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Posted Date: 2 July 2024

doi: 10.20944/preprints202407.0148.v1

Keywords: Bicuspid Aortic Valve Stenosis(BCAS); Congenital Heart Disease(CHD); endothelial mesenchymal transformation (EndoMT); Magnetic Field; Cardiogenesis; Signaling Pathway

 doi:10.20944/preprints202407.0148.v1

Article

Higher Incidence of Congenital Aortic Valve Stenosis in Higher Magnetic Latitudes Countries: New Insights and Potential Therapies

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Introduction

Morphogenesis in biology constitute miraculous fact of our life on the planet. Decoding the mysteries of morphogenesis and the struggle to solve the complexity of the puzzle of creature started very late in human species time line. Deviation in the normal developmental steps of morphogenesis result in congenital anomalies which constitute the leading cause of death in most world countries. The most common congenital anomaly is congenital malformation of the human heart. Diverging from the prevailing view that ventricular septal defect is the commonest congenital heart disease (CHD),Bicuspid Aortic valve stenosis is in fact the most common CHD surpassing the incidence of all CHDs collectively(3% versus 1% of all live birth). Most of the causes of congenital heart diseases(CHD) are still ,until the moment, obscure and unknown. CHD constitute major health ,social ,psychological and economic burden on individuals , families as well as world communities and nations. The most powerful scientific directive scout to solve the puzzle of causes of diseases is epidemiology. Epidemiology must be the guiding force towards the different scientific efforts to discover diseases in an attempt to look for therapeutic options , as well as, to discover preventive measures. Genetic as well as epigenetic and environmental risk factors play a significant role in manifestations of aortic valve disease in the congenital population. Towards the dream of aborting the process of cardiogenesis in humans, we established a nationwide epidemiological project devoted to discovering risk factors of CHD. The philosophy of the project was to adopt an etiological perspective based on collecting massive genetic and environmental data on each CHD, followed by statistical management to establish correlations and causes. A critical yet overlooked epigenetic manipulator of the process of morphogenesis is the planetary electromagnetic field effect. Every cell in our body is immersed in an environment of both external and internal fluctuating magnetic fields that can affect virtually every cell and circuit in biological systems to a certain degree, depending on the specific biological system and the nature of the magnetic fields. We established the second Global Coherence Initiative (GCI) system in the CHD project area. Another 6 monitoring systems are located in strategic locations around the planet in California in the USA, Edmonton in Canada, United Kingdom, Lithuania, NewZyland and South Africa. The Global Coherence Initiative (GCI) system is the first global network of GPS time stamped detectors designed to continuously measure magnetic signals that occur in the same range as human physiological frequencies such as the brain and cardiovascular systems. The detector system consists of ultrasensitive magnetic field detectors (sensitivity 10^{-12} T) specifically designed to measure the magnetic resonances in the earth/ionosphere cavity, resonances that are generated by the vibrations of the earth's geomagnetic field lines and ultra-low frequencies that occur in the earth's magnetic field. We record the alternating magnetic field strengths in 3 dimensions over a relatively wide frequency range (0.01-300 Hz) while maintaining a flat frequency response. This paper is devoted to exploring the potential impact of the fluctuating variable electromagnetic forces in the aortic valve biogenesis and its signaling molecular pathways,

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towards the discovery of therapeutic and preventive measures for congenital aortic stenosis in the human species.

Materials and Method

Genetic and environmental risk factors of congenital heart defects (CHD) project expands to cover the whole populated area of the Kingdom of Saudi Arabia. It includes Hospitals, primary health care centers, and pediatric cardiology centers concerned with care of CHD. We define Congenital heart disease (CHD) as a gross structural abnormality of the heart or intrathoracic great vessels that is actually or potentially of functional significance [1]. Arrhythmias in a normally structured heart were excluded because of uncertainty about their congenital origin. Participants in the project constitute a unique national sample of live born infants in the first year of life. The main objective of the project was to shed light on probable environmental and genetic risk factors implicated in the etiology of Congenital Heart Disease (CHD). Cases were defined as infants born alive with CHD in the five years of the study period to parents who were residents of the study area. Disease status was defined as CHD present at birth (coded 1) else, it is absent for the (coded 0). Data sheets were designed to filter and encode the information from the questionnaires and qualitatively controlled (Figure 1).

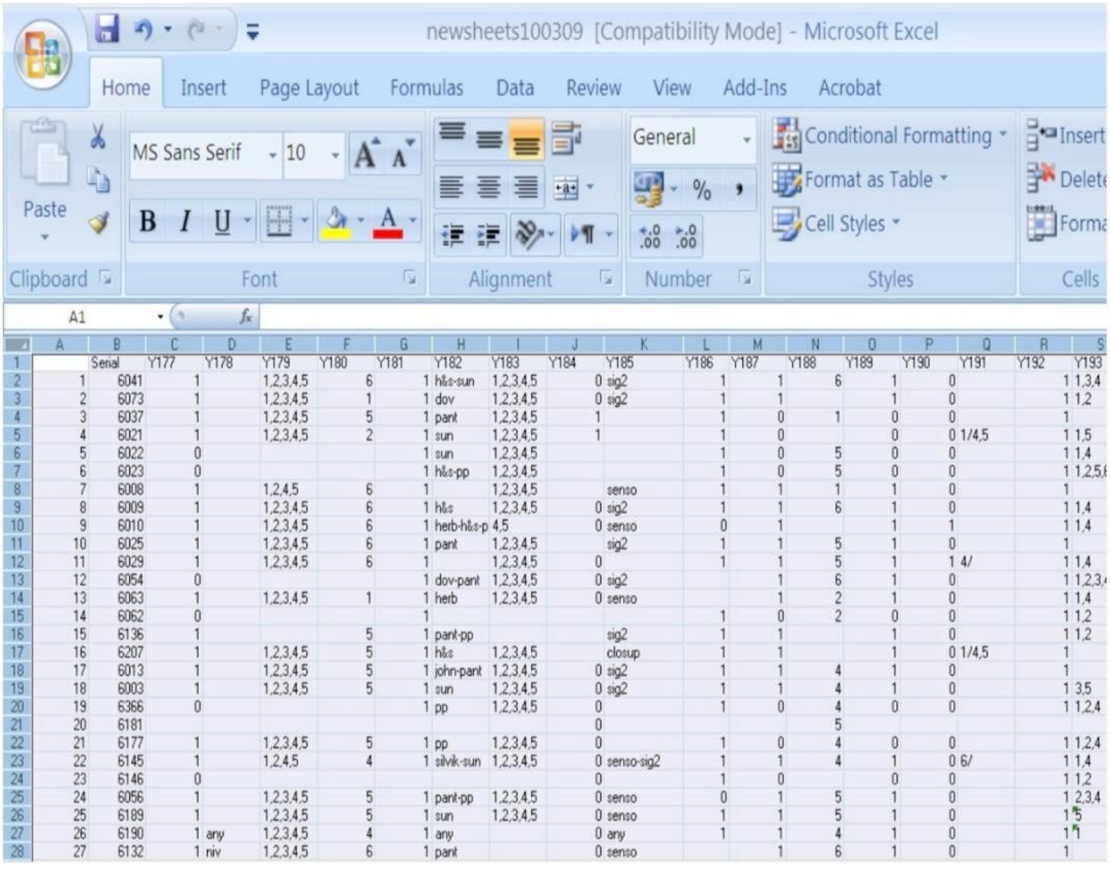

Figure 1. Sample of data entry sheet used to obtain 3,018,724 statistical variables of potential risk factors of congenital heart malformations.

CHD diagnosis was confirmed before 1 year of age by certified pediatric cardiologists, according to a hierarchical classification system (Figure 2). This hierarchy is divided into 49 morphogenetic landmarks adopted to pinpoint the chronobiological timing of the embryogenic insult giving rise to the specific congenital heart disease subtype. One of the most important difficulties was the decision of the timing of the complex anomalies. For purity of data trying as much as possible to hunt the cause or the risk factor under investigation, the decision was to consider the diagnosis according to

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the timing of the first insult of the complex collection of anomalies according to the hierarchy in Figure 2 [2]. Each subtype of the 4491 affected cases with congenital heart diseases received 412 questions and accordingly 412 statistical variables. Questionnaires were expanded to include a detailed inquiry about exposures to various environmental and genetic factors [3]. 7327 questionnaires for affected cases and controls were fulfilled by trained interviewers. 97 cases were isolated aortic valve stenosis, constituting 2.16% of the whole affected population. All interviews were completed with a physical confrontation with parents mainly mothers. Parents are interviewed about a wide range of genetic, physiological, medical and exposure to environmental factors that occurred during and before the pregnancy, assessing exposures at home, job and other sites. Vulnerability period in our project was unique as we define it as the six months period , three months before conception and three months post conception.

1. First fusion of epimyocardial layers of bilateral heart primordia	25. Upstream (proximal) division of bulbus with closure of interventricular foramen complete
2. Completion of fusion of primordia of bulbus cordis and primordia of ventricles	26. Appearance of intercalated swellings of semilunar valves
3. First appearance of myofibrils in myocardium	27. Semilunar valves achieve grossly mature form
4. First myocardial contractions	28. Atrioventricular valves achieve grossly mature form
5. Blood flow through heart begins	29. Aortic arches I definitive
6. Appearance of external atrioventricular and bulboventricular grooves or sulci	30. Dorsal aortas fuse
7. Earliest heart curvature apparent	31. Aortic arches I disappear
8. Achievement of S-shaped curve	32. Aortic arches II definitive
9. Expansion and ventromedial rotation of primordium of right ventricle	33. Aortic arches II disappear
10. Atrial septum primum appears	34. Aortic arches III definitive
11. Perforations (ostium secundum) in atrial septum first seen	35. Aortic arches IV definitive
12. Atrial septum secundum first definable	36. Dorsal aortas between arches III and IV disappear
13. Alignment of right atrial cavity with primordium of right ventricular cavity	37. Dorsal aorta (right or left) distal to arch IV disappears
14. Ventral and dorsal endocardial cushions first definable	38. Aortic arches VI definitive
15. Ostium primum closed by fusion of septum primum with endocardial cushions	39. Dorsal portion of one (right or left) aortic arch VI disappears
16. Ventral and dorsal endocardial cushions unite	40. Buds of main pulmonary vein projects from atrium
17. Cells first seen in cardiac jelly	41. Main pulmonary vein unites with pulmonary venous plexus
18. Trabeculations first seen in regions of ventricles	42. Buds of coronary veins from coronary sinus first definable
19. Muscular ventricular septum first definable	43. Buds of coronary arteries first definable
20. Aortic-pulmonary septum first definable	44. Left anterior cardinal vein obliterated
21. Internal division of aortic sac by aortic-pulmonary septum complete	45. Mesenteric portion of interior vena cava first definable
22. Rotation of downstream (distal) segment of bulbus cordis	46. Conduction system first definable histologically
23. Septa or ridges of bulbus cordis first definable	47. Main conduction system organized in its major form
24. Downstream (distal) division of bulbus cordis completed	48. Purkinje system can be identified
	49. Nervous tissue first definable histologically in heart or great arteries
From Sissman HJ. Developmental landmarks and cardiac morphogenesis: comparative chronology. Am J Cardiol 1970; 25:141.	

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Figure 2. Developmental landmarks of the chronobiology of human cardiogenesis. Land marks 24,25,26 and 27 are witnessing the formation of the aortic valve [2].

Original data was strictly maintained and adhered to standardization protocol. Every single CHD subtype was comprehensively investigated with demographic data, pregnancy history, drug history, residency, parental profession, social and income history, maternal exposures as well as paternal exposures during the 6 month vulnerability period. The project questionnaire was in the form of published book devoted for this project and for future investigators [3]. A cohort composed of 2604 patients was studied for the proportion of each cardiac type in the four most populated regions of the country. This cohort was established to overcome the referral bias as most of the cardiac centers in the country are in the central region. For planetary magnetic field detection, we use ultrasensitive magnetic field detectors (sensitivity 10-12 T) specifically designed to measure the magnetic resonances in the earth/ionosphere cavity, capable of detecting the local alternating magnetic field strengths in 3 dimensions over a relatively wide frequency range (0.01-300 Hz).

Results

Isolated aortic valve (AS) pathology , mostly bicuspid aortic valve stenosis was found in 97 cases out of the project 4491 cases(2.16%) (Table 1).

Table 1. There are 97 cases of AS from the total of 4491 subject with CHD.

AS	F req.	Percent	Cum.
No	4,394	97.84	97.84
Yes	97	2.16	100
Total	4,491	100	

Percentage of cardiac lesions in 2604 patients with congenital heart disease in the 4 most populated regions in Saudi Arabia is shown in Table 2.

Table 2. Distribution of valvular aortic stenosis and other most important CHD subtypes in the four most populated regions of the country.

Lesion	Al Hassa		South east		North central		West		Overall	
	No.	%	No.	%	No.	%	No.	%	No.	%
VSD	292	39.5	109	32.5	123	38.4	359	29.7	883	33.9
ASD	85	11.5	35	10.4	37	11.6	314	26.0	471	18.1
PS	66	8.9	34	10.1	29	9.1	195	16.1	324	12.4
PDA	64	8.6	53	15.8	25	7.8	159	13.2	301	11.6
AVSD	26	3.5	12	3.6	16	5.0	38	3.1	92	3.5
TOF	31	4.2	18	5.4	15	4.7	26	2.2	90	3.5
AS	26	3.5	9	2.7	9	2.8	20	1.6	64	2.5
COA	20	2.7	11	3.3	6	1.9	23	1.9	60	2.3
D-TGA	14	1.9	5	1.5	14	4.4	22	1.8	55	2.1
Other	116	15.7	49	14.6	46	14.4	53	4.4	264	10.1

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Total	740	100.0	335	100.0	320	100.0	1209	100.0	2604	100.0

VSD = ventricular septal defect; ASD = atrial septal defect; PS = pulmonary stenosis; PDA = patent ductus arteriosus; AVSD atrioventricular septal defect; TOF = tetralogy of Fallot; AS = aortic stenosis; COA = coarctation of aorta; D-TGA = dextro-transposition of great arteries.

Higher incidence of valvular aortic stenosi(VAS) is observed as we move away from the equator toward the north. In incremental pattern the incidence of valvular aortic stenosi(VAS) is increasing moving from low magnetic latitudes to high magnetic latitudes countries(lowest in Nigeria then Japan then Saudi Arabia then the United State then the United Kingdome then Denmark then Sweden and highest in Canada), Table 3.

Table 3. Distribution of most frequent Congenital Heart Diseases in 9 countries ranging from equator level with low latitude to north pole level with high latitude.

Lesion	Saudi Arabia % (n = 2604)	Sweden[a] % (n = 369)	USA[b] % (n= 163)	Nigeria % (n = 635)	Denmark % (n = 5249)	USA[c] % (n = 420)	UK[d] % (n = 338)	Canada[e] % (n = 464)	Japan % (n = 773)	Hungary % (n = 43)
VSD	33.9	27.1	31.3	35.0	24.0	32.1	28.1	31.0	60.0	20.9
ASD	18.1	4.3	6.1	7.5	9.4	7.4	8.3	11.2	5.3	10.4
PS	12.4	3.8	13.5	9.0	5.9	8.6	2.7	10.8	9.6	10.4
PDA	11.6	9.5	5.5	22.0	12.6	8.3	6.5	7.1	3.6	11.9
AVSD	3.5	3.0	3.7	-	2.6	3.6	7.4	-	1.8	4.5
TOF	3.5	4.1	3.7	10.0	5.8	5.0	8.6	8.0	5.8	4.5
AS	2.5	5.4	3.7	0.6	4.7	3.8	4.1	8.4	1.0	11.0
COA	2.3	9.8	5.5	2.0	7.0	6.7	5.6	3.4	2.7	6.0
D-TGA	2.1	6.0	3.7	4.5	4.8	2.6	5.6	2.6	2.2	4.5
Other	10.1	27.0	23.3	9.4	23.2	22.0	23.1	17.5	9.5	15.9

[a]Gothenburg; [b]California; [c]Multi-centre; [d]Blackpool; [e]Toronto. VSD = ventricular septal defect; ASD = atrial septal defect; PS = pulmonary stenosis; PDA = patent ductus arteriosus; AVSD = atrioventricular septal defect; TOF = tetralogy of Fallot; AS = aortic stenosis; COA = coarctation of aorta; D-TGA = dextro-transposition of great arteries. - = not measured.

The strength of Earth's magnetic field over Saudi Arabia is typically recorded at 25,000 to 35,000 nanoteslas (μT) compared to 55,500 nanoteslas in several hundred kilometers from the north pole in Edmonton to 64,000 nanoteslas recorded in the northern magnetic pole where the earth magnetic field lines enter the planet surface in the Canadian Arctic Archipelago.

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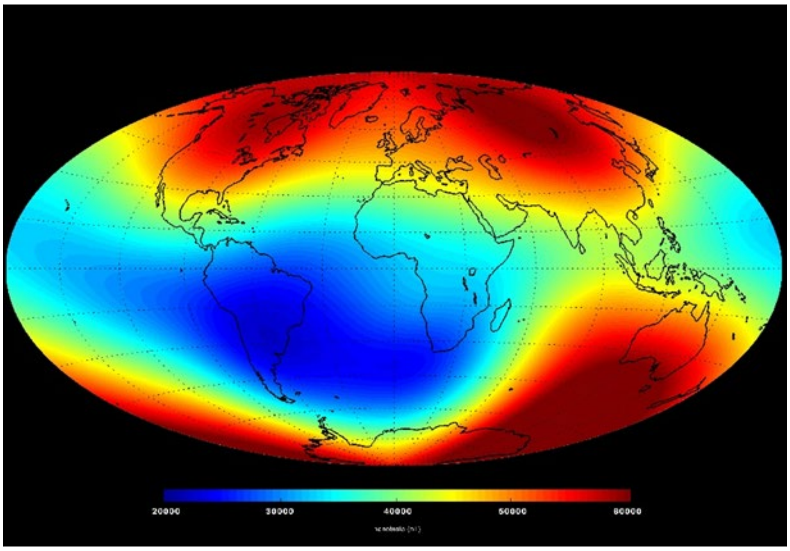

Figure 1. The strength of Earth's magnetic field over the project region , Saudi Arabia is typically around 25,000 to 35,000 nanoteslas (nT) at the surface. This range is similar to the magnetic field strength observed at the equator. The strength of Earth's magnetic field at the North Pole in the Canadian Arctic Archipelago is approximately 65,000 nanoteslas (nT).

Discussion

Valvular Aortic Stenosis (VAS) is the most prevalent valvular heart disease in the congenital as well as the acquired disease population in the planet. Valvular AS(VAS) was found in 2.16% of the our whole national project population (Table 1). Rigorous exemption of other left ventricular outflow tract obstruction was employed. Lower incidence of the congenital valvular aortic stenosis of 2.5% was documented also in previous study of congenital heart diseases CHDs in Saudi Arabia (Table 2) [4].Most of valvular aortic stenosis (VAS) cases were bicuspid aortic valve. During the author practice in different geographic locations worldwide we observe that higher incidence of congenital VAS is reported as we move away from the equator toward the north magnetic pole. In incremental pattern congenital VAS incidence is increasing moving from low magnetic latitudes to high magnetic latitudes (lowest in Nigeria then Japan then Saudi Arabia then United State then United Kingdome then Denmark then Sweden and highest in Canada) (Table 3). It is worth noting that the magnetic field strength experienced by cardiac cells in vivo is primarily influenced by the magnetic field of the earth, which is on the order of nanoteslas(nT). In the northern hemisphere, specifically at the north pole, the magnetic field lines are more concentrated and closer to the surface of the Earth, resulting in a stronger magnetic field. Our monitoring site detects the local alternating magnetic field strengths in 3 dimensions over a relatively wide frequency range (0.01-300 Hz) while maintaining a flat frequency response. The strength of Earth's magnetic field over Saudi Arabia is typically around 25,ooo to 35,000 nanoteslas (nT) at the surface. This range is similar to the magnetic field strength observed at the equator. The strength of Earth's magnetic field at the North Pole is approximately 6,000 nanoteslas (nT) Figure 1. The sensitivity of human hearth’s rhythm to the fluctuations of Earth’s local magnetic field is known to be variable [5]. Not only cardiac rhythm but also cardiogenesis is affected by planetary magnetic field. Studies about the effects of electromagnetic fields that we are exposed to with intensity of 100 nT and frequency of 50 1OO Hz on various species of animal embryos (fish, chick, fly, sea urchin, rat, and mouse) indicate that early stages of embryonic development are responsive to fluctuating magnetic fields [6]. The difference between the strength of a planetary magnetic field and the frequency of a magnetic field is delicate but deserve consideration. The strength of the Earth's magnetic field can influence the orientation and movement of certain molecules and ions within human cells, particularly those involved in cellular signaling pathways. Certain biomolecules, such as radical pairs and magnetite-containing particles, can interact with the

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Earth's magnetic field and potentially affect cellular processes, including gene expression, cell proliferation, and neural function. On the other hand ,magnetic frequency especially the extremely low-frequency magnetic field (ELF) can potentially influence the behavior of charged particles, ion channels, and other biomolecules involved in cellular signaling pathways. The concept of astrophysical resonance and its implementations in physiological as well as astrophysical rhythms is of critical significance for life on earth and to human consciousness experience [7]. The resonance-like responses of biological systems to low-frequency magnetic field (LFMF) with a specific frequency and amplitude, have been discussed in recent publications.[8]. In our opinion the resonance-like response is the most plausible explanation to interpret the electromagnetic field effect on biological systems. Other possible mechanisms include fluid shear stress, hydrostatic pressure, substrate strains, trophic factors, and others. During embryogenesis, tissues are generated by morphogenetic events which are tightly controlled by temporally defined mechanical forces. Recently, short-term mechanical tissue perturbations as well as long-term cytoskeleton remodeling of neural tube in human embryo organoid was induced using a weak magnetic field [9].Perturbation of the critical organogenesis step known as Endothelial-to-mesenchymal Transformation (EndMT) in addition to the signaling pathways regulating it will yield a malformed aortic valve [10]. In normal physiological conditions, EndMT plays a fundamental role in forming the cardiac valves of the developing heart. EndMT, in addition, is contributing to the development of various cardiovascular diseases (CVD), such as atherosclerosis, fibrosis, and pulmonary arterial hypertension (PAH) [11]. Epithelial-mesenchymal transition (EMT) and endothelial–mesenchymal transition (EndMT) are physiological processes required for normal embryogenesis and healing. EndMT is often considered a subcategory of EMT since the endothelium is a specialized type of epithelial cell specifically lining blood vessels. However, these processes can be hijacked in pathological conditions to facilitate tissue fibrosis and cancer metastasis [12]. ***Therefore, a deeper understanding of the cellular and molecular mechanisms underlying EndMT in congenital as well as acquired heart diseases is expected to open a new era in reversing heart disease in the human species***. The most common signaling molecules linked to EndMT in human valvular heart disease are : transforming growth factor-β (Tgfβ), bone morphogenetic protein (BMP) , Wnt, Notch and vascular endothelial growth factor A (Vegf). During our journey in the last 25 years in investigating planetary electromagnetic field and its effect on biology on Earth we recognize that EndMT and its signaling pathways are delicately affected by low magnetic field exposure and fluctuations. As a matter of fact, *all biological systems on the planet are exposed to* geomagnetic and solar electromagnetic fields affecting a wide range of human rhythmic systems*. These fields* which is complex, an extremely wide-spectrum changing, both on long-term basis as well as on micro-time scale , *can affect virtually every cell and circuit to a greater or lesser degree* from our embryonic stage existence until the elderly [13,14]. *The manipulating of the EndoMT signaling pathways with specific frequencies has the potential capability to reverse its aberrant behavior in valave diseases and other cardiovascular diseases . This step may provide unprecedented therapeutic potentials to treat aortic valve stenosis non invasively in human. Manipulation of EndoMT related signaling molecular proteins ,was actually, practiced in other specialties. Transforming growth factor-beta (TGF-β) is a key cytokine orchestrating both EMT and EndMT*. Inhibition of the EndMT process, e.g., by inhibiting TGF-β signaling pathway, is being pursued for the treatment of diseases associated with/caused by EndMT [15]. The TGF-β/ BMP signaling pathway plays an important regulatory role in bone repair. TGF-βs and BMPs, as multifunctional growth factors, belong to the TGF-β super family. The promotional effects of Pulsed electromagnetic field (PEMF) on osteogenesis and angiogenesis in bone repair have been well established in either vitro or in vivo animal studies. Pulsed electromagnetic field (PEMF) is known to stimulate Bone Morphogenetic Protein-2 in human and result in dramatic revolutionary improvement of bone diseases thought to be incurable in the past like bone loss and bone defective repair mechanisms brought by trauma, osteonecrosis, osteoporosis, arthritis and tumors [15]. The Wnt signal transduction pathway, might be activated with PEMF [16] Targeting those molecular signaling pathways which is in common with valve formation and heart disease is exciting potential to incorporate biomagnetism and magnetic frequency therapies in heart disease therapeutics. More targeted precision in biomagnetism application is exposing the cells and its related pathways to magnetic frequencies utilizing Magnetic NanoParticles (MNPs). The mechanical force produced by MNPs in a low-frequency vibrating magnetic field is promising for the destruction of tumor cells [17]. This low frequency vibration either of natural planetary origin or intentionally introduced through MNPs might modify the signaling pathway of human heart valve formation. *It seems that the increasing strength of the earth electromagnetic field cruising from the equator toward the pole (Figure 1) with its inherent fluctuation has a significant contribution to the perturbation of the Endothelial-to-mesenchymal Transformation (EMT) and its delicate signaling pathways in the first 7 weeks of embryogenesis, yielding higher incidence of bicuspid aortic stenosis(BCAS) as we depart away from the equator.* Implementation of this new knowledge can be taken in two directions. ***First: Wisdom dictates that Increasing awareness of aortic valve disease in high latitude countries is an alert calling for more intensive diagnostic and therapeutic measures in those communities. Second : The potential to manipulate EndoMT and its signaling pathways or to reverse it with external electromagnetic power remains an exciting therapeutic option for wide array of congenital and acquired heart diseases including bicuspid aortic stenosis (BCAS).***

References

1. Alabdulgader A. Congenital heart disease in 740 subjects: epidemiological aspects. Annals of tropical paediatrics. 2001; 21: 111-118.
2. The science and practice of pediatric cardiology, second edition: Volumes I and II: Edited by Arthur Garson Jr, J Timothy Bricker, David J. Fisher, and Steven R. Neish Williams & Wilkins, Baltimore (1998) 3,200 pages, ISBN: 0-683-034 17-0. Clin Cardiol. 1999; 22: 54.
3. Abdullah Alabdulgader,Congenital Heart Disease Project in Kingdom of Saudi Arabia.Alahssa1427H.ISBN:1-2-901-56-9960.King Fahad National Library. Riyadh, Saudi Arabia.
4. Alabdulgader A. Congenital heart disease in Saudi Arabia: current epidemiology and future projections. East Mediterr Health J. 2006; 12: 157-167.
5. Alabdulgade, A.; Maccraty, R.; Atkinson, M.; Vainoras, A.; Berškienė, K.; Mauricienė, V.; Navickas, Z.; Šmidtaitė, R.; Landauskas, M.; Daunoravičienė, A. Human heart rhythm sensitivity to earth local magnetic field fluctuations. *J. Vibroeng.* 2015, *17*, 3271–3278. [Google Scholar]
6. Cameron IL, Hardman WE, Winters WD, Zimmerman S, Zimmerman AM. Environmental magnetic fields: influences on early embryogenesis. J Cell Biochem. 1993 Apr;51(4):417-25. doi: 10.1002/jcb.2400510406. PMID: 8496244.
7. Abdullah Abdulrhman Al Abdulgader. Quantum Consciousness and the Heart Based Resonant Frequencies Theory. Arch Neurol & Neurosci. 9(4): 2021. ANN.MS.ID.000719
8. Krylov VV, Osipova EA. Molecular Biological Effects of Weak Low-Frequency Magnetic Fields: Frequency-Amplitude Efficiency Windows and Possible Mechanisms. Int J Mol Sci. 2023 Jul 1;24(13):10989. doi: 10.3390/ijms241310989. PMID: 37446167; PMCID: PMC10342092.
9. Abdel Fattah, A.R., Kolaitis, N., Van Daele, K. et al. Targeted mechanical stimulation via magnetic nanoparticles guides in vitro tissue development. *Nat Commun* 14, 5281 (2023). https://doi.org/10.1038/s41467-023-41037-8
10. Lincoln J, Garg V. Etiology of valvular heart disease-genetic and developmental origins. Circ J. 2014;78(8):1801-7. doi: 10.1253/circj.cj-14-0510. Epub 2014 Jul 7. PMID: 24998280; PMCID: PMC7313685.
11. Peng, Q.; Shan, D.; Cui, K.; Li, K.; Zhu, B.; Wu, H.; Wang, B.; Wong, S.; Norton, V.; Dong, Y.; et al. The Role of Endothelial-to-Mesenchymal Transition in Cardiovascular Disease. *Cells* 2022, *11*, 1834. https://doi.org/10.3390/cells11111834
12. Shu DY, Butcher E, Saint-Geniez M. EMT and EndMT: Emerging Roles in Age-Related Macular Degeneration. Int J Mol Sci. 2020 Jun 16;21(12):4271. doi: 10.3390/ijms21124271. PMID: 32560057; PMCID: PMC7349630.
13. Alabdulgader, A., McCraty, R., Atkinson, M. et al. Long-Term Study of Heart Rate Variability Responses to Changes in the Solar and Geomagnetic Environment. Sci Rep 8, 2663 (2018). https://doi.org/10.1038/s41598-018-20932-x
14. S. Subrahmanyam, P. V. Sanker Narayan and T. M. Srinivasan. Effect of Magnetic Micropulsations. on the Biological Systems - a Bioenvironmental Study Int. J. Biometeor. 1985, vol. 29, no. 3, pp. 293-305.

 doi:10.20944/preprints202407.0148.v1

15. Flatscher J, Pavez Loriè E, Mittermayr R, Meznik P, Slezak P, Redl H, Slezak C. Pulsed Electromagnetic Fields (PEMF)-Physiological Response and Its Potential in Trauma Treatment. Int J Mol Sci. 2023 Jul 8;24(14):11239. doi: 10.3390/ijms241411239. PMID: 37510998; PMCID: PMC10379303.
16. Kulkarni NH, Wei T, Kumar A, Dow ER, Stewart TR, Shou J, N'Cho M, Sterchi DL, Gitter BD, Higgs RE, Halladay DL, Engler TA, Martin TJ, Bryant HU, Ma YL, Onyia JE: Changes in osteoblast, chondrocyte, and adipocyte lineages mediate the bone anabolic actions of PTH and small molecule GSK-3 inhibitor. J Cell Biochem 2007;102:1504-1518
17. *CS Appl. Nano Mater.* 2022, 5, 8, 10118–10136 Publication Date: August 15, 2022 https://doi.org/10.1021/acsanm.2c02014.