-Wiedemann syndrome and Wilms' tumour. Human molecular genetics, 17 (10): 1427–1435. https://doi.org/10.1093/hmg/ddn031
22. **Jung H, Suh Y (2015):** Regulation of IGF -1 signaling by microRNAs. Frontiers in genetics, 5: 472. https://doi.org/10.3389/fgene.2014.00472
23. **Li N, Zhou H, Tang Q (2018)**: miR-133: A Suppressor of Cardiac Remodeling?. Frontiers in pharmacology, 9: 903. https://doi.org/10.3389/fphar.2018.00903
24. **Bach L (2018)**: IGF-binding proteins. Journal of molecular endocrinology, 61 (1): T11–T28. https://doi.org/10.1530/JME-17-0254
25. **Kamei H, Duan C (2021):** Alteration of organ size and allometric scaling by organ-specific targeting of IGF signaling. General and comparative endocrinology, 314: 113922. https://doi.org/10.1016/j.ygcen.2021.113922
26. **Sui Y, Zhang W, Tang T *et al.* (2020):** Insulin-like growth factor-II overexpression accelerates parthenogenetic stem cell differentiation into cardiomyocytes and improves cardiac function after acute myocardial infarction in mice. Stem cell research & therapy, 11 (1): 86. https://doi.org/10.1186/s13287-020-1575-4
27. **Shen H, Gan P , Wang K *et al.* (2020):** Mononuclear diploid cardiomyocytes support neonatal mouse heart regeneration in response to paracrine IGF2 signaling. eLife, 9: e53071. https://doi.org/10.7554/eLife.53071
28. **Bogush N, Tan L , Naib H *et al.* (2020):** DUSP5 expression in left ventricular cardiomyocytes of young hearts regulates thyroid hormone (T3)-induced proliferative ERK1/2 signaling. Scientific reports, 10 (1): 21918. https://doi.org/10.1038/s41598-020-78825-x
29. **Xin M , Kim Y , Sutherland L *et al.* (2013)**: Hippo pathway effector Yap promotes cardiac regeneration. Proceedings of the National Academy of Sciences of the United States of America, 110 (34): 13839–13844. https://doi.org/10.1073/pnas.1313192110.