INTRODUCTION

Hypertension is a common health problem worldwide and in Africa especially in Egypt owing to its long term cardiovascular complications. The National Hypertension Project (NHP) is a collaborative Egyptian-American effort aiming at determining the prevalence of hypertension Egyptian adults and it related clinical complications and to identify environmental factors that were associated with hypertension. [1]

Data from the National Hypertension Project (NHP) study conducted in 6 governorates with a probability sample of 600 households in the years from 1991-1994 showed that 26.3% of adult Egyptians (≥ 25 years) and more than 50% of individuals older than 60 years suffered from hypertension. [1]

As mentioned before hypertension causes a financial burden on developing countries due to its long term cardiovascular complications which are high in prevalence in Egypt as the survey showed due to low awareness rates where only 38% of all Egyptian hypertensive patients were aware of having high blood pressure and only 24% of them were receiving treatment. [1]

Definition and types of Hypertension:

Hypertension is defined as a value ≥140 mmHg Systolic BP (SBP) and/or ≥90 mmHg diastolic BP (DBP) and these cut off values are universal and haven't changed in the ESH/ESC

guidelines from 2003 to 2007 as and they aim to simplify the diagnostic approach and to facilitate the decision about treatment. [2]

Grading of Hypertension: [2]

Hypertension can be graded into

- Grade 1 hypertension (SBP140–159) and/or (DBP 90–99)
- Grade 2 hypertension (SBP160–179) and/or (DBP100–109)
- Grade 3 hypertension (SBP ≥180) and/or (DBP ≥110)
- Isolated systolic hypertension ≥140 and <90

Table (1): Definitions and classification of office blood pressure levels (mmHg) [2]

Category	Systolic		Diastolic
Optimal	<120	and	<80
Normal	120–129	and/or	80–84
High normal	130–139	and/or	85–89
Grade 1 hypertension	140–159	and/or	90–99
Grade 2 hypertension	160–179	and/or	100–109
Grade 3 hypertension	≥180	and/or	≥110
Isolated systolic hypertension	≥140	and	<90

Hypertension can be either primary (essential hypertension) or could be secondary to any other medical disease. Essential, primary, or idiopathic hypertension is

defined as high BP in which secondary causes such as reno-vascular disease, renal failure, pheochromocytoma, hyperaldosteronism, or other causes of secondary hypertension are not present.[2]

Essential hypertension accounts for 95% of all cases of hypertension. In most people with established essential hypertension, increased peripheral vascular resistance accounts for the high pressure. Many mechanisms have been proposed to account for the rise in peripheral resistance in hypertension particularly abnormalities in the intrarenal renin-angiotensin aldosterone system (RAAS) which is a hormonal auto regulatory system responsible for maintaining blood pressure and fluid balance and will be discussed with more details in coming chapters. [3]

Long standing uncontrolled hypertension is one of the major risk factors for multi organ failure. It is a risk factor for coronary heart disease, myocardial infarction, cerebrovascular stroke, chronic renal failure, atrial fibrillation, peripheral vascular disease, retinopathy, left ventricular hypertrophy (LVH) and congestive heart failure.[4]

Left ventricular hypertrophy (LVH) is defined as an increase in the mass of the left ventricle, which can be secondary to an increase in wall thickness which is called "Concentric LVH", an increase in cavity size which is called

"Eccentric LVH", or both. It is a common finding in patients with hypertension. [5]

LVH is a major risk factor for coronary artery disease and congestive heart failure as it causes supply demand mismatch as the blood supply to the hypertrophied myocyte becomes inadequate especially during exertion. This increase in mass predominantly results from a chronic increase in afterload of the LV caused by the hypertension which causes increase in the number and /or size of sarcomeres within each myocardial cell. [5]

Few researches have showed that there is a direct relationship between Angiotensin II level and occurrence of LVH especially in long standing uncontrolled hypertension. Angiotensin II in addition to its vasoconstrictor and aldosterone-stimulating action, it also drives cell growth and replication in the cardiovascular system which may result in myocardial hypertrophy and hyperplasia. [6]

Aim of the Work

To study the relationship between serum Angiotensin II serum level and concentric left ventricular hypertrophy in patients with long standing (five years or more) essential uncontrolled treated hypertension.

Chapter 1

HYPERTENSION AND CARDIOVASCULAR RISK

Hypertension and cardiovascular risk assessment:

Hypertension affects most of body organs and only small fraction of the hypertensive population has an elevation of BP alone with the majority exhibiting additional cardiovascular risk factors. So we can say that blood pressure values alone can't be used to quantify the total cardiovascular and to determine the need to and the type of treatment used. In 1994, the ESC, ESH and European Atherosclerosis Society (EAS) developed joint recommendations on prevention of coronary heart disease (CHD) in clinical practice and emphasized that prevention of CHD should be related to quantification of total cardiovascular risk. [(7)]

Furthermore, Elevated blood pressure combined with other cardiovascular risks can potentiate and aggravate each other causing a higher total cardiovascular risk that is greater than the sum of each risk alone. [(7)]

Cardiovascular risk quantification is very crucial because it will guide the therapeutic approach in treatment initiation and intensity and drug combinations which will be different in high risk patients than low risk ones. [(8)]

Several computerized methods have been developed for estimating total CV risk including the Systematic Coronary Risk Evaluation (SCORE) model which has been developed based on large cohort studies. The model uses different demographic and anthropometric data and laboratory findings and blood pressure values to estimate the risk of dying from CV disease (not just coronary disease) over 10 years. [9]

The most important factor affecting total CV risk is age. It is so strong that younger adults (particularly women) are unlikely to reach high-risk levels even when they have more than one major risk factor and a clear increase in relative risk. By contrast, many elderly men (e.g. 70 years) reach a high total risk level despite having little risk factors. [10]

This information lead to most resources to be concentrated in older individuals who despite intervention have a relatively short life span and little attention is given to young individuals who have a relatively longer life span. These young subjects if left untreated combined with high relative CV risk will lead to a partly irreversible risk situation in middle age with potential shortening of their otherwise longer life expectancy. [10]

Table (2): Factors other than office BP influencing prognosis and used for stratification of total CV risk. [2]

Risk factors
Male sex
Age (men ≥55 years; women ≥65 years)
Smoking
Dyslipidaemia
Total cholesterol >4.9 mmol/L (190 mg/dL), and/or
Low-density lipoprotein cholesterol >3.0 mmol/L (115 mg/dL), and/or
High-density lipoprotein cholesterol: men <1.0 mmol/L (40 mg/dL), women <1.2 mmol/L (46 mg/dL), and/or
Triglycerides >1.7 mmol/L (150 mg/dL)
Fasting plasma glucose 5.6–6.9 mmol/L (102–125 mg/dL)
Abnormal glucose tolerance test
Obesity [BMI ≥30 kg/m^2 (height^2)]
Abdominal obesity (waist circumference: men ≥102 cm; women ≥88 cm) (in Caucasians)
Family history of premature CVD (men aged <55 years; women aged <65 years)

Table (2): Cont…

Diabetes mellitus
Fasting plasma glucose ≥7.0 mmol/L (126 mg/dL) on two repeated measurements, and/or
HbA_{1c} >7% (53 mmol/mol), and/or
Post-load plasma glucose >11.0 mmol/L (198 mg/dL)
Established CV or renal disease
Cerebrovascular disease: ischaemic stroke; cerebral haemorrhage; transient ischaemic attack
CHD: myocardial infarction; angina; myocardial revascularization with PCI or CABG
Heart failure, including heart failure with preserved EF
Symptomatic lower extremities peripheral artery disease
CKD with eGFR <30 mL/min/1.73m^2 (BSA); proteinuria (>300 mg/24 h).
Advanced retinopathy: haemorrhages or exudates, papilloedema

BMI=body mass index, CV=cardiovascular, CHD=coronary heart disease, CKD=chronic kidney disease, GFR=glomerular filtration rate, EF= ejection fraction, BSA=body surface area, CABG= coronary artery bypass grafting.

Identification of asymptomatic end organ damage (EOD) is very crucial in CV risk stratification since it indicates the progression of HTN and increases the total CV risk which guides treatment strategy. [(11)]

Table (3): Stratification of total CV risk in categories of low, moderate, high and very high risk. [2]

Other risk factors, asympto-matic organ damage, or disease	Blood Pressure (mmHg)			
	High normal SBP 130–139 or DBP 85–89	Grade 1 HT SBP 140–159 or DBP 90–99	Grade 2 HT SBP 160–179 or DBP 100–109	Grade 3 HT SBP ≥180 or DBP ≥110
No other RF		Low risk	Moderate risk	High risk
1–2 RF	Low risk	Moderate risk	Moderate to high risk	High risk
≥3 RF	Low to Moderate risk	Moderate to high risk	High risk	High risk
OD, CKD stage 3 or diabetes	Moderate to high risk	High risk	High risk	High to very high risk
Symptomatic CVD, CKD stage ≥4 or diabetes with OD/RFs	Very high risk	Very high risk	Very high risk	Very high risk

SBP= systolic blood pressure, DBP=diastolic blood pressure, OD= organ damage, RF=risk factor, CVD=cardiovascular disease, CKD=chronic kidney disease.

Hypertension and Asymptomatic End organ damage:

Because asymptomatic organ damage is a very important determinant of overall CV risk, signs of organ involvement should be sought carefully by appropriate techniques beside blood pressure measurement. [12]

There are four important markers of organ damage:

Microalbuminuria, increased Carotid pulse wave velocity (PWV), left ventricular hypertrophy (LVH) and carotid plaques. Each marker can predict CV mortality independent of SCORE stratification which assures the importance of careful assessment of EOD in daily clinical practice. [13]

I) Hypertension effect on the heart:

A. Hypertension and Concentric left ventricular hypertrophy:

When the heart faces a hemodynamic burden, it can do the following to compensate:

1) Use the Frank-Starling mechanism where the stroke volume increases in response to cardiac muscle stretch.
2) Augment muscle mass to bear the extra load.
3) Recruit neuro-hormonal mechanisms to increase contractility.

The first mechanism is limited in its scope, and the third is deleterious as a chronic adjustment. [14]

Cardiomyocytes respond to pressure overload by parallel addition of sarcomeres which causes an increase in myocyte width, which in turn increases wall thickness and ratio of wall thickness/chamber dimension (Relative wall thickness > 0.42 with increased LVM) which is called concentric hypertrophy. [15]

Thus, increasing mass assumes a key role in the compensation for hemodynamic overload. This increase in mass is due to the hypertrophy of existing myocytes rather than hyperplasia.

According to La Place's Law, the load on any region of the myocardium is given as follows:

$$\textbf{Load} = \frac{\text{Pressure x Radius}}{\text{2 x Wall thickness}}$$

Thus, an increase in pressure can be offset by an increase in wall thickness. On the Other hand, Volume overload in conditions such as chronic aortic regurgitation, mitral regurgitation, or anemia leads to myocyte lengthening by sarcomere replication in series and an increase in ventricular volume which is called eccentric hypertrophy. [15]

This pattern of eccentric hypertrophy where there cavity dilatation with a decrease in ratio of wall thickness/chamber dimension (Relative wall thickness < 0.42 with increase in

LVM) is also initially compensatory helping the heart to maintain a high stroke volume in diseases causing volume overload. However, chronic hypertrophy may have a deleterious effect because it increases the risk for the development of heart failure and premature death. [16]

Concentric LVH can by diagnosed by electrocardiogram criteria and echocardiography which is much more sensitive than electrocardiography in diagnosing LVH**.** It also helps in a more precise stratification of overall risk and in determining therapy. [17]

B. Role Of Echocardiography in diagnosis of concentric LVH:

Echocardiography is one of the most used methods for assessment of concentric LVH which allows us to properly evaluate LV dimensions which are used to calculate the LV mass. Proper evaluation of the left ventricle in hypertensive patients includes linear measurements of interventricular septal dimension and posterior wall thickness and internal end diastolic and end systolic diameters using M-mode and two-dimensional imaging. All these dimensions are used to calculate the Left ventricular mass (LVM). Calculation of LVM is performed according to the American Society of Echocardiography formula. [18]

Left ventricular mass is generally calculated as the difference between the epicardium delimited volume and the left ventricular chamber volume multiplied by an estimate of myocardial density. M-mode imaging allows better endocardial border definition as it has greater resolution due to higher frame-rate, as long as adequate ultrasound beam positioning is ensured and ventricular shape approaches normality. [19]

The current recommended formula for calculating LM mass is the American society of echocardiography equation. [20]

The formula is as follows:

LV mass = 0.8 (1.04 ([LVEDD + PWTD + IVSTD]^3- [LVEDD]^3))+ 0.6 g

- LVEDD= Left ventricular end-diastolic diameter.
- PWTD= Posterior wall thickness in diastole.
- IVSTD= Interventricular septum thickness in diastole.

Left ventricular mass is commonly indexed by the body surface area to define left ventricular mass index (g/m^2). [20]

Although the relation between LVM and CV risk is continuous, thresholds of 95 g/m^2 for women and 115 g/m^2 for men are widely used for estimates of clear cut LVH. [20,21]

Concentric LVH also causes abnormal filling of LV which is defined as diastolic dysfunction. Diastolic dysfunction

can induce symptoms/signs of heart failure even when ejection fraction (EF) is still normal (heart failure with preserved EF). [22]

The Doppler trans-mitral inflow pattern can quantify filling abnormalities and predict subsequent heart failure and all cause mortality but is not sufficient to completely stratify the hypertensive clinical status and prognosis. So it should be combined with pulsed Tissue Doppler of the mitral annulus. Reduction of the Tissue Doppler-derived early diastolic velocity (e') is typical of hypertensive heart disease and, often, the septal e' is reduced more than the lateral e'. [22]

Diagnosis and grading of diastolic dysfunction is based on e' (average of septal and lateral mitral annulus) and additional measurements including the ratio between trans-mitral E and e' (E/e' ratio) and left atrial size. This grading is an important predictor of all-cause mortality in a large epidemiological study. [22]

Diastolic dysfunction can also be diagnosed using pulmonary venous flow which is studied by placing a pulsed Doppler cursor at the entry of the pulmonary veins into the left atrium which can be seen using the color flow in an apical 4 chamber view.

The normal pulmonary vein flow profile is usually biphasic with a predominant systolic forward flow (S wave) and a less prominent diastolic forward flow wave (D wave).