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Contents **Page**

International Journal of Anatomical Sciences, 2013, 4(2): 03-10.

Research Paper

Ageing Induced Changes in Ventricular Myocardium: A Histological and Histomophometrical Study

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Key Words: Ageing effects – myocardial changes

Abstract: The objective of the present study is to evaluate the ageing mediated alteration in the cardiac tissue by histological and histomorphometrical prospective. The Wistar albino rats were divided in to two groups. Group I – Young (3-5 months) and Group II – Aged (28 months). Animals were sacrificed with transcardial perfusion with 4 % paraformoldehyde in PBS (pH 7.2) and heart was dissected out and post fixed in same fixative. The tissue was subjected to various analyses like morphological, histopathological, histomorphometrical, fibrotic changes (Trichrome staining) and apoptotic cell death (DAPI staining). The result showed significant increase in the size ($p<0.01$), weight ($p<0.01$) and volume ($p<0.01$), left ventricular wall thickness ($p>0.001$) and diameter of ventricular cavity ($p<0.001$) of the aged animal when compared to the control. The histological observation of aged rat heart showed marked alteration like hypertrophy of the cardiomyocytes, lymphocyte infiltration and the pyknotic nucleus and increased collagen deposition (tichrome staining). Histomorphometrical study showed significant increase in diameter ($p<0.001$) and volume of muscle fiber ($p<0.001$) with reduction of numerical density ($p<0.001$) in aged heart when compared to control. From the study it is hypothesized that cardiac hypertrophy, fibrosis and apoptosis in ventricular myocardium might be due to overload induced maladaptive response. Whether this aging-associated event progresses with senescence and becomes the most significant factor for the development of heart failure in the elderly requires further investigation.

Aging is the natural phenomenon, which is the process of growing old and is usually defined as the gradual biological impairment of normal function which has direct impact on the functional ability of organs and on the biological systems. These irreversible series of changes inevitably end in death. The numbers of aged people in North America are going to be double in next 25 years. In India it will increase from 76 million to 131 million in the period between 2001 – 2021. As the number of people over age 65 in North America is expected to double over the next 25 years. India it will increase from 76 million in

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2001 to 137 million by 2021 and having second largest aged population in the world.

Progressive fibrosis is a hallmark of aging in various organs such as kidney (Gagliano et al., 2000), liver (Gagliano et al., 2007), pancreas (Glaser and Stienecker, 2000) and lung (Calabresi et al., 2007). In the cardiovascular system a progressive age-related deposition of collagen in the vascular wall and in the cardiac interstitial and perivascular space leads to reduction of myocardial and arterial compliance (Lakatta and Levy, 2003). Cardiac aging is associated with diastolic dysfunction and heart failure with preserved systolic function (Lakatta and Levy, 2003; Kitzman et al., 2001). Some have demonstrated overt systolic dysfunction with age (Biesiadecki et al., 2010), but others have not (Barouch et al., 2003; Ma et al., 2010). Still other groups have shown that aging is associated with normal baseline cardiac function, but reduced cardiac response to inotropic stimuli (Lakatta and Sollott, 2002)

Furthermore, ageing mediated cardiomyocyte apoptosis and autophagy to the cardiomyopathy of aging have not been fully described. To describe and quantify these pathologies is the first step toward developing disease-specific approaches to the treatment of age-related cardiomyo-pathy. Though number of studies has been reported, the exact mechanism of ageing dependent collagen accumulation and their relation to apoptosis of cardiac myocytes is still unclear. Thus the present study was to evaluate the association of ageing induced ventricular fibrosis and apoptosis and their role in cardiac hypertrophy.

Materials and Methods

40 thigh specimens from adult human cadavers and 10 thigh specimens from dead born fetuses were made use of. Conventional dissection method was used for the study.

Observations

Animals

Animals were maintained as per the national guidelines and protocols, approved by our institutional ethical committee (IAEC No. 01 / 031 / 05). Healthy male Wistar albino rats (Rattus norvegicus) are divided into four groups: group I – control (young weighing 175–200 g 3–6 month); group II – aged (weighing 425 – 450 g 26 – 28 month old rats). The animals was maintained in 12 h light–dark cycle under controlled conditions and in room temperature (23 ± 2 ^{0}C), humidity (50 ± 5%). The animals were fed with standard rat pellet diet and drinking water ad libitum. The animals were sacrificed by trancardiac perfusion.

Tissue harvesting Morphology and histological study

At the end of experimental period animals were sacrificed by over dose of anesthesia (i.p), and followed by transcardial perfusion using 4 % paraformaldehyde in 0.1 M phosphate buffered saline. Hearts were dissected out and gross measurements (like size, weight, volume, thickness of ventricular wall and diameter of ventricular cavity) were measured. The tissues were postfixed in 4 % paraformaldehyde till the further analysis. A small piece of ventricular tissue was cut and it was processed for paraffin technique. Sections were stained using hematoxylin (Harris's) and eosin and observed under light microscope (Nikon. Japan).

Histomorphometry and stereological analyses

The conventional stereological principles and accepted morphometric procedures as outlined by Elias and Hyde, (1980) were used to obtain quantitative information, details of the procedure have been described previously (Prakash et al., 2008). Systematic unbiased random sampling (SURS) protocol was adopted. All the data's are expressed in relative value.

Masson Trichrome staining

The sections were subjected to Trichrome staining by the methods described by suresh and Prakash, (2011). The sections were deparaffinized in xylene and were dehydrated in graded alcohol and brought to distilled water. The nuclei were stained with Celestin blue hematoxylin methods and differentiated with 1% acid alcohol then washed well in tap water. After that the slides stained with acid fuchsin solution (acid fuchsin, glacial acetic acid and distilled H_2O) for 5 min and rinsed in distilled water. Treat the sections with phosphomolybdic acid solution for 5 min, drain the excess solution from the sections and then stain with methyl blue (Methyl blue, glacial acetic acid, distilled H_2O) for 3 min, treat the section with 1 % acetic acid for 2 min after washing with distilled water. Sections were dehydrated through alcohol, cleared in xylene and mounted with DPX.

Apoptotic study by DAPI staining

The apoptotic changes were studied by chromatin staining with DAPI. The paraffin sections were deparaffinized in xylene, dehydrated in graded alcohol and brought to distilled water and finally exposed to DAPI (2 µg/ ml) for 10 min at room temperature. The excess stain was removed by washing with PBS twice 5 min each and examined under ultraviolet illumination with a fluorescence microscope (Olympus Optical, Tokyo, Japan).

Statistical analysis

The significant difference between the mean value of control and experimental groups were analyzed according to the method of Zar (1974). All the data were subjected to Student't' test and data showing p value <0.05 was considered as statistically significant.

Observations

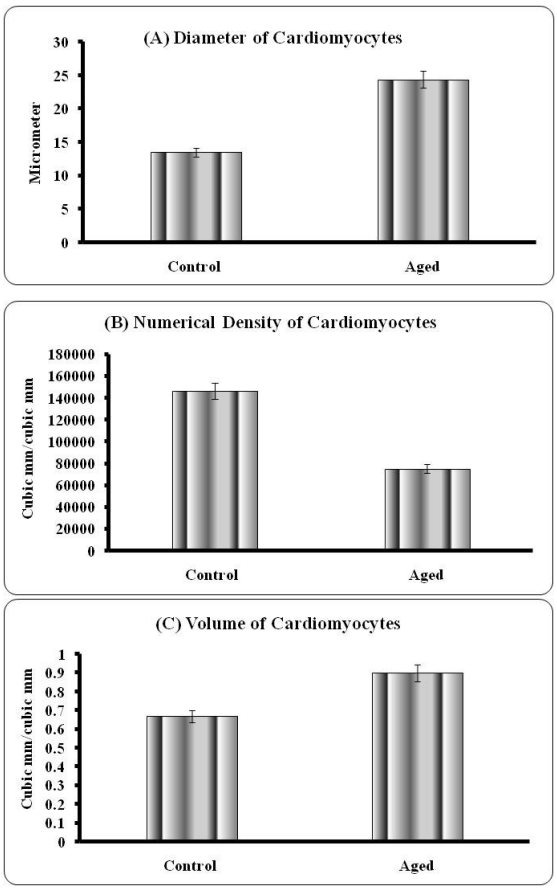
Morphology and histological study

Ageing mediated alteration in the morphology of the heart was studied. The data indicates that there was a significant increase in the size, volume ($p<0.01$) and weight ($p<0.01$) of the aged heart when compared to control. However the ventricular wall thickness was also found to be significantly ($p<0.001$) increased with concomitant reduction of ventricular cavity diameter in aged animal compared to control (Fig. 1). The histological of aged heart showed marked alteration like hypertrophy of the cardiomyocytes, neutophile infiltration and pyknotic nucleus when compared to young control (Fig. 2A & 2B).

Histomorphometrical study

Quantitative analyses of histological changes were done by the means of hisomorphometrical analysis. The result showed that the aged heart showed significant increase in diameter ($p<0.01$), volume (0.001) and significant reduction in numerical density ($p<0.001$) of the fibers when compared to control (Graph – A to C).

Graphs: Histomorphometry of cardiomyocyte in young and aged heart tissue. Each bar indicates mean ± SEM of n=6 animals. 'a' – control, ** - P< 0.01 and *** - p<0.001.



IJAS, 2013, 4(2): 03-10.

Massion's trichrome

The fibrotic changes in the heart were evaluated by special staining (massion trichrome). The data indicates that the young control heart showing negative for the trichrome staining but the aged animal showed more positive sites for trichrome. The positive sites are represented as presence of collagen fiber which is stained by blue, nucleus are stained by hematoxilin and the cytoplasm are stained by the brown (Fig. 2C & 2D).

Apoptotic study by DAPI staining

Ageing mediated cardiac myocyte apoptosis was studied by 4,6- diamidino-2-phenyl indoledihydrochloride (DAPI) staining. Both qualitative and quantitative study indicates that the aged heart showed significant increase in nucleus with apoptotic morphology when compared to control (Fig. 3).

Discussion

Ageing mediated structural and functional impairment of body systems is one of the leading health problems in the elderly population which finally leading to mortality. In the present study increased overall heart size was observed in aged animal particularly the left ventricle is showing marked alteration compared to right ventricle.

Fig. 1

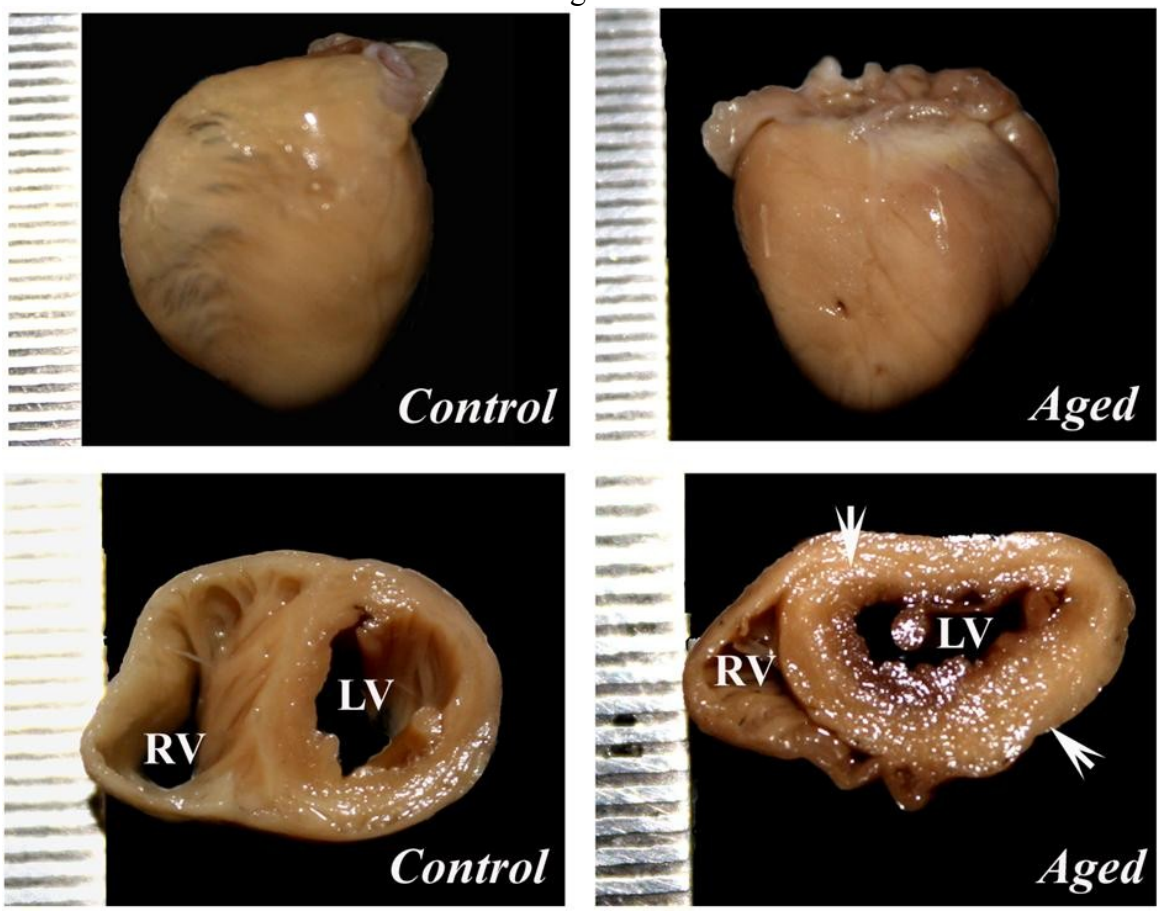
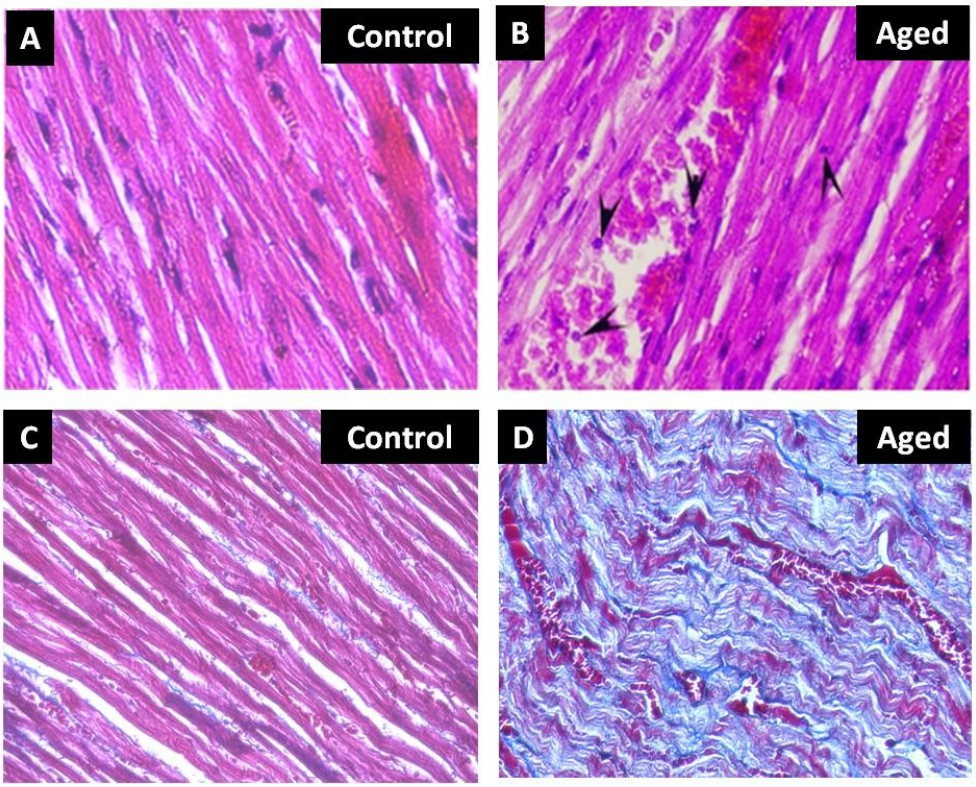


Figure 1 (A & B): showing the morphology of the heart in young and aged animal. The panel of C & D showing the cross section of the ventricles of control and aged heart. The arrow indicates that the increased wall thickness of in left ventricle of aged heart. RV – Right ventricle and LV – Left ventricle

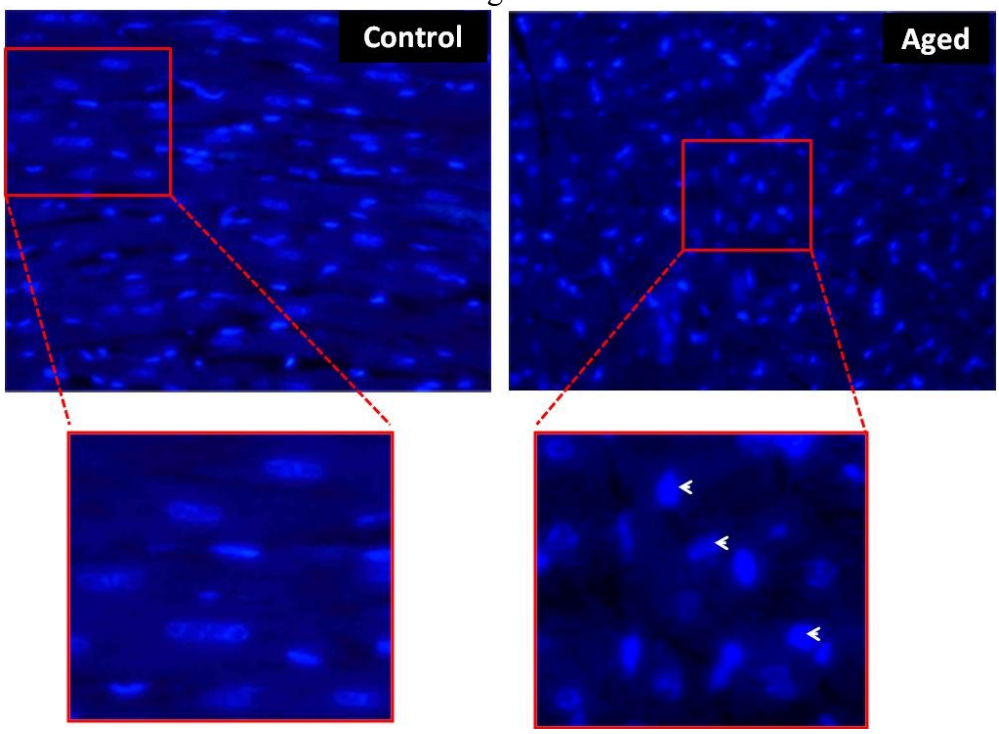
IJAS, 2013, 4(2): 03-10.

Fig. 2



(A & B): showing the histology of heart in young and aged heart tissue stained with H & E. The 2 (C & D) showing the heart tissue section stained with trichrome staining. The blue colour indicates the collagen fibres and the red indicates the muscle fibre.

Fig. 3



Nuclear morphology of the rat myocardium in control and aged heart tissue stained with DAPI. The aged myocardium showing the apoptotic nuclear morphology (arrow) compared to control

These changes might be due to the maladaptive process induced by biomechanical stress, be it extrinsic, such as in arterial hypertension or valvular heart disease, or intrinsic, as in familial hypertrophic cardiomyopathy (Frey and Olson, 2003). Furthermore, the increasing blood volume with body mass can be expected to result in an increased volume load on the heart, a condition in which an identical additional work demand is applied to both ventricles. However, the left ventricle is subjected to a greater pressure load because systemic arterial pressure is significantly higher than pulmonary pressure (Anversa et al., 1986; Isoyama and Nitta-Komatsubara, 2002). The combination of these effects on the left ventricle associated with a deficit in the coronary microcirculation may exceed its compensatory capacity, leading to myocyte necrosis.

Histological study increased the hypertrophy of the cardiac myocytes and neutrophil infiltration and the pignotic nucleus was observed in the aged animals when compared to young. These histological changes might be the normal ageing changes. However the lymphocytes infiltration clearly indicates that ageing mediated inflammatory reaction which is mainly due to increased serum cholesterol levels thereby it stimulate hypertension (Omoigui, 2007; Cieslik et al., 2011) which ultimately leading to increase work load to the cardiac tissue. As a result of overload the ventricular tissue increase their size as adaptive mechanism but it is maladaptive leads to hypertrophy of the muscle fiber. Furthermore, the ageing heart also showing the pyknotic nucleus which might be due to the increased inflammation reaction and the inflammation mediated oxidative stress (Pashkow, 2011) fabricate the irreversible changes in chromatin and karyorrhexis which finally leading to necrosis or the apoptosis. Consistent with histological alteration the DAPI staining conforming the ageing induced apoptosis in ventricular myocardium.

Histomorphometrical study revealed that ageing mediated increased size of the ventricular myocytes plays a crucial role in increased ventricular wall thickness. These changes mainly due to increased physical stress in ageing by activation of various endocrine, paracrine, and autocrine factors that activate a variety of receptors (Cooper, 1997; Chien 1999; Chien and Olson, 2002). These receptors trigger multiple cytoplasmic signal transduction cascades that regulate gene expression (Molkentin and Dorn, 2001), resulting in increased cell size due to increased synthesis of sarcomeric and other proteins together with reorganization of myofibrillar structures.

Masson's trichrome study showing marked increase in the fibrotic tissue in the aged heart than the control. These increased collagen deposition might be due to the ageing induced oxidative stress and the inflammatory reaction (Pashkow, 2011). These altered pathways might activate the fibroblast to synthesis of collagen (Siwik et al., 2001; Cheng et al., 2003) or the replacement (scar formation) mechanism in the apoptotic cardio myocytes (Isoyama and Nitta-Komatsubara, 2002). This increased cardiac fibrosis which disrupts normal cell-to-cell coupling and increases muscle stiffness this is usually reflected by incomplete relaxation during early diastolic filling, and presumably account for the decrease in early left ventricular diastolic compliance. The accumulation of collagen within the myocardium also disturbs the myocardial function which might be the main factor for ageing related ventricular tachycardia and fibrillation (Morita et al., 2009).

From the present study it is hypothesized that the ageing mediated ventricular dysfunction as a result of multi-factorial casus in particular oxidative stress and inflammation induced ventricular cardiac

myocyte apoptosis and fibrosis. Hence, it appears plausible that an increased cardiac cell size and increased extracellular collagen might contribute towards impairment of cardiac health and longevity in ageing. The mechanistic pathways for increased age-related collagen accumulation, apoptosis and cell size in the aged hearts will need to be further elucidated.

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Research Paper

Phenytoin Induced Up-regulation of LPL Gene in Albino Rat Testis Gene Microarray Analysis

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Key Words: micro array analyses – gene expression – LPL gene – phenytoin effects

Abstract: Phenytoin is widely used against all types of partial and tonic-clonic seizures. Phenytoin may alter the release and action of different hormones which may contribute to sexual dysfunction. The present study is aimed at the effect of phenytoin induced differential regulation of LPL gene in albino rat testis. The albino rats were divided into two groups, control and test. The test group was given 150mgs/kg/body weight of phenytoin orally and equal amount of normal saline was given for the control group. After 45 days with the rat under deep anesthesia, the testis were removed from the scrotum and stored in liquid nitrogen. The stored specimens of testis of control and tests group were subjected to cDNA microarray analysis. This study showed the differential expression of gene LPL in test group when compared with the control group.

Phenytoin is an anticonvulsant used to control grandmal and psychomotor seizures. It produces chromosomal anomalies. Phenytoin is excreted in human semen in small quantities and this may possibly affect testosterone levels. Reduced plasma concentration of free testosterone has been detected in male epileptic patients receiving phenytoin. Meng *et al.* observed possible mutagenic effect on human sperm cells. According to Bauer *et al.* and Kuhn-Velter *et al.,* phenytoin acts directly on the testis to inhibit testosterone synthesis by leydig cells. Researches done by Rebuff et al. points out increased levels of testosterone increases lipolytic potential and decrease the LPL activity of adipose tissue. The lipoprotein lipase encoded by LPL genes. The LPL is secreted by adipose tissues. The testis is covered by connective tissue capsule called tunica albuginea, internal to which is a vascular layer of loose connective tissue, called the tunica vasculosa. The connective tissue extends inward from the tunica vasculosa into the testis to form interstitial connective tissue, which surrounds, binds and supports seminiferous tubules. It contains blood vessels loose connective tissue containing adipocytes which secretes LPL. The endothelium of testicular blood vessels also secretes LPL. The present study is to assess the effect of phenytoin on rat testicular LPL genes.

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Materials and Methods

Animal treatment and sample collection

Male adult albino rats were segregated into control and test groups, The test group were treated with phenytoin 150mgs/kg body weight/day orally for 45 days similarly control groups were given equal amount of normal saline. In life study protocols, including animal housing, dosage, sacrifice and tissue harvesting were as per IAEC guidelines. After 45 days the tissue samples from test and control were collected in Rnase free tubes and snap frozen in liquid nitrogen. Frozen tissues were stored in RNA later at-70 c until processed for RNA extraction

RNA Isolation and DNA Microarray Hybridization And Analysis

RNA was extracted from the testis preserved in RNA later using QIagen's RNeasy minikit Cat#74104 and checked for purity and concentration. The extracted mRNA labeled with Agilent's Quick-Amp labeling kit (p/n5190-0442) Hybridized with Agilent's in situ Hybridization kit5188-5242 and scanned using high throughput Agilent scanner with "Surescan" technology.

Comprehensive Data Analysis

Data analysis includes automated feature extraction using Agilent feature extraction Software, Normalisation and statistical analysis and pathway and gene ontology analysis using Agilent's Genespring GXv1o==10.0 Biological interpretation of significant gene using Genotypics Biointerpreter Tool with literature curated information.

Observations

Phenytoin induced 3.2 up regulated LPL gene expression was observed in phenytoin treated group when compared with untreated control group.

Discussion

In bulls, LPL expressed in testis, heart, kidneys, adrenal gland and the spleen (Elkattawy *et al.*). LPL encodes lipoprotein lipase. Lipoprotein lipase is a member of lipase gene family. It is water soluble enzyme that hydrolyses triglycerides in lipoprotein which are found in chylomicrons and very low density lipoproteins into two free fatty acids and one monoacylglycerol molecules, Research work done by Vijay *et al.* pointed out intratesticular level of testosterone treated with phenytoin showed considerable decline in the 2nd to 7th week of sampling time. According to Bauer *et al.* and Kuhn-Velteer *et al.,* phenytoin acts directly on the testis to inhibit testosterone synthesis by Leydigs cells. In the present study phenytoin treated test group showed 3.2 fold change of LPL gene expression which possibly reveals the reciprocal relationship between testosterone and LPL.

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Research Paper

Coronary Venous Anatomy and its Relevance

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Key Words: coronary sinus, cardioplegia, thebesian valve, cardiac resynchronization therapy

Abstract: Coronary veins are not given its due importance unlike the arteries. It is being increasingly used in cardiothoracic surgeries and electrophysiological studies. Hence, the present study has been taken up to know the pattern of coronary venous anatomy and its relevance in the clinical field. The coronary sinus and its tributaries were studied by anatomical dissection in 25 adult human cadaveric hearts, which had been fixed in formalin solution. Coronary sinus was studied in relation to its location, length, and arteries accompanying it, tributaries and their variations. From the present study it has been found that the length of coronary sinus varies in between 2 cm to 5.5 cm. It was always located in the coronary sulcus, to the left of crus. It was accompanied by circumflex artery in half of the cases and also by right coronary in few. One specimen had middle cardiac vein directly opening into the right atrium. The great cardiac vein and middle cardiac vein was present in all specimens. In 64% of the hearts thebesian valve was membranous and crescentic. In 20% the ostium was valve less. This study highlights the importance of coronary venous anatomy. It is of relevance in catheterization of the coronary sinus for various procedures like in cardioplegia and electrophysiology.

Variations pertaining to the coronary arterial system have been described but less attention has been paid to the venous system. Coronary veins are not affected by atherosclerosis. In hearts affected by arteriosclerosis of arterial system, there is a richer, more uniform venous network in the subendocardial zone (Permyos *et al.*, 2001).

The cardiac venous system, has many applications in invasive cardiology which are 1) targeted drug delivery 2) retrograde cardioplegia administration 3) providing potential conduits to bypass coronary artery stenosis and 4) to deliver stem cells to the infracted myocardium (Singh *et al.,* 2005).

Coronary sinus is utilized to access the left atrial and left ventricular epicardium. Diagnostic and mapping maneuvers can be done through this route to determine the type of arrhythmia and also permit the delivery of ablative energy (Cappato *et al.,* 1997).

For cardiac resynchronization therapy in patients with heart failure, endocardial implantation will be successful if the left ventricular lead can be positioned in a vein draining that region with the latest mechanical activation (Nico *et al.*, 2006). Failure of left ventricular lead placement has been attributed to the inability to insert

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catheter in the coronary sinus and the lack of suitable side branches (Abraham 2003, Puglisi *et al.*, 2004).

The venous system is a useful conduit for delivery of percutaneous transcatheter treatment. Retrograde cardioplegia is achieved through the cardiac veins during cardiac surgeries and may help to flush the distal emboli from the arterial system (Iyer Praveen B, 2006).

Hence the present study was undertaken to know the coronary venous anatomy in cadaveric hearts in this region.

Materials and Methods

The coronary sinus and its tributaries were studied by anatomical dissection in 25 adult human cadaveric hearts, which had been fixed in formalin solution. Coronary sinus was studied in relation to its location, length, and arteries accompanying it. Length of the coronary sinus was measured from the point where oblique vein of left atrium opens the coronary sinus. Second point was taken at the junction, where coronary sinus pierces the wall of the right atrium.

The tributaries were also studied by careful dissection on the epicardial surface. Small, great, posterior, and middle cardiac vein were the first order tributaries, as they are made out well during routine dissection. Hence these have been mentioned in the present study. But the second and third order tributaries were difficult to dissect.

We measured the cranio caudal and transverse dimensions of the coronary sinus ostium and looked for the shape of the ostium, morphology of the thebesian valve. All the measurements were done using vernier caliper

Observations

Table 1 Coronary veins in relation to various studies

	Ortale J 2001	Gerber TC 2001	Longbloed 2005	Present study 2012
Great cardiac vein	100%	> 90%	100%	100%
Middle cardiac vein	100%	> 90%	100%	100%
Small cardiac vein	54%	*	46%	64%
Left marginal vein	97%	<50%	61%	92%
Vein of left ventricle	*	<50%	95%	92%
Anterior cardiac vein	*	*	*	16%
Oblique vein of left atrium	*	*	34%	36%

* Percentages of that tributary was not mentioned in that particular study

Table 2 Diameters of the coronary sinus ostium

	With valve (in mm)		Without valve (in mm)		
	Present study 2012	Gary S Mak 2009	Present study 2012	Gary S Mak 2009	Jongbloed 2005
Transverse diameter	5.04	7.3±2.8	10.11	9.4±2.9	14.7±4.4
Cranio caudal diameter	6	7.9±2.7	7.44	9.3±2.9	11.9±3.5

IJAS, 2013, 4(2): 14-19.

Table 3 Thebesian valve morphology

	Morphological characters	Herman *et al.*	Present study
1	Valveless	14.7%	20%
2	Crescentic, membranous	38%	46%
3	With fenestrations	5.3%	6%
4	Common Eustachian and thebesian valve	6%	8%
5	In some- completely occluding the ostium	30.7%	20%

Table 4 Arteries accompanying coronary sinus

Name of the artery	Incidence	
	Out of 25	%
Circumflex artery	13/25	52%
Right coronary artery	5/25	20%
Not accompanied by any vessels	5/25	20%
Both vessels	1/25	4%

Length of the Coronary sinus

The coronary sinus has been reported to be as long as 5.4 cm but is usually about 2.5 cm in length(Susan Standring, 2008). In the present study the length of coronary sinus varied from 2 to 5.5cm. Oblique vein of left atrium was observed in very few cases. Duct of cuvier was absent in the all the specimens. Middle cardiac vein directly opened into right atrium in one case. In a few, coronary sinus was intramural i.e. covered by few myocardial fibers.

Fig 1 Coronary sinus opening with a small muscular valve

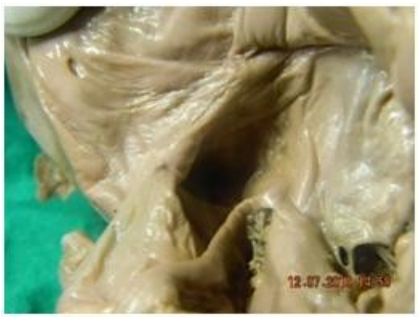

Fig 2 Coronary sinus opening with crescentic valve

Fig 3 Coronary sinus opening with membranous valve

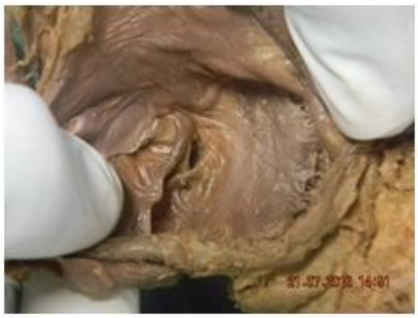

Fig 4 Coronary sinus opening without valve

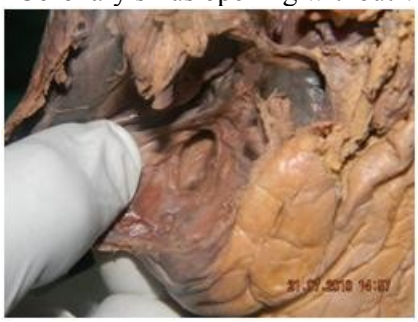

Fig 5 Location of great cardiac vein in the anterior interventricular groove

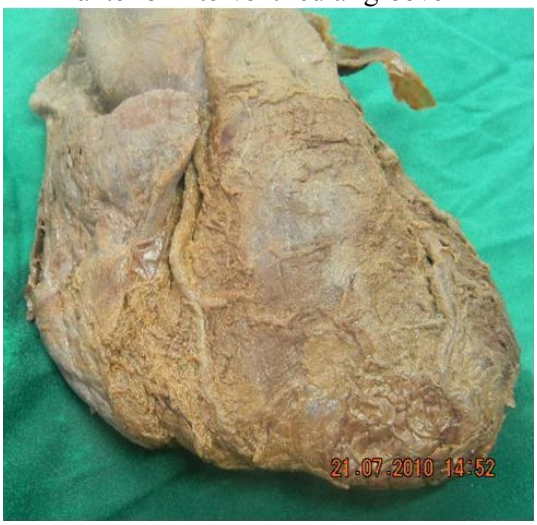

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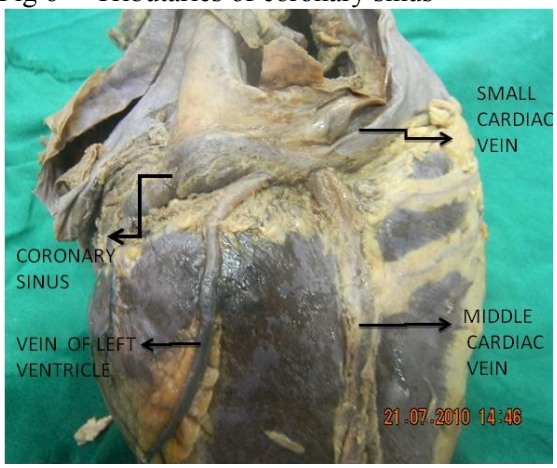
Fig 6 Tributaries of coronary sinus



Discussion

There are three venous systems that drain the heart: the coronary sinus, the anterior cardiac veins, and the venae cordis minimae. The coronary sinus receives all cardiac veins except venae cordis minimae and anterior cardiac veins. The coronary sinus opens into the right atrium between the opening of the inferior vena cava and the tricuspid orifice. It returns blood to the right atrium from nearly all regions of the heart, including the septa, and accounts for 75% of the coronary venous circulation. Studies to categorize variations in cardiac venous circulation based on the regions drained by cardiac veins have not produced any accepted pattern (Susan Standring, 2008).

According to the direction of flow of blood, two major variants can be distinguished: a majority (70%) in which the small cardiac vein is independent, small or absent. And a less frequent pattern (30%) in which this vein connects both coronary and anterior cardiac systems (Susan Standring, 2008).

Coronary sinus may be obliterated or absent. The great cardiac vein then drains into the superior venacava or left brachiocephalic vein via the right superior venacava. Several veins, including the middle cardiac vein, may converge to empty into a common opening into the right atrium. Coronary sinus may open into left atrium (Ronald *et al.*, 2010). In the present study coronary sinus was present in all the cases.

Variations of the coronary veins, may cause non homogenous distribution of retrograde cardioplegia and result in inadequate myocardial protection. In 1987, Ludinghausen examined 350 hearts and defined five groups (Types A, B, C, D & E) of cardiac vein variations (Permyos *et al., 2001)*.

Type A anterior and small cardiac veins enter the right atrium

Type B all major veins enter the coronary sinus

Type C anterior cardiac veins enter the right atrium

Type D great cardiac vein and vein of left ventricle enter the coronary sinus.

Type E Only veins of the left ventricle enter the coronary sinus.

In the present study the cardiac veins belonged to Type A in majority of cases (64%). Remaining hearts belonged to Type B (22%). Only in one case(4%) middle cardiac vein opened directly into right atrium.

Types D & E causes non-homogenous distribution of cardioplegia, hence inadequate myocardial protection.In some cases left ventricle and interventricular septum are poorly perfused due to inadequate drainage by the veins i.e. middle and small cardiac veins (Type D & E).

Great and middle cardiac vein was present in all cases as observed by previous authors. Even in the present study these veins were present in all the specimens (Table 1). But left marginal and vein of left ventricle are present in 50-75% of the heart (Ortale *et al.*, 2001; Gerber *et al.*, 2001; Morique *et al.*, 2005). In the present study,

these veins were present in 92%. This can be explained because; those cases where left marginal vein is absent had a previous history of myocardial infarction. This may limit optimal left ventricular lead positioning for cardiac resynchronization therapy (Nico *et al.*, 2006).

It has been observed that richer, more uniform venous network exists in the subendocardial zone of both ventricles in those with heart disease (Permyos Ruengsakulrachann *et al.*, 2001). Hence cardiac veins are being preferred for cardioplegia. Not only the lack of suitable side branches but also obstruction and ostial narrowing (e.g., by a thebesian valve) may complicate left ventricular lead implantation (Monique *et al.*, 2005)

Thebesian valve morphology (Table 2 & 3)

Coronary sinus opening is guarded by Thebesian valve. Six types of variations were observed involving valve of the coronary sinus ostium (Herman K, 1951). Thebesian valve was found to be present in majority of the hearts. Of these, 16% had a valve morphology covering greater than 75% of the ostium. It could be fibrous, fibromuscular, or muscular composition and devoid of fenestrations. These make them potentially complicating structures interfering with the cannulation of coronary sinus (Gary *et al.*, 2009). In the present study 20 % were valveless, crescentic and membranous in 46% and in remaining fenestrations were present. Hence catheterization may be difficult in some of the cases.

Embryology

Coronary sinus is derived from the left horn and body of the sinus venosus. Valve of the coronary sinus is derived from lower part of right venous valve. Variations in the shape of the thebesian valve could be due to defective formation or absorption of lower end of the right venous valve.

Conclusion

Since in many specimens coronary sinus was accompanied by coronary arteries, the arteries may help in venous return by their pulsations. Anatomy of coronary valve and variations are important in catheterization of the coronary sinus. There are numerous variations of the coronary veins, coronary sinus, valves, all of which may affect the degree of myocardial protection provided by retrograde cardioplegia. More anatomical studies can be done using radiology to know the segmental drainage of the heart and coronary venous anatomy as it is relevant in cardiac resynchronization therapy and electrophysiological studies.

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Case Report

Branching Pattern of Arch of Aorta – A Case Report

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Key Words: aorta, aorta branching pattern

Abstract: An anomaly in the branching pattern of arch of aorta observed during routine dissection classes for medical graduates is reported here for its academic value and interest.

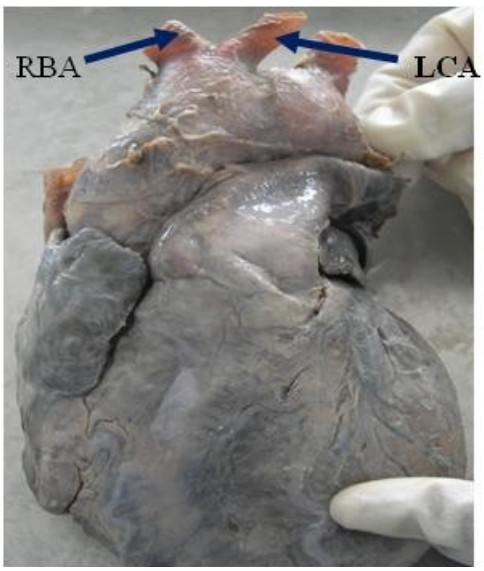
The arch of aorta begins behind the right border of the sternum at the level of the second costal cartilage and extends up to the left of body of fourth thoracic vertebra (McVay *et al.*, 1984). The aortic arch gives rise to three classical branches the brachio cephalic trunk, left common carotid artery & left subclavian artery (Williams *et al.*, 1989). Branches of the aorta vary in its origin but in some rare cases the position also varies. If it is high and is at the root of the neck, a most dangerous position in emergency tracheostomy. During the routine dissection of root of the neck and superior mediastinum the anomaly observed was reported.

Case Report

By careful dissection the arch of aorta and its branches are traced.

Left common carotid artery was arising in common with brachiocephalic trunk (Fig 1) and was crossing from the right to left side at the root of the neck (Fig 2). They were crossed by the left brachiocephalic vein in front. (Fig. 3). The crossing of the left common carotid artery took place 2.5 cm below the isthmus of the thyroid gland in front of the trachea about 1 cm above the suprasternal notch of the sternum (Fig 4).

Fig. 1 Shows Left common carotid artery arising in common with brachio-cephalic trunk from the arch of the aorta.



(RBA – Right brachiocephalic trunk LCA – Left common carotid artery)

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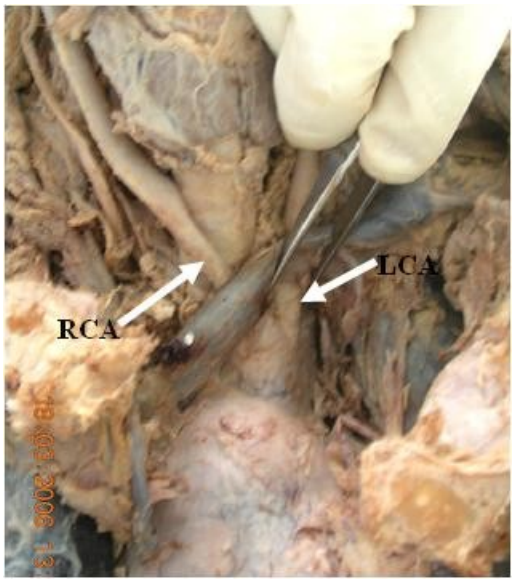
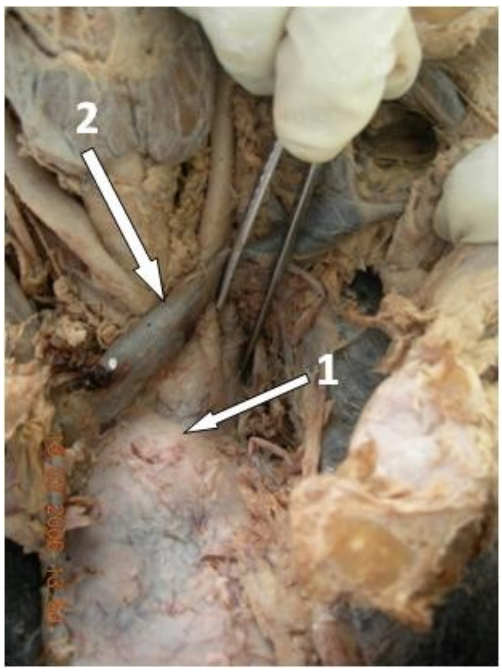
Fig. 2 Shows left common carotid artery crossing from right side to the left side.



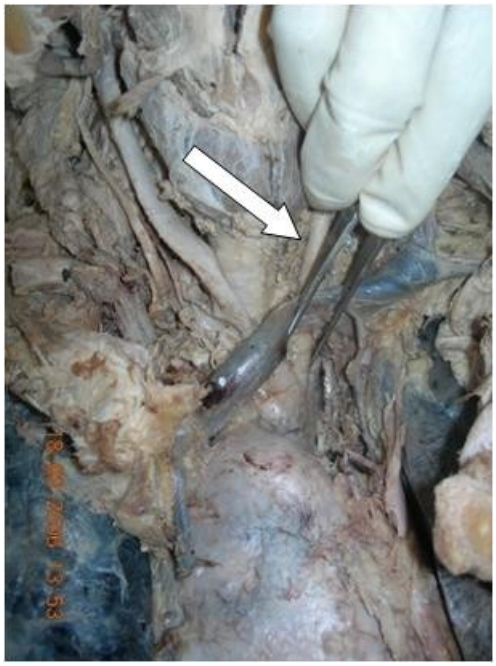
(RCA – Right common carotid artery LCA – Left common carotid artery)

Fig. 3 Common origin of brachiocephalic artery & left common carotid artery being crossed by left brachio-cephalic vein.



(1 – Left common carotid artery; 2 – Left brachiocephalic vein)

Fig. 4 Left common carotid artery crossing the trachea 2.5cms below the isthmus of the thyroid gland



Discussion:

As far as the branches of the aortic arch are concerned there are plenty of variations in their origins.

Anson *et al.* (1963) made an analysis of variations in the branches from thousand aortic arches and showed the following findings – The most common patterns 65% is formed by the separate origin of three branches springing from the vessel's convex aspect, in 27%, the left common carotid artery originates from the brachiocephalic trunk. In 2.5% each of the four arteries originates independently from the arch of the aorta separately, the remaining showed a great variety of patterns, the commonest being 1.2% symmetrical right and left brachio cephalic trunks (Anson, 1963). According to Mc Donald and Anson (1940) the so called normal type of branching apparently occurs only in a little more than 50% of Negroes, but in almost 75% of Whites. The most common variation from this, said to occur approximately twice as often (in almost

40% of cases) in Negroes, is the origin of the innominate and the left common carotid artery together; the common stem for these may be extremely short, hardly more than a slight bulge in the aorta, or , rarely quite long (Williams *et al.*, 1989).

Conclusion

Because of many changes involving in the transformation of the embryonic aortic arch system into the adult arterial pattern, it is understandable that variations may occur. This anomaly has to be remembered and care must be taken while doing emergency tracheostomy – a life saving maneuver. Additionally, a variant of origin and course of a great vessel arising from the aortic arch is of great clinical value, because of the ignorance on behalf of the surgeon of such a variation may cause serious surgical complications during procedures performed in the superior mediastinum and at the root of the neck.

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Case Report

Abnormal Communication Between Radial and Ulnar Nerves

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Key Words: radial nerve; ulnar nerve; median nerve; communications; schwanoma

Abstract: Variations in the branching pattern of the brachial plexus is not uncommon. But the variation found in the present case in a male cadaver during routine dissection is a rarest one. A communication was found between the radial and ulnar nerves in the upper arm. In addition the median nerve was formed by three roots, one medial and two lateral roots. Knowledge of the variations of brachial plexus will provide useful information for the surgeons for doing flap surgeries and also to minimize the possible complications of regional anesthesia.

Variations of the brachial plexus in its formation, course, branching pattern and distributions are commonly reported (Kerr, 1918; Linell, 1921; Yang *et al.,* 1995; Aktan *et al*, 2001; Utysal, 2003; Choi *et al.,* 2005; Das and Paul, 2005; Melani Rajendran and Nivedha, 2004 & 2005). Most common variations reported were the branching pattern and communications between median nerve and musculocutaneous nerves (Choi *et al.,* 2002; Loukas and Aqueelah, 2008). Absence of musculocutaneous nerve (Kosugi *et al.,* 1992; Nayak, 2007; Sathyanarayana, 2009), Martin - Gruber anastomosis (Lee *et al.,* 2005; Azhagiri, 2012), communication between radial and ulnar nerves on the dorsum of the hand (Maria Loukas *et al.,* 2008).

Case Report

During routine dissection, the variation was found in a male cadaver only on the right side. A communication was observed between the radial and ulnar nerves. It arose from the radial nerve before entering into the radial groove and joined the ulnar nerve about 15cms above the intercondylar line. The communication was approximately 8 cms length and it gave off branches to brachialis and medial head of triceps brachii and then joined the ulnar nerve (Fig. 1).

The ulnar nerve showed a localized solitary swelling approximately 12cms above the intercondylar line. It was ovoid in shape and measured about 3 cms x 1.5 cms. It was hard in consistency and free from the surrounding tissues and can be considered as schwanoma (Fig. 2).

Besides these observations, in addition, the median nerve was formed by three roots i.e., two roots from the lateral cord and one root from the medial cord. The additional root from the lateral cord was given off at the level of origin of musculocutaneous nerve and joined the median nerve at a lower level anterolateral to the third part of the axillary artery. The medial root was shorter from the medial cord which had normal course and relations (Fig. 3).

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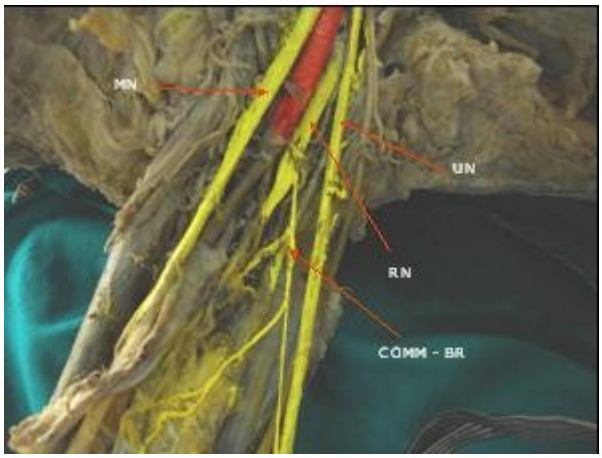
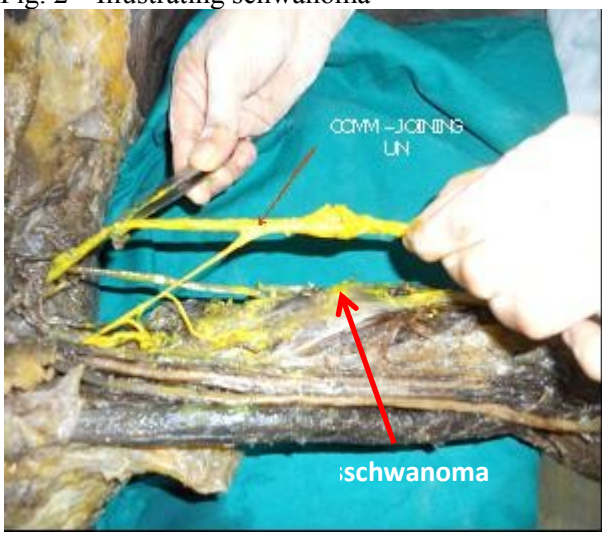
Fig. 1 Communication between radial and ulnar nerves



(RN-radial nerve UL-ulnar nerve MN-median nerve com.br–communication br –giving branches to brachialis and medial head of triceps brachii)

Fig. 2 Illustrating schwanoma

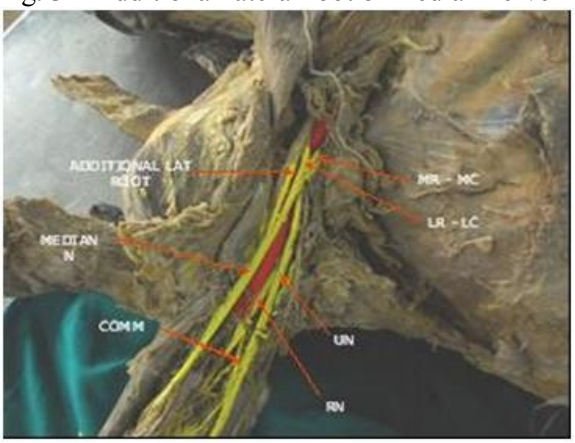


Discussion:

The variations in the formation of the median nerve may not affect the limb functioning but gains importance in clinical, neurosurgical and orthopedic procedures. Variation between the radial and ulnar nerves is rare and the percentage value is missing in the literature.

Variations in the branching pattern and communications between the median and musculocutaneous nerves are reported by many authors (Kerr,1918). Among the variations, the communication between the median and musculocutaneous nerves are also reported (Sarikeioglu *et al.,*2001; Choi *et al.,* 2002; Loukas and Aqueelah, 2008; Ozguner *et al.,* 2010) viz.communication between the median and ulnar nerves were also reported (Kazakos *et al.,*2005); Martin-Gruber anastomosis (Azhagiri and Melani Rajendran,2012); communication between the radial and ulnar nerves in the dorsum of the hand (Leucas *et al.,*2008;16% cases (Leis and Wells, 2008). Although the communication between the radial and ulnar nerves in the dorsum of the hand reported, the communication between these nerves in 6the arm is not reported in the literature and this is a rare variation. These communications can cause inappropriate nerve blockage in anaesthesia.

Fig. 3 Additional lateral root of median nerve



(LR LC- lateral root MR MC-medial root UN-ulnar nerve MN-median nerve)

The presence of two lateral roots of median nerve was reported by many others. Ischemic pain or variable arterial insufficience due to occlusion of the axillary artery by such variant additional roots of the median nerve during certain postural maneuvers of shoulder joint (Saeed and Rufai, 2003)

Embryology

In humans, the muscles of the upper limb develop from the mesenchyme of the paraxial mesoderm during the fifth week of embryonic life(Larsen,1977) and the neurons proliferate into the mesenchyme in different directions.Probably, the neurons of the nerve in this observation would have also taken such aberrant course.

Conclusion

Variation in nerves with abnormal origin, course and distribution are usually more prone to iatrogenic injuries and entrapment neuropathies (Roberts, 1992). Knowledge of such variations will also aid proper diagnosis of sensorimotor symptoms (Pontell *et al*, 2011), in any trauma of the arm and reconstructive repair surgery.

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Case Report

A Rare Case of Bilateral Small Kidneys in an Elderly Female – A Case Report

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Key Words: Renal aplasia, renal agenesis, bilateral small kidneys, solitary kidneys

Abstract: The objective present study is to report a rare case of bilateral small kidneys in elderly female age 75 years. This study was done in Bangalore district Bangalore. This was studied was during the month of April 2013. An elderly female aged 75 years old underwent general examination as outpatient at St .John's Medical College Hospital for her extreme weakness heaviness in the chest and breathlessness since one month. A detailed history revealed that she is non diabetic, non hypertensive, and not suffering from ischemic heart disease. There was a definite family history of congenital renal anomalies .Her second daughter aged 50 years has absence of right kidney since birth. Her elder son had Horse shoe shaped kidneys associated with diabetes and hypertension, Thorough examination was done here and investigated She underwent all investigation like complete haemogram, 2D ECHO and ultrasound of abdomen which revealed Bilateral small kidneys with grade 1 parenchymal changes and left renal exophytic cyst. Renal agenesis and renal aplasia are known to cause anomalies of kidneys like congenital solitary kidneys which are more prone for renal failure. Familial history of anomalies and associated anomalies are known to cause higher incidence of renal agenesis.than renal aplasia . There is difficulty in differential diagnosis of renal agenesis and renal aplasia.It is said Renal agenesis which is diagnosed clinically is more due to renal aplasia. This study on bilateral small kidneys is rare may due to renal aplasia which is diagnosed clinically by ultrasonographically, which is very rare entity; hence studied and reported.

Severe abnormalities of kidneys are due to renal agenesis and renal dysplasia that causes diseases which requires either dialysis or renal transplantation in the first year of life. Classical example is multi-cystic diseases of kidney where nephrons fail to develop and ureteric bud fails to branch. If there is failure of interaction occurs between metanephric mesoderm and ureteric bud occurs, then renal agenesis occurs. Renal agenesis also occurs when there is mutation of genes that regulates expression of signaling of GDNF1. There may be absence of one or both kidneys. It is called as Agenesis. There may be underdevelopment of one or both kidneys known as Hypoplasia of kidneys. There may be over development of kidney known as

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Hyperplasia of kidney. Sometimes there may be presence of adrenal tissue. In some cases, there may be distention of pelvis occurs due to urine resulting in urinary passages obstruction. This condition is known as hydronephrosis (Singh and Pal, 2007).

Case Report

An elderly female aged 75 years came to outpatient department of cardiology at St. John's Medical College Hospital for her extreme weakness heaviness in the chest and breathlessness since one month. A detailed history of personal history, drug history, past history, family history, history similar episodes in the past were taken. She was non diabetic, non hypertensive, and not suffering from ischemic heart disease. But there was definite family history of renal Anomalies. Her second daughter aged 50 years has absence of right kidney since birth, her elder son had Horse shoe shaped kidneys associated with diabetes and hypertension, Later thorough general and local examination were done here and investigated So she underwent relevant investigations like complete haemogram, 2D ECHO, X-Ray of the chest and ultrasound of abdomen were also done which revealed small bilateral kidneys with grade 1 parenchymal changes and left renal exophytic cyst.

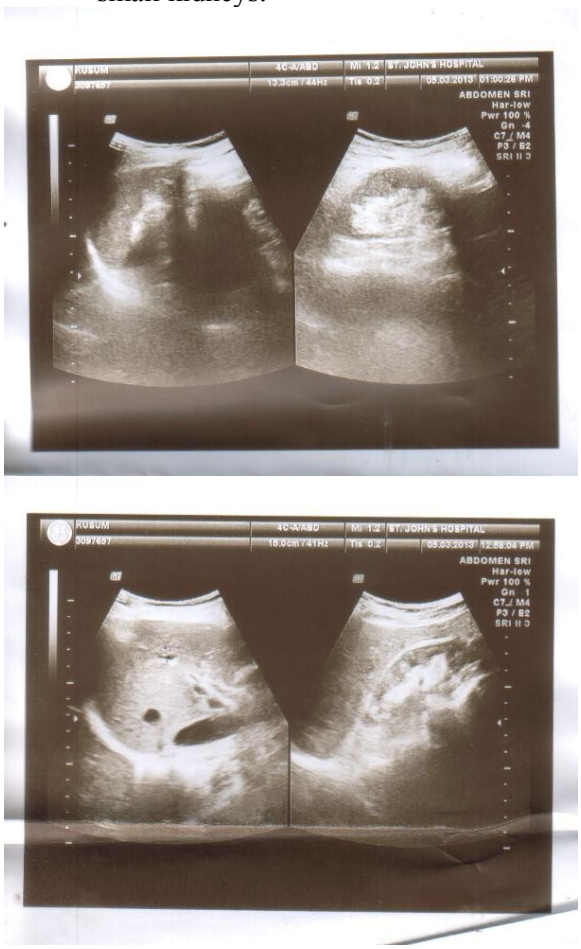
Ultrasound of abdomen was done here at St John's Medical College Hospital which is as follows:

i. Liver span is 10.6cm with no focal lesion
ii. Gall bladder is distended with CBD -3.5 cm, no caliculi
iii. Spleen is normal in size measuring 6.7 cm with no focal lesions
iv. Pancreas is normal with no duct dilatation.
v. Peripancreatic region is normal.
vi. No lymphadenopathy in the para aortic space.
vii. Kidney: The measurement of kidneys are as follows:

DESCRIPTIONS	RIGHT KIDNEY	LEFT KIDNEY
Bipolar length	8.1cm	7.2cm
Parenchymal thickness	0.8cm	0.9cm

Bilateral kidneys are smaller in size with grade 1 renal parencymal changes. Left kidney shows exophytic simple cyst measuring 2.3 cm x 2.2 cm in the upper pole of left kidney (left renal exophytic cyst). Urinary bladder–minimally distended. No free fluid in the abdomen.

Fig. 1 Ultrasonogram pictures showing small kidneys.



(Ultrasound photographs shows

- Both kidneys are small in size
- Subtle Obscuration and cortico medullary differentiation.
- Upper pole cortical cyst and size is 2.3cm and 2.2cmseen in left kidney.

IJAS, 2013, 4(2): 26-29.

- No evidence of any calculus nor pelvicalceal dilatations
- Right kidney measures 8.1cm in length,. Left kidney measures 7.2 cm)

Discussion:

During life, kidneys are reddish brown organs measuring 10cm in length, 5 cm in width, and 2.5 cm in thickness and moves with respiration of 2-3 cm in the vertical direction during the movement of diaphragm.

Primary screening was done in 52 babies for suspicion of small kidneys and one baby for multicystic kidney. But there was no renal agenesis. After one month, again second ultra sound was done .Three babies showed small kidneys with further decrease in size .They had no function .So they were diagnosed Renal Aplasia The incidence of Renal Aplasia is 1 in 1300. Again ultrasound was done which showed further regression in all three babies .By the end of one year kidney were hardly seen. These regressions may be due to Renal Aplasia (Masahiro *et al.* 2002). It is the genetic mutation or environmental factors that cause derangement in expression of genes (Woolf and Winnyard, 1998). In the autopsies studies, the most important cause of congenital solitary kidneys is Renal Agenesis (Fortune, 1927). A mother of two male children aged 45 years has absence of right kidney since birth There was no other anomaly in her body. Ultrasound of the abdomen showed on visualization of right kidney –Empty right renal fossa (Bilodi and Gangadhar, 2012). Her mother now has bilateral small kidneys since birth. DMSA Renoscintigraphy was done in nine children. There were 8 children with small kidneys & one with Multicystic dysplastic kidney. There were 4 kidneys which were non functioning, one showed bilateral hypoplasic kidney, four patient showed unilateral hypoplastic kidney. All five with hypoplastic kidneys were boys. No other congenital anomalies were present in these children. While passing urine, cystourethrography showed association of vesico urethral reflex in all hypoplastic kidneys (Masahiro *et al.*, 2002). There may be genetical relation between Renal genesis, renal aplasia and multicystic dysplastic kidney (MCDK) (Taxy, 1985). These anomalies are found in the members of same families (Bankier *et* al, 1985). Aplastic kidneys do have shape of reniform. They are small at birth but not rudimentary. These findings suggest that aplastic kidneys do grow almost to normal size. They have abnormal architecture. MCDK is not an end stage organ but said highly active in terms of genetic expression (Woolf and Winyard, 2000).

Retrospective evaluation was done to differentiate between scintigraphy patterns of congenital reflux nephropathy from that of acquired scarring in children with primary vesicoureteral reflux. They retro-specttively evaluated the frequency and pattern of renal scintigraphy abnormalities in 41 patients with prenatally detected primary vesicoureteral reflux. Dimercapto-succinic acid scintigraphy had been performed on 4-6 and 1-4 months. There was prenatal defect of vesico urethral reflex. Three types of renal damage were diagnosed. There was decreased uptake of renal radionuclide in 20-40% followed by, focal defects in uptake and shrunken kidney with relative uptake less than 20%. Scintigraphy revealed renal damage in 12 prenatally detected cases of vesicoureteral reflux, including decreased uptake in 58% and shrunken kidney in 42%, and in 111 cases of reflux detected at urinary tract infection (Polito *et al.*, 2000).

In the present study, an elderly female aged 75 years has bilateral small kidney as per ultrasound reported She is not diabetic nor hypertensive. She has no any clinical symptoms involvement renal system. All her parameters were normal; but she had mild degree of incompetence of valves in her heart No history of ischemic heart disease but there was strong family

history of anomalies of renal system. She is mother of 5 children; out of them two has congenital anomalies of renal system. Her elder son had horse shoe shaped kidney, while her elder daughter has an absence of right kidney. So this condition of bilateral small kidneys may be due to shrinking that might have taken place during the antenatal period. These types of kidneys are known as aplastic kidneys which may be due to mutation of genes or may be due to environmental factors in causing the derangement of genes. So, she has these bilateral small kidneys.

Conclusion

This study reports about bilateral shrunken kidney. It may be renal aplasia which is having an incidence of 1 in 1300. Being a rare anomaly, it has been studied and reported.

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