BCL-2 AND LEFT VENTRICULAR DIMENSIONS, FUNCTIONS AND PERIPHERAL VASCULAR RESISTANCE IN HYPERTENSION

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ABSTRACT:

Aim of the work:

1- Evaluation of the existence of apoptosis in hypertension by detecting serum anti-apoptotic factor; B- cell lymphoma-2 (Bcl-2) in hypertensive patients.

2- Investigating the role of anti-apoptotic factor (Bcl-2) in hypertension induced cardiac remodelling to block apoptosis and preserve ventricular geometry and function and its relation to peripheral vascular resistance.

3- Checking whether hypertensive patients with early cardiac affectation in the form of diastolic dysfunction exhibit an excess of apoptosis or not.

Patients and methods*:* The study included 3 groups:

Group (1): 95 females as controls

Group (2): 54 hypertensive patients without left ventricular hypertrophy (LVH).

Group (3): 41 hypertensive patients with LVH.

***Patients and controls were subjected to the following*:**

History taking, body mass index (BMI), blood pressure measurement, electrocardiography, echocardiography and serum BCL-2.

Results:

- Serum BCL-2 exhibits significant increase in hypertensive patients without LVH compared to controls and hypertensive patients with LVH. Also, there is significant decrease in serum BCL-2 in hypertensive patients with LVH compared to controls and hypertensive patients without LVH.
- There is significant negative correlation between serum BCL-2 level with systolic, diastolic and mean blood pressure.
- There is significant negative correlation between serum Bcl-2 and LV wall thickness, left ventricular mass (LVM) (g), left ventricular mass index (LVMI) (g) and peripheral vascular resistance.
- There is significant positive correlation between serum BCL-2 and preservation of LV diastolic function.

Conclusions: (1) Apoptosis is abnormally stimulated in myocardium of patients with hypertension. (2) Early cardiac disorder in the form of diastolic dysfunction exhibits an excess of apoptosis in spite of normal systolic function. (3) Anti-apoptotic factor BCL-2 has a role in preservation of left ventricular structure preventing LVH and it exhibits negative correlation with PVR.

KEY WORDS:

BCL-2 Hypertension

INTRODUCTION:

Programmed cell death (PCD) is the necessary mechanism complementary to proliferation that ensures homeostasis of all tissues. It has been estimated that 50 to 70 billion cells perish each day in the average adult because of PCD, a process by which, in a year, each individual will produce and eradicate a mass of cells equal to

its entire body weight. This process needs to be highly regulated since defects in the apoptotic machinery will lead to extended cell survival and may contribute to neoplastic cell expansion and creates a permissive environment for genetic instability and accumulation of mutations (Andreeff et al., 2003).

Apoptosis is also called programmed cell death because it is a genetically directed process that takes place in response to internal or external stimuli. Apoptosis should be contrasted to necrosis which is considered a non-regulated and non-physiological form of cell death (Yuan, 1995).

Dysregulation of apoptotic signalling can play a primary or secondary role in various diseases. Insufficient apoptosis leads to cancer, autoimmunity and persistent infections. Whereas excessive apoptosis contributes to neurodegeneration as Alzheimers' disease and ischaemia including stroke and myocardial infarction (Reed, 2002).

Apoptosis in the heart

It has been classically accepted that adult cardiomyocytes are not capable of proliferation and thus are resistant to develop apoptosis and the existence of a balance between apoptotic cell death and cell regeneration in the heart has been denied until recently. The involvement of cardiomyocyte apoptosis in hypertensive cardiac remodelling and its determinant role in the transition to heart failure is being confirmed in experimental and human hypertension (Fortuño et al, 2001).

Observations have been made showing that cardiomyocyte apoptosis occurs in diverse conditions; of these conditions is hypertensive heart disease (HHD) and LVH which is defined as the presence of a greater than normal left ventricular mass in the absence of a cause other than arterial hypertension and by the development of complex changes in myocardial composition that are responsible for the structural remodelling of the myocardium. One of these changes is a diminished number of cardiomyocytes due to enhanced cell death, including apoptotic cell death (Regula and Kirshenbaum 2005).

In fact, cardiomyocyte apoptosis has been shown to be abnor-mally stimulated in the hypertrophied left ventricle of patients with essential hypertension even with no angiographic evidence of coronary artery disease and normal cardiac function (Gonza´ lez et al., 2002).

It has been proposed that in hypertension, the local factors that may trigger the apoptotic program of cardiomyocytes include growth factors and when growth signals persist chronically in terminally differentiated cells, they produce a contradictory genetic demand and trigger the apoptotic response (Narula et al., 2000).

Apoptosis secondary to chronic remodelling is implicated as a mediator of heart failure (Chatterjee, 2002), but there are still many controversies surrounding the presence and the significance of apoptosis in heart failure. These controversies spring largely from the limitations of the techniques used to detect apoptosis and the difficulties in translating these findings to the ultimate significance of apoptosis in heart failure (Kang and Izumo 2000).

Interestingly, apoptotic nuclei were more abundant in hearts with eccentric hypertrophy than in hearts

with concentric hypertrophy, probably reflecting different myocardial conditions and anticipating a worse prognosis when more cardiomyocytes are lost (Yamamoto et al., 2000).

The occurrence of cardiomyocyte apoptosis in cardiac remodelling may contribute to worsen the prognosis of hypertensive heart disease, facilitating the transition from adaptive hypertrophy to heart failure. The possibility that blocking this process could prevent or slow cardiac failure progression opens new strategies in the treatment of cardiac disease (Fortuño et al., 2001).

The knowledge that cardiomyocyte apoptosis promotes a worsening of prognosis in hypertensive cardiomyopathy raises 2 different strategies to achieve the prevention of heart failure; the inhibition of apoptotic signals that trigger the process and the direct blockade of the intracellular apoptotic mechanisms. Several currently used antihypertensive drugs have demonstrated anti apoptotic effects on cardiomyocytes, especially those that counteract neurohormonal systems. Alternatively, molecules that blunt or regulate the mechanisms of cardiomyocyte apoptosis should be assayed as new targets in the multimodal prevention of hypertension-induced heart failure (Fortuño et al., 2001).

Cardiomyocyte apoptosis may be prevented by regulating the local factors that trigger the process or by directly blunting the intracellular apoptotic pathways. Although antihypertensive drugs will modulate environmental signals that cause apoptosis, the knowledge of the precise intracellular apoptotic mechanisms in these terminally differentiated cells is necessary to block them (Fortuño et al., 1999).

Long-term pharmacological interference of the renin-angiotensin system prevents the increment of cardiomyocyte apoptosis (Fortuño et al., 1999).

Renin-angiotensin system intervention and β-adrenergic blockade produce an increment of apoptosis in parallel to cardiac hypertrophy regression, calcium channel antagonists produce a time window of apoptosis after the first week of administration, whereas hydralazine and hydrochlorothiazide did not modify either cardiac hypertrophy or DNA fragmentation. Also, administration of doxazosin, an α1-receptor blocker, has been shown to reduce cardiac cell apoptosis and the presence of Bax–Bcl-2 complexes without affecting left ventricular mass (Rodriguez-Feo et al., 2000).

The Bcl-2 family

The BCL-2 family consists of both anti- apoptotic and pro- apoptotic proteins which share sequence homology within conserved regions known as BCL-2 homology (BH) domains. All anti apoptotic members such as BCL-2 and BCL-XL and a subset of pro apoptotic family members such as BAX and BAK are multi domain proteins sharing sequence homology within three to four BH domains (Wang, 1996).

Bcl-2 is the first example of an oncogene that inhibits cell death rather than promoting proliferation. It is found in follicular lymphoma and frequently linked to an immunoglobulin locus by the chromosome translocation t (14:18). B cells transfected with Bcl-2 were shown to be rendered resistant towards apoptosis

induced by Interleukin -3 withdrawal (Vaux et al., 1988). In mammals, up to 30 relatives have been described of which some belong to a group of pro-survival members and others to a group of pro-apoptotic members (Borner, 2003).

Effects of arterial hypertension:

Cardiac remodelling exist in hypertension is defined as the progressive changes in shape or dimensions of the heart following cardiac injury. It involves myocardial hypertrophy, dilatation of the heart chambers & changes in the shape and function of the ventricles. It may have adaptive or maladaptive character resulting in the development of overt heart failure and increased mortality and morbidity. It is a very complex phenomenon in which many cellular and molecular changes are involved; myocyte hypertrophy, necrosis, apoptosis, fibrosis, increased fibrillar collagen, fibroblast proliferation, on going myocyte loss, myocyte length-ening, slippage and disruption of collagen fiber (Cohn et al., 2000).

Moreover, vascular remodelling in hypertension exist through apoptosis, inflammation and fibrosis (Intengan and Schiffrin, 2001).

In both humans and animal models, pressure overload is characterized by a period of compensation in which left ventricular concentric hypertrophy normalizes systolic wall stress and contractile function is preserved. The period of adaptation which may last for weeks in rodents and months to years in humans, is inexorably followed by a transition to cardiac failure. This transition is characterized by impaired survival, the onset of chamber dilatation with the failure of further concentric hypertrophic growth to normalize load and progressive contractile dysfunction. A number of observations suggest that beside changes in the composition of motor unit and cytoskeleton of cardiomyocytes, the transition from hypertrophy to failure relates mainly to alterations in the histological composition of the myocardium as a result of both alterations in the metabolism of extracellular matrix (namely, fibrillar collagen) and cardiomyocyte loss due to multiple mechanisms of death including apoptosis (Gonza´ lez et al., 2003). Beside reduction in the number of cardiomyocytes, apoptosis may contribute to heart failure (Fortuño et al., 2003).

It has been suggested that alterations of the collagen framework in the myocardium may play an important role in the genesis of diastolic dysfunction of hypertensive origin (Diez et al., 2005). This has been supported by the finding that fibrillar collagen deposition in the cardiac interstitium of hypertensive patients increases left ventricular chamber stiffness and compromises left ventricular filling during diastole (Dı´ez et al., 2002). The problem concerns whether this type of interstitial alteration occurs through activation of fibroblasts via humoral or mechanical factors in the absence of cardiomyocyte loss, or whether cell death is required for the stimulation of the growth response of the non cardiomyocyte compartment of the myocardium (Olivetti et al., 1994). Besides histologic remodelling of the myocardium, cardiomyocyte apoptosis may also contribute to geometric remodelling of the left ventricular chamber. In fact, severe cardiomyocyte apoptosis may lead to side-to-side slippage of cells, mural thinning and chamber dilatation. Thus, wall restruc-turing secondary to severe cardio-myocyte apoptosis may create an irreversible state of the myocardium, conditioning

progressive dilatation and the continuous deterioration of cardiac hemodynamics and ventricular performance with time (Chandrashekhar 2005).

AIM OF THE WORK:

1- Evaluation of the existence of apoptosis in hypertension by detecting serum anti-apoptotic factor B- cell lymphoma-2 (Bcl-2) in hypertensive patients and its relation to peripheral vascular resistance.

2- Investigating the role of the anti-apoptotic factor (Bcl-2) in hypertension induced cardiac remodelling to block apoptosis and preserve ventricular geometry and function.

3- Checking whether hypertensive patients with early cardiac affectation in the form of diastolic dysfunction exhibit an excess of apoptosis or not.

PATIENTS AND METHODS:

This research was conducted at Assiut university hospital over the period of May 2010 to January 2012. The study included 95 newly discovered stage 2 hypertensive female patients (patient group) attending internal medicine outpatient clinics of Assiut university hospital with ages (55.64 ± 10.34) and another age and body mass index matched 95 female subjects were chosen as (control group) with ages (56.4 ± 10.21).

***Patients and controls were subjected to the following*:**

History taking, body mass index (BMI), blood pressure measurement, electrocardiography, echocardiography and serum BCL-2

The study included 3 groups:

Group (1): 95 females as controls

Group (2): 54 hypertensive patients without left ventricular hypertrophy (LVH).

Group (3): 41 hypertensive patients with LVH.

***Inclusion criteria*:**

Newly discovered stage 2 hypertensive female patients

Exclusion criteria:

Patients have the following parameters were excluded from the study:

1- Male patients.

2- Age > 60 years old.

3- Females suffering from other systemic illnesses.

4- Females with other causes of cardiac dysfunction such as cardiac arrhythmias, rheumatic or ischemic heart disease.

5- Females have left ventricular systolic dysfunction.

Methods:

I. History taking including: history and symptoms suggestive of any systemic illnesses.

II. Clinical examination: with special regard to:

- Blood pressure (BP) with calculation of mean blood pressure (diastolic BP +1/3 pulse pressure), normal mean arterial pressure range is between 70 to 110 mmHg (Cnossen et al., 2008).
- According to JNC-7 (The seventh report of the joint national committee on prevention, detection, evaluation, and treatment of high blood pressure) hypertension could be classified into (Pickering et al., 2005).

Study groups:

blood pressure Classification	systolic blood pressure. (mm Hg)	diastolic blood pressure (mm Hg)
Normal	<120	<80
Pre hypertensive	120–139	80–89
Stage 1 hypertension	140–159	90–99

blood pressure Classification	systolic blood pressure. (mm Hg)	diastolic blood pressure (mm Hg)
Stage 2 hypertension	≥160	≥100

- Body mass index (BMI) was calculated according to the formula : BMI= (weight in kg)/(height in meter)² (Molnar et al., 2000).
- Cardiac examination.

III. Laboratory investigations:

1- Investigations to exclude systemic illnesses as serum glucose and serum creatinine.

2- Serum B- cell lymphoma-2 (Bcl-2) level.

Principles of the test:

- An anti-Bcl-2 monoclonal coating antibody is adsorbed onto microwells.
- Bcl-2 present in the sample or standard binds to antibodies adsorbed to the microwells; a biotin-conjugated monoclonal anti-Bcl-2 antibody is added and binds to Bcl-2 captured by the first antibody.
- Following incubation unbound biotin conjugated anti-Bcl-2 is removed during a wash step.
- Streptavidin-HRP (Horse-radish perioxidase) is added and binds to the biotin conjugated anti-Bcl-2.
- Following incubation unbound Streptavidin-HRP is removed during a wash step, and substrate solution reactive with HRP is added to the wells.
- A coloured product is formed in proportion to the amount of Bcl-2 present in the sample. The reaction is terminated by addition of acid and absorbance is measured at 450nm. A standard curve is prepared from seven Bcl-2 standard dilutions and Bcl-2 sample concentration determined. Serum Bcl-2 kits were supplied by IBL (immuno-biological laboratories).

IV- Electrocardiography

A standard 12-lead ECG was recorded at 25 mm/s and 1 mV/cm standardization to exclude cardiac abnormalities detected at ECG.

V- Echocardiography

Ultrasound echocardiography using Agilent HP SONOS 4500 PHILIPS, U.S.A. with a 3.8 MHz transducer. Images of the heart were obtained from the parasternal and apical windows with the subject in the left lateral decubitus position. The ECG was recorded simultaneously. Examinations were recorded on super-VHS videotape and measurements were made using digitization software integral to the ultrasound system.

Echocardiographic examination including the following:

1- LV dimensions.

2- Left ventricular mass (LVM) (g).

3- Left ventricular mass index (LVMI in g/m²) using the following formula:

LVMI= 1.05 ([LVIDD + PWTD + IVSTD]^3- [LVIDD]^3) -13.6 *)* / BSA (g/m^2) (Devereux and Reichek, 1977), Where: LVIDD = left ventricular internal diameter in diastole, PWTD = posterior wall thickness in diastole and IVSTD = interventricular septum thickness in diastole.

LVH was defined as a left ventricular mass index (LVMI) exceeding 150 g/m^2 in men or 120 g/m^2 in women (Dörr et al., 2005).

Left ventricular geometry pattern in hypertrophy can be classified into:

- Normal:

- LVMI ≤ 50 gm/m^2; h/r < 0.44

- Concentric remodelling:

- LVMI ≤ 50 gm/m^2; h/r ≥ 0.44

- Concentric hypertrophy:

- LVMI > 50 gm/m^2; h/r ≥ 0.44

- Eccentric hypertrophy:

- LVMI > 50 gm/m^2; h/r < 0.44.

Where h/r is left ventricular hypertrophy index = [(PWTd + IVSTd) /2] /(LVIDD /2) with normal range= 0.33-0.41 (Reichek et al., 1982).

4- Analysis of LV systolic function:

Left ventricular M-mode fractional shortening and ejection fraction were calculated.

5- LV diastolic function:

The normal values of Doppler indices for adult more than 50 years old (Klein and Cohen, 1992) as follow:

Item	Normal value
Peak E velocity (cm/sec)	72 ± 14
Peak A velocity (cm/sec)	40 ± 10
Decelaration time (DT) (msec)	179 ± 20
Isovolumic relaxation time (IVRT) (msec)	76 ± 11

All Doppler echocardiographic examinations were obtained by averaging those taken from at least three cardiac cycles.Transmitral blood flow from the left atria to the LV was measured using pulsed Doppler to determine early (E) and late (A) diastolic peak filling velocity.

The sample volume was carefully positioned in the LV inflow tract at the tips of the mitral valve when maximally opened. In the apical four-chamber view mitral deceleration time was measured as the time from the peak to the end of the Doppler E-wave. Isovolumic relaxation time (IVRT) was measured as the time between the closing artifact of the aortic valve and the earliest detection of trans-mitral blood flow (Gates et al., 2003).

There are four basic echo-cardiographic patterns of diastolic heart failure which are graded from I to IV:

Grade (I): The mildest form is called an abnormal relaxation pattern. On the mitral inflow Doppler echocardiogram there is reversal of the normal E/A ratio.

Grade (II): is called "pseudonormal filling dynamics". This is considered moderate diastolic dysfunction and is associated with elevated left atrial filling pressures.

Grade (III): reversible restrictive diastolic dysfunction.

Grade (IV): fixed restrictive diastolic dysfunction.

Grade III and IV are both severe forms of diastolic dysfunction and patients tend to have advanced heart failure symptoms (Topol and Califf, 2010).

6- Peripheral vascular resistance (PVR):

PVR = mean blood pressure (MBP) x 80/Cardiac output (CO)

normal PVR= 900-1200 dyn·s/cm^5 (Rosa et al., 2001).

STATISTICAL ANALYSIS:

This research is a case control study and comparison between patient

group regarding presence or absence of cardiovascular events was done.

This research is a case control study and comparison between patient group regarding presence or absence of cardiovascular events was done.
Data analysis was done using SPSS 20.0 application (Statistical package for social science). Quantitative data described using range, mean, standard deviation and median. Independent samples T-test used to compare between two groups of normal quantitative data where Mann-Whitney U used to compare between two groups of not normal quantitative data and person correlation used to assess the relation between quantitative variables. P-value of less than 0.05 was considered to be statistically significant.

RESULTS:

The study included 95 newly discovered stage 2 hypertensive female patients (patient group) attending internal medicine outpatient clinics of Assiut university hospital with ages (55.64 ± 10.34) and another age and body mass index matched 95 female subjects were chosen as (control group) with ages (56.4 ± 10.21). The study included 3 groups:

Group (1): 95 females as controls
Group (2): 54 hypertensive patients without left ventricular hypertrophy (LVH).
Group (3): 41 hypertensive patients with LVH.

Table (1) shows baseline characterristics of controls and hypertensive patients where there is no significant difference between controls and hypertensive patients regarding age and BMI while there is significant difference between controls and hypertensive patients regarding systolic, diastolic and mean blood pressure with P-value (0.001,0.002 and 0.001 respectively).

Table (2) shows serum Bcl-2 levels in controls and hypertensive patients with and without left ventricular hypertrophy where there is significant increase in serum BCL-2 in hypertensive patients without LVH compared to controls with P-value (0.03). Also, there is significant decrease in serum BCL-2 in hypertensive patients with LVH compared to controls and hypertensive patients without LVH with P-value (0.001 and 0.01 respectively) with median value (23.7 U/ML, 39 U/ML, 4.6 U/ML) in controls, hypertensive patients without LVH and hypertensive patients with LVH respectively.

Table (3) displays correlation between serum Bcl-2 and blood pressure in hypertensive patients where there is significant negative correlation between serum BCL-2 level with systolic, diastolic and mean blood pressure.

Table (4) presents echocardiographic dimensions and peripheral vascular resistance in hypertensive patients where there is significant increase in diastolic interventricular septum thickness (IVSD) (cm) (p-value=0.003), diastolic posterior wall thickness (PWD)(cm) (P-value=0.004), left ventricular mass (LVM)(g) (P-value=0.02), left ventricular mass index (LVMI)(g) (P-value=0.01) and peripheral vascular resistance (PVR) (dyne·sxcm-5) (P-value=0.000) in hypertensive patients with LVH compared to hypertensive patients without LVH.

Table (5) reveals the correlation between serum Bcl-2 with LV hypertrophy and peripheral vascular resistance in hypertensive patients

where there is significant negative correlation between serum Bcl-2, diastolic interventricular septum thickness (IVSD) (cm), diastolic posterior wall thickness (PWD)(cm), left ventricular mass (LVM)(g), left ventricular mass index (LVMI)(g) and peripheral vascular resistance (PVR) (dyne·sxcm-5) in hypertensive patients.

Table (6) shows significant echocardiographic LV diastolic dysfunction in hypertensive patients with LVH compared to hypertensive patients without LVH in the form of decreased peak E velocity (cm/sec), increased peak A velocity (cm/sec), prolonged DT (msec) and prolonged IVRT (msec).

Table (7) displays the correlation between serum Bcl-2 and LV diastolic function in hypertensive patients where there is significant positive correlation between peak E velocity (cm/sec) while there is significant negative correlation between serum BCL-2 and peak A velocity (cm/sec), DT (msec) and IVRT (msec).

Table (1): Baseline characteristics of controls and hypertensive patients

Parameters	Controls (95)	Hypertensive Patients (95)	P-value
Age (years)	56.4 ± 10.21	55.64 ± 10.34	0.791
Body mass index (BMI) (kg/m2)	26.23 ± 9.34	26.24 ± 4.45	0.971
Systolic blood pressure (SBP)	115±7	160±15	0.001
Diastolic blood pressure (DBP)	76±6	100±10	0.002
Mean blood pressure (MBP)	80±15	115±17	0.001

Table (2): Serum Bcl-2 levels in controls and hypertensive patients with and without left ventricular hypertrophy

		Controls 1 (95)	Hypertensive Patients without LVH 2 (54)	Hypertensive Patients with LVH 3 (41)	P-value		
					1 versus 2	1 versus 3	2 versus 3
Serum Bcl-2 (U/ mL)	**range**	7.5-53.5	30-65	2.5-7.5	-	-	-
	mean ± SD	17.05±13.34	25.83 ± 15.33	9.53± 4.80	0.03	0.001	0.01
	Median	23.7	39	4.6	-	-	-

Table (3): Correlation between serum Bcl-2 and blood pressure in hypertensive patients

	Serum BCL- 2	
	r	**P-value**
Systolic blood pressure (SBP)	r = -0.695	0.005
Diastolic blood pressure (DBP)	r = -0.324	0.03
Mean blood pressure (MBP)	r = -0.796	0.000

Table (4): Echocardiographic dimensions and peripheral vascular resistance in hypertensive patients with and without hypertrophy

Parameter	**Hypertensive patients without LVH**	**Hypertensive patients with LVH**	**P-value**
Diastolic interventricular septum thickness (IVSD) (cm)	0.74 ± 0.10	1.34 ± 0.21	0.003
Diastolic posterior wall thickness (PWD)(cm)	0.84 ± 0.10	1.30 ± 0.11	0.004
Left ventricular mass (LVM)(g)	113.8 ± 12.4	179.85 ± 178.2	0.02
Left ventricular mass index (LVMI)(g)	80.52 ± 9.40	103.86 ± 68.99	0.01
Peripheral vascular resistance PVR (dyne·sxcm-5)	1097.52±135.02	1542.19±274.03	0.000

Table (5): Correlation between serum Bcl-2 with LV hypertrophy and peripheral vascular resistance in hypertensive patients

	Serum BCL- 2	
	r	**P-value**
Diastolic interventricular septum thickness (IVSD) (cm)	r = -0.350	0.03
Diastolic posterior wall thickness (PWD)(cm)	r = -0.313	0.02
Left ventricular mass (LVM)(g)	r = -0.350	0.03
Left ventricular mass index (LVMI)(g)	r = -0.571	0.000
Peripheral vascular resistance (PVR)	r =- 0.600	0.000

Table (6): Echocardiographic LV diastolic function in hypertensive patients with and without hypertrophy

Parameter	Hypertensive patients without LVH	Hypertensive patients with LVH	P-value
Peak E velocity (cm/sec)	78.36 ± 4.64	68.62 ± 13.21	0.003
Peak A velocity (cm/sec)	50 ± 10	56.49 ± 12.55	0.001
Declaration time (DT) (msec)	171.62 ± 5.2	183.93 ± 13.73	0.000
Isovolumic relaxation time (IVRT) (msec)	52.87 ± 3.61	85.69 ± 18.14	0.000

Table (7): Correlation between serum Bcl-2 and LV diastolic function in hypertensive patients

	Serum BCL- 2	
	r	P-value
Peak E velocity(cm/sec)	r = 0.916	0.000
Peak A velocity(cm/sec)	r = -0.841	0.002
Decelaration time (DT) (msec)	r = -0.751	0.01
Isovolumic relaxation time (IVRT) (msec)	r = -0.920	0.000

DISCUSSION:

The study included 95 newly discovered stage 2 hypertensive female patients (patient group) and another age and body mass index matched 95 females subjects were chosen as (control group).

There were no significant differences between controls and hypertensive patients regarding age and BMI while there were significant differences between controls and hypertensive patients regarding systolic, diastolic and mean blood pressure.

Selection of the study groups having the same BMI is important as BCL-2 serum level is affected by BMI as BCL-2 is positively correlated with BMI values (Tarantino et al., 2011).

There is significant increase in serum BCL-2 in hypertensive patients without LVH compared to controls with significant decrease in serum BCL-2 in hypertensive patient with LVH compared to controls and hypertensive patient without LVH, this coincided with Buemi et al., (1999) who have concluded that Bcl-2 concentration was higher in hypertensive than in normotensive subjects moreover, they concluded that the increase in pressure due to a cold pressor test caused a further increase in blood BCL-2 concentration in both hypertensive and normotensive subjects. Furthermore, they have concluded that treatment of hypertensive patients with hypotensive drugs caused a reduction in BCL-2 concentrations (Buemi et al., 1999).

This finding was not matched with Teiger et al., (1996) who concluded that there was no association between hypertension or LVH and apoptosis.

The existence of a balance between apoptotic cell death and cell regeneration in the heart has been denied until recently. It has been classically accepted that adult cardiomyocytes are not capable of proliferation and thus are resistant to develop apoptosis. In the past decade, however, observations have been made showing that cardiomyocyte apoptosis occurs in diverse conditions (Regula and Kirshenbaum 2005); one of these conditions is hypertensive heart disease (Gonza´ leza et al., 2006).

Also, Fortuño et al., (2003) and González et al., (2002) concluded that, apoptosis of cardiac myocytes as well as non-myocytes was more common in hypertensive patients than in normotensive subjects.

Another prove that apoptosis is stimulated in hypertension is that; when two groups of hypertensive patients were treated with either an angiotensin receptor blockers (ARBs) or a calcium antagonist, there was a highly significant decrease in apoptotic cells with (ARBs) treatment; however, in contrast, there was a failure of the calcium antagonist to reduce the apoptotic cells (González et al., 2002).

The mechanisms of increased cardiac apoptosis in arterial hypertension are not well known. As suggested by experimental in vitro studies Cheng et al., (1995) and Teiger et al., (1996) have concluded that physical forces induce cardiac apoptosis in conditions of experimentally induced pressure overload of the heart but the role for long-term hemodynamic overload cannot be excluded in enhanced cardiac apoptosis in hypertensive patients. An alternative explanation is that humoral factors such as angiotensin II stimulate cardiac apoptosis in arterial hypertension (Cheng et al., 1995 and Teiger et al., 1996).

There is significant negative correlation between serum BCL-2 level with systolic BP, this finding disagreed with Díez et al., (1997) who stated that Bcl-2 expression was directly correlated with systolic pressure but this finding agreed with Fabris et al., (2007) who found a negative correlation between hypertension and BCL-2 (Fabris et al., 2007).

But we have concluded that there was significant increase in serum BCL-2 in hypertensive patients without LVH compared to controls this mean that BCL-2 exhibit a biphasic response with early increase in early hypertension and then decrease this may be explained by the onset of cardiac remodelling especially LVH. In support of this possibility is the observation that the intensity of cardiomyocyte apoptosis parallels the time of exposure to hypertension and not the degree of elevation of blood pressure (Diez et al., 1997).

Also there was significant negative correlation between serum BCL-2 level with diastolic and mean blood pressure and to our knowledge no previous studies concluded this result regarding diastolic and mean blood pressure

There was significant increase in diastolic interventricular septum thickness (IVSD), diastolic posterior wall thickness(PWD), left ventricular mass (LVM), left ventricular mass index (LVMI) and peripheral vascular

resistance (PVR) in hypertensive patients with LVH compared to hypertensive patients without LVH. This agreed with Di-Bello et al., (2010) who found that hypertensive patients compared to controls presented larger dimensions of both ventricles, thicker left ventricular walls, higher LV mass and mass index. (Di-Bello et al., 2010).

In this study all cases with LVH were concentric hypertrophy and in experimental hypertension, cardiomyocyte loss seen in the hypertrophied left ventricle of patients with arterial hypertension may be due to enhanced cardiomyocyte apoptosis. An ongoing process of cardiomyocyte apoptosis will progressively deteriorate myocardial function, leading to the so-called early failure that characterizes hypertensive cardiomyopathy and facilitating the progression to end-stage heart failure (Yamamoto et al., 2000).

Although the origin and the time course of this switch in cardiomyocyte response remain unknown, it is plausible to think that if the early cardiomyocyte hypertrophy is followed by the apoptotic response because of the persistence of growth stimuli, the morphological expression of cardiac tissue remodelling will be the development of concentric compensatory hypertrophy, followed by chamber dilation. (Yamamoto et al., 2000).

Alternatively, Yamamoto et al., (2000) have concluded that direct development of eccentric hypertrophy with its intrinsically worse prognosis could indicate a predominant apoptotic response in cardiomyocytes with a higher number of apoptotic nuclei in hearts with eccentric hypertrophy than in hearts with concentric hypertrophy. (Yamamoto et al., 2000)

All cases with concentric hypertrophy had an elliptic left ventricle and high peripheral vascular resistance this agreed with Dávila et al., (2008). Furthermore, they concluded that in the contrarily eccentric hypertrophy is characterized by a spherical left ventricle and low peripheral vascular resistance (Dávila et al., 2008).

There is significant negative correlation between serum Bcl-2, IVSD, PWD, LVM, LVMI and PVR in hypertensive patients. This finding coincided with Weisleder et al., (2004) who concluded that over expression of BCL-2 have reduced the occurrence of fibrotic lesions in the myocardium resulted in prevention of cardiac hypertrophy, restoration of cardiomyocyte ultrastructure and significant improvement of cardiac function. Moreover they have concluded that introduction of BCL-2 in the heart was able to prevent structural dilation of the heart.

It is clear that the ratio of anti apoptotic to pro apoptotic members of the BCL-2 family alters the cell fate either toward or away from death (Korsmeyer et al ., 1993).

To our knowledge no previous research explain the relation between BCL-2 and PVR, but we can explain the significant negative correlation between serum Bcl-2 and PVR by the resistant nature of BCL-2 to apoptosis, counterbalancing cellular proliferation and maintenance of tissue integrity (Thompson,1995), this can maintain normal architecture of the walls of blood vessels in favour of normal PVR.

With the low endogenous level of BCL-2 in the heart it is possible that an increase in BCL-2 could provide additional protection over what would be seen from over expression of other members of the BCL-2 family. Increase in BCL-2 expression in cardiomyocytes has little effect until the level reaches a threshold where the ratio of BCL-2 family members is sufficient to favor cell survival (Weisleder, 2004).

In the context of hypertension, the local factors that may trigger the apoptotic program of cardiomyocytes include mechanical forces, oxidative stress, hypoxia, and an unbalanced presence of growth factors and cytokines (eg, angiotensin II) or neurotransmitters (eg, norepinephrine). Importantly, the apoptotic signals are those that have largely been demonstrated to produce an enlargement of cardiomyocytes (Narula et al., 2000).

A molecular explanation for this double response may be that persistent growth stimuli can drive hypertrophied cardiomyocytes to lose intracellular survival signals that normally suppress the development of the apoptotic process as a consequence, growth factors turn into apoptotic factors. Another possibility is that intrinsic genetic predisposition directly determines whether cardiomyocytes enter apoptosis or develop hypertrophy in response to local environmental conditions (Bing1994).

Weisleder et al (2004) stated that overexpression of Bcl-2 in the rat heart resulted in correction of mitochondrial defects, reduced occurrence of fibrotic lesions in the myocardium, prevention of cardiac hypertrophy and restoration of cardiomyocyte ultrastructure. Moreover, the levels of molecular markers of hypertrophy such as skeletal actin were reduced in all animals carrying a Bcl-2 transgene.

Kirshenbaum and De-Moissac (1997) demonstrated that over expression of Bcl-2 rendered the heart more resistant to injury. Furthermore, Chen et al (2001) reported that Bcl-2 was capable of preventing p53-induced PCD of neonatal ventricular myocytes. Moreover, in human myocytes, the expression of Bcl-2 may play an important pathophysiological role in the protection or acceleration of apoptosis after ischemia and/or reperfusion (Misao et al., 1996).

There is significant echocardiographic LV diastolic dysfunction in hypertensive patients with LVH compared to hypertensive patients without LVH in the form of decreased peak E velocity (cm/sec), increased peak A velocity (cm/sec), prolonged DT (msec) and prolonged IVRT (msec).This coincided with Avdić et al., (2007) who concluded that patients with LVH had a longer IVRT, lower E/A ratio, A wave growth (Avdić S et al., 2007 and Di- Bello et al ., 2010).

All our cases have had normal LV systolic function although they exhibited diastolic dysfunction this coincided with Bing, (1994) who has been proposed that LV diastolic dysfunction preceded LV systolic dysfunction and apoptosis-induced cardiomyocyte loss precedes the impairment in ventricular pump function and may be implicated in the initiation of ventricular mal adaptation and the transition to heart failure in hypertensive heart disease (Bing, 1994).

There was significant positive correlation between peak E velocity (cm/sec) while there was significant negative correlation between serum BCL-2 and peak A velocity (cm/sec),

DT (msec) and IVRT (msec), this indicated that BCL-2 besides serving as a protective way for systolic function, it also protects diastolic function of the heart.

Findings showed that cardio-myocyte apoptosis was increased in patients with hypertensive heart disease and chronic heart failure compared with hypertensive patients with normal cardiac function (Goikoetxea et al., 2006).

Thus, it seems that cardiomyocyte apoptosis precedes the impairment in ventricular function and its exacerbation accompanies the development of heart failure in patients with hypertensive heart disease (Gonza´ leza 2006).

Cardiomyocyte death commonly contributes to the development of many cardiac disease states including cardiomyopathy and heart failure. Recent efforts toward treatment of cardiac disease have focused on prevention of cell death (Gill et al., 2002).

Moreover, BCLl-2 cardiac overexpression have provided signi-ficant improvement of an inherited form of cardiomyopathy, revealing the potential for BCL-2 and perhaps other genes in the family, as therapeutic agents for heart disease of many types including inherited forms (Weisleder, 2004).

So we suggest that BCL-2 could serve as a protective factor in the heart although BCL-2 is expressed at low levels in cardiomyocytes, this potent modulator of cell death is a promising therapeutic agent for heart disease because it has been shown to reduce cell death during ischemia (Chen et al., 2001).

CONCLUSIONS:

The main findings of this study are as follows:

(1) Apoptosis is abnormally stimulated in myocardium of patients with hypertension.
(2) Early cardiac disorder in the form of diastolic dysfunction exhibits an excess of apoptosis in spite of normal systolic function.
(3) Anti apoptotic factor BCL-2 has a role in preservation of left ventricular structure preventing LVH and it exhibits negative correlation with PVR.

Recommendations:

Further studies along this line of research are clearly necessary to provide further evidence that apoptosis is responsible for the development and reversal of cardiac structural and functional alterations and to discover anti apoptotic factors promoting and reversing the risk associated with apoptosis with consideration of multiple cardiac and inflammatory risk factors.

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بي- سي- إل2 و أبعاد وو ظائف البطين الأيسر و المقاومة الوعائية الطرفية في ضغط الدم المرتفع

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الملخص العربى

الهدف من العمل:
1 - تقييم وجود موت الخلايا المبرمج في مرض ضغط الدم المرتفع عن طريق الكشف عن مستوى بي- سي- إل 2 في مرضى ضغط الدم المرتفع .
2 - فحص دور بي- سي- إل 2 فى إعادة تشكيل وبناء القلب الناتج عن ارتفاع ضغط الدم لتعطيل موت الخلايا المبرمج والحفاظ على هندسة البطين الأيسر ووظيفته وكذلك المقاومة الوعائية الطرفية
3 - التحقق ما إذا كان مرضى إرتفاع ضغط الدم الذين لديهم إختلال وظيفي إنبساطي مبكر لديهم وجود فائض من موت الخلايا المبرمج أم لا.

المرضى وطرق البحث : شملت الدراسة 3 مجموعات:
المجموعة (1) : 95 أنثى كمجموعة ضابطة
المجموعة (2) : 54 أنثى لديهن ارتفاع ضغط الدم وليس لديهن تضخم فى البطين الأيسر.
المجموعة (3) : 41 أنثى لديهن ارتفاع ضغط الدم مع تضخم البطين الأيسر .
وتم عمل الفحوصات للمريضات والمجموعة الضابطة وهى : أخذ التاريخ المرضى، مؤشر كتلة الجسم ، قياس ضغط الدم ، تخطيط القلب الكهربائي ، تخطيط صدى القلب بالموجات فوق الصوتية, ومستوى بي- سي- إل فى الدم2

النتائج :
- بي- سي- إل 2 يزداد بشكل ملحوظ في مريضات ارتفاع ضغط الدم اللاتي ليس لديهن تضخم فى البطين الأيسر مقارنة مع الضوابط و مريضات ارتفاع ضغط الدم اللاتي لديهن تضخم البطين الأيسر .
- هناك انخفاض كبير في مستوى بي- سي- إل 2 في مريضات ارتفاع ضغط الدم مع تضخم البطين الأيسر مقارنة مع الضوابط و مريضات ارتفاع ضغط الدم دون تضخم البطين الأيسر.
- هناك علاقة سلبية ذات دلالة إحصائية بين مستوى بي- سي- إل 2 مع الضغط الانقباضي، والانبساطي ومتوسط ضغط الدم
- هناك علاقة سلبية ذات دلالة إحصائية بين مستوى بي- سي -إل 2 و سمك جدار البطين الأيسر، كتلة البطين الأيسر و مؤشر كتلة البطين الأيسر و المقاومة الوعائية الطرفية
- هناك علاقة إيجابية ذات دلالة إحصائية بين مستوى بي- سي- إل 2 و الحفاظ على وظيفة القلب الانبساطية

الاستنتاجات :
(1) يتم تحفيز موت الخلايا المبرمج بشكل غير طبيعي في عضلة القلب فى المرضى الذين يعانون من ارتفاع ضغط الدم.
(2) مريضات ضغط الدم المرتفع اللاتي لديهن إعتلال القلب في وقت مبكر في شكل إختلال وظيفية القلب الإنبساطية معرضات لوجود فائض من موت الخلايا المبرمج بالرغم من سلامة وظيفة القلب الانقباضية .
(3) بي- سي- إل 2 له دور في الحفاظ على هيكل البطين الأيسر ومنع تضخم البطين الأيسر فى ضغط الدم المرتفع.

الكلمات الرئيسية : بي- سي- إل 2 وارتفاع ضغط الدم