INTRODUCTION

According to the World Health Organization(WHO), overweight and obesity are defined as abnormal or excessive fat accumulation that presents a risk to health. The body mass index (BMI) is a simple index of weight-for-height that is commonly used to classify underweight, overweight and obesity in adults. A person with a BMI of 25 or more is considered by the WHO to be overweight, while obesity is defined as having a BMI of 30 or more.In 2014, more than 1.9 billion adults, 18 years and older, were overweight. Of these over 600 million were obese.Raised BMI is a major risk factor for noncommunicable diseases such as cardiovascular diseases (mainly heart disease and stroke), which were the leading cause of death in 2012; diabetes, osteoarthritis, some cancers (endometrial, breast, and colon)(1).

According to the World Health Organization,the prevalence of overweight & obesity in adult Egyptians is 66%.The mean BMI(kg/m^2) of adult Egyptians shows a rising trend; in 1980, 24.1 in males & 25.5 in females while in 2009 it overshooted to 26.8 in males & 30.2 in females(2).

Arterial stiffness is the resistance of arteries to deformation(3). Higher body fat percentage -when age, sex and systolic blood pressure were adjusted for- was associated with lower aortic pulse wave velocity (PWV), a measure of central arterial stiffness(4,5).

Central obesity measures plays an important role in the association between obesity and arterial stiffness, identifying a greater arterial stiffness in Australian overweight ⁄ obese women(6).

Another study suggests that the cardiovascular system of young adults may be capable of adapting to the state of obesity and that an adverse association between body fat and aortic stiffness is only apparent in later life(7).

A meta-analysis including more than 15,000 subjects confirmed that aortic stiffness is an independent predictor of adverse cardiovascular events and all-cause mortality. An increase of aortic pulse wave velocity of 1 m/s raises cardiovascular risk by more than 10%(8).

Circulatory (MARC[arterial, renal &cardiac markers]) syndrome is a new concept aiming at refinement of the metabolic syndrome to include additional cardiovascular risk markers for with synergic effects which included arterial stiffness(9).

Increased arterial stiffness is now being considered as an intermediate cardiovascular endpoint to assess target organ damage(10).

Obesity is associated with concentric left ventricular remodelling and sustained 10-year weight loss results in lower cavity size, wall thickness and mass(11).

Another study has shown that obesity, in the absence of hypertension, was associated with elevated left ventricular mass when compared to normal weight normotensive subjects(12).

Inappropriate LV mass predicts a risk of cardiovascular events, independently of risk factors, and remains a significant predictor of risk either in the presence or in the absence of traditionally defined LV hypertrophy(13).

AIM OF THE WORK

Primary outcomes:

1- Effect of obesity on arterial stiffness

2- Effect of obesity on left ventricular mass index

Secondary outcome parameters:

1- Effect of obesity on left atrial & left ventricular dimensions.

2- Effect of obesity on left ventricular diastolic function.

ARTERIAL STIFFNESS

Anatomy of the artery

The human artery is comprised of a lumen surrounded by a series of concentric layers, which work together cohesively to assist in propagating blood from the heart to the periphery. The arterial wall itself is divided into 3 major regions: the tunica intima, media and adventitia(14).

Types of arteries:

There are twotypes of arteries; elastic and muscular.

A) Elastic arteries:(Figure(1)):

The aorta and its branches (brachiocephalic, subclavian, pulmonary, beginning of common carotid and iliac) are distinguished by their great elasticity. This helps them smooth out the large fluctuations in blood pressure created by the heartbeat. During systole, their elastic laminae are stretched and reduce blood pressure. During diastole, the elastic rebound helps maintain arterial pressure(14).

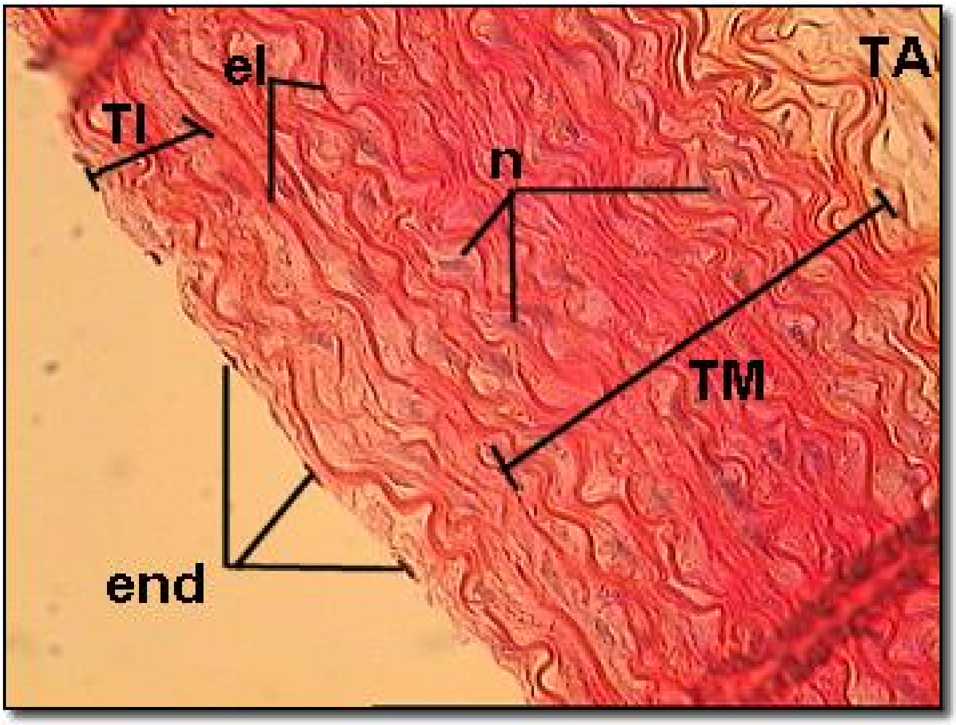

Figure (1): High power view of the aorta. The tunica media is the thickest of the three layers. The elastic lamellae are the most conspicuous features of both the intima and media.The number of lamellae increase with age (few at birth, 40-70 in adult) and with hypertension. The tunica adventitia is a relatively thin layer.(**el**: elastic lamellae, **end**: endothelial cell nuclei, **n**: smooth muscle cell nuclei, **TA**: tunica adventitia, **TI**: tunica intima, **TM**: tunica media)(14).

B) <u>Muscular arteries:</u> (Figure(2)):

The majority of named arteries are medium (muscular or distributive) arteries. There is no sharp dividing line between elastic (large) and muscular (medium) arteries; in areas of transition, arteries may appear as intermediates between the two types. Medium arteries have less elastic tissue than large arteries, the predominant constituent of the tunica media is smooth muscle(14).

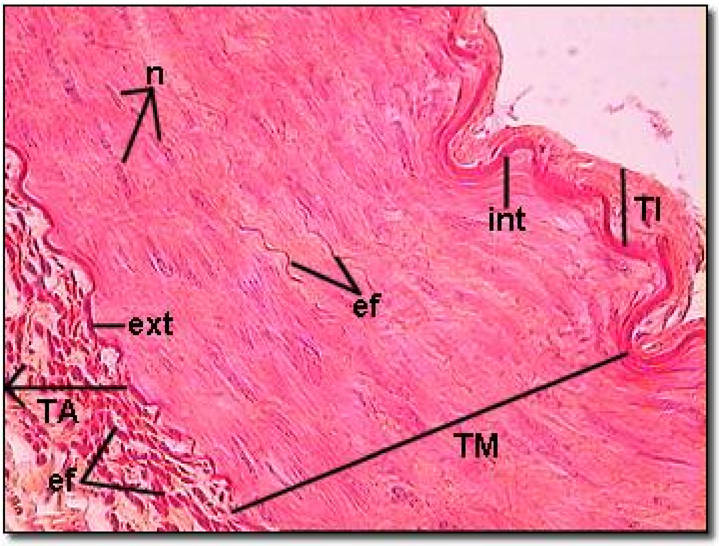

Figure (2): High power view of a muscular artery: The tunica intima is thinner than in large arteries&has a prominent internal elastic membrane.The large media consists mainly of smooth muscle cells.The tunica adventita is relatively larger than in elastic arteries.(**ef**: elastic fibre, **ext**: external elastic membrane, **int**: internal elastic membrane, **n**: nuclei of smooth muscle cells, **TA**: tunica adventitia, **TI**: tunica intima, **TM**: tunica media**)**(14).

The composition of the arterial wall, in particular the elastin and collagen content, changes from central to peripheral arteries. Starting in the proximal aorta, elastin is the dominant component. At the abdominal aorta the content of collagen and elastin appears similar, and by the periphery collagen becomes dominant (15).

As collagen is 300 times stiffer than elastin (elastic modulus 1000 x 10^6 dyne/cm2 vs. 5 x 10^6), the altering arterial wall composition causes an increasing -stiffness gradient- down the arterial tree. Elastin and collagen cause the pressure–diameter relationship at any specific area on the arterial tree to be nonlinear(16). At low distensions, pressure is mainly governed by elastin fibers, which are quite compliant and the resulting curve is more linear, where at higher tensions it is governed by the supporting latticework of collagen content, which is much stiffer, resulting in a steeper slope (a greater required pressure for a given diameter change)(17).

Models of the circulatory system

The oldest model of the arterial system is the *Windkessel model*—the inverted air-filled dome of old fashioned fire engines that transformed pulsatile flow from a steam or hand-activated pump into a steady stream through the fire hose nozzle (Figure (3,4)). In this model, the dome represents the cushioning function of the arteries, and the nozzle, the peripheral resistance(18). Although conceptually useful, this model is unrealistic because elastic properties are not present at just one site but are distributed along the aorta and major arteries. The pressure wave has a finite wave velocity in arteries, and in addition, pressure waveforms are different in amplitude and contour in central and peripheral arteries(18).

The value of the Windkessel model is seriously limited as a comprehensive explanation of arterial behavior under differentcircumstances, although under some specific circumstancesthe very elderly, the very hypertensiveit may appear realistic.

The most *realistic* model of the arterial system is the *propagative* model*;* a simple tube with one end representing the peripheral resistance,and with the other end, receiving blood in spurts from the heart (Fig. 3A)(18).A wave generated by cardiac activity travels along the tube toward the periphery and is reflected back from the periphery. The pressure wave at any point along the tube is a resultant of incident and reflected wave.

When the tube is distensible, as in youth, the wave velocity is slow, therefore reflection returns late to the heart, in diastole. When the tube wall is stiffened, as in the elderly, wave travel is fast, and the reflected wave merges with the systolic part of the incident wave, causing a high pressure in systole and corresponding low pressure in diastole throughout the tube (18).

When modelling the arterial tree,it was suggested that because the tube’s end has a high level of resistance, waves are reflected and retrograde waves are generated. This would account for the secondary fluctuations of the pressure waveform in diastole and differences in the amplitude of the pressure wave between central and peripheral arteries and fits well with pathophysiological observations. In particular, it explains why an increase in the arterial stiffness increases central PP, with an associated increased systolic BP(19).

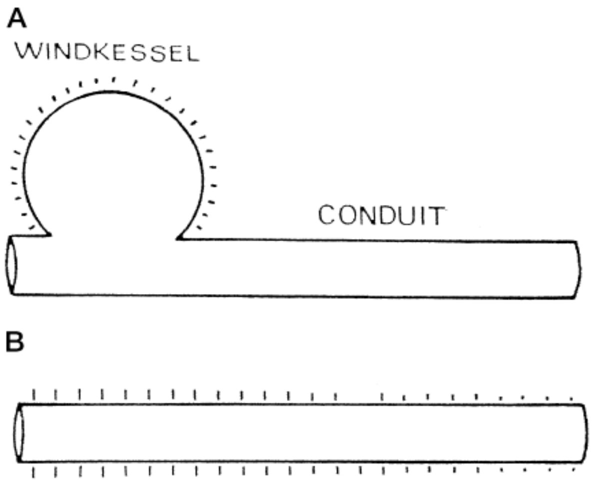

Figure (3): The cushioning and conduit functions of the arterial system may be represented separately by a proximal Windkessel with peripheral distributing tube (A) or by a single distensible tube in which both functions are combined (B). The left end of the tube represents the ascending aorta, and the right end, the summation of all arterial/arteriolar junctions(19).

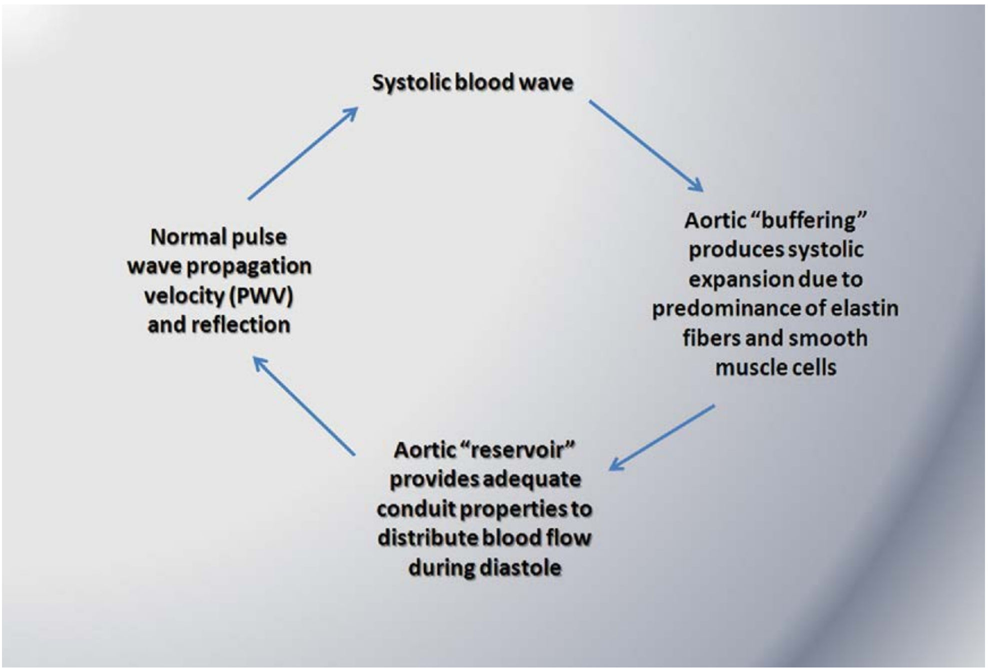

Figure (4): Physiologic Properties of the Aorta as a Reservoir and Conductive System: The Windkessel Principle(3).

Methods for determining arterial stiffness

Assessment of arterial stiffnessis through devices measuring regional, local, and systemic arterial stiffness and wave reflections(20)& others.

I. Regional Stiffness:

❖ Aortic pulse wave velocity:

Carotid-femoral PWV is considered as the 'gold-standard' measurement of arterial stiffness(20).

Principle of measurement:

The pressure pulse generated by ventricular ejection is propagated throughout the arterial tree at a speed determined by the elastic and geometric properties of the arterial wall and elastic conduits, energy propagation occurs predominantly along the arterial wall and not through the incompressible blood(21).The material properties of the arterial wall, its thickness and lumen diameter are the major determinants of PWV.

A) This concept has been formalized in a mathematical model in which the PWV is given by the Moens-Korteweg equation:

$$PWV=\sqrt{}(\frac{Eh}{2\rho r})(22)$$

Or by the Bramwell-Hill equation: which is derived from distensibility.

PWV=$\Delta PV/\Delta V\rho$(22)

(E:Young modulus of the arterial wall; h: wall thickness; r: arterial radius; ρ: blood density; and ΔP and ΔV: changes in pressure and volume respectively).

B) Another method for the measurement of carotid-femoral PWV is made by dividing the distance[d] (from the carotid point to the femoral point) by the transit time[TT] (the time of travel of the foot of the wave over the distance).

Hence,PWV=D(meters)/TT(seconds)(20)(Figure(5)).

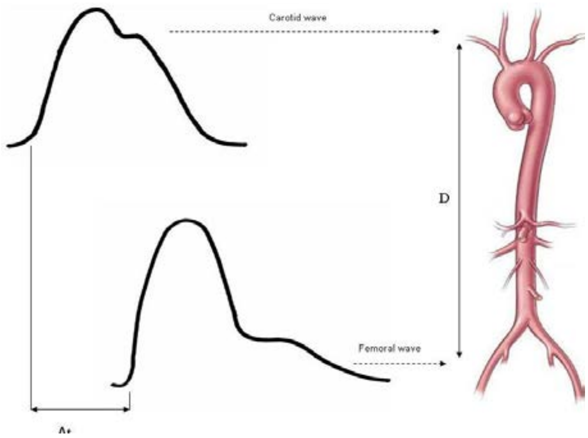

Figure (5): Pulse wave velocity determination. Transit time is estimated by the foot-to-foot method. The foot of the wave is defined at the end of diastole, when the steep rise of the waveform begins. The transit time is the time of travel of the foot of the wave over a known distance(23).

- **Manual calculation of PWV:**

For the manual determination of PWV two different pressure waves obtained at two sites (at the base of the neck for the common carotid artery and over the right femoral artery) were recorded simultaneously on a paper recorder at high speed (150 mm/sec).

Transit time was determined from time delay between the corresponding foot waves: the proximal (A) and the distal (B) pulse waveforms. The foot of the wave is identified as the beginning of the initial upstroke. When this point could not be identified precisely, a tangent was drawn to the to the last part of the preceeding and to the upstroke of the next wave, and the foot wave was taken as the intersection point of these two lines. The distance traveled by the pulse was obtained from superficial measurement of the distance between the two transducers (A and B). The PWV was calculated on the mean basis of 10 consecutive pressure wave forms to cover a complete respiratory cycle(24).

- **Automatic calculation of local PWV:**

i. **Mechanotransducers: Complior System® (Colson, Les Lilas, France)**

This system employs dedicated *mechanotransducers* directly applied on the skin. The transit time is determined by means of a correlation algorithm between each simultaneous recorded wave. The operator is able to visualize the shape of the recorded arterial waves and to validate them. Three main arterial sites can be evaluated, mainly the aortic trunk (carotid-femoral) and the upper (carotid-brachial) and lower (femoral-dorsalispedis) limbs(24)(Figure(6)).

Figure (6): The Complior.The left panel shows the carotid sensor.The right panel shows the femoral sensor held by the operator and the transit distance between the red circles(25).

ii. <u>Applanation tonometer: SphygmoCor® system (ArtCor, Sydney, Australia)</u>

Transit time between arterial sites is determined in relation to the R wave of the electrocardiogram (ECG). A single high-fidelity *applanation tonometer* (Millar, Houston, TX) is used to obtain a proximal and a distal pulse recorded sequentially a short time apart. Then transit time is obtained by subtraction from the delays between ECG and both pulses(26).

To select a fiducial point on the pulse wave curve used as the reference point, the SphygmoCor Pulse Wave Velocity system provides the user with a choice of four possible algorithms;which are (a) the point of minimum diastolic pressure, (b) the point at which the first derivative of pressure is maximum, (c) the point at which the second derivative of pressure is maximum, and (d) the point yielded by the intersection of a line tangent to the initial systolic upstroke of the pressure tracing and a horizontal line through the minimum point(27).

iii. **Oscillometer:Arteriograph® (TensioMed, Budapest, Hungary)**

The main principle of PWV estimation behind the Arteriograph device is to record oscillations detected on the upper-arm cuff by a special high fidelity *oscillometer*. Measurements are performed when cuff pressure exceeds systolic BP by 35–40mmHg, with a completely occluded brachial artery(28).It does not measure propagation time from carotid–femoral waveform recordings or the distance between carotid and femoral arterial recording sites.This measurement is based on the fact that during systole, blood volume ejected into the aorta generates a pulse wave, the so-called 'early systolic peak'. As this pulse wave runs down, it reflects from the bifurcation of the aorta, creating a second wave the 'late systolic peak'. It is recommended to refer to this method when measuring 'aortic PWV'.

Return time (S35) is calculated as the difference in milliseconds between the first and the reflected systolic wave, when cuff pressure is 35mmHg over systolic BP. Aortic PWV (PWV S35) is calculated from (return time S35) as pulse transit time and the distance travelled by the pulse wave. The manufacturer's recommended technique is based on measuring the distance between the sternal notch and the pubic symphysis, two characteristic anatomical points(29).

The Complior system was used in most of the epidemiological studies demonstrating the predictive value of PWV for CV events(20).