

Hypertension-induced left ventricular concentric remodeling. Early diagnosis

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Abstract

Left ventricular concentric remodeling is frequently seen in hypertensive patients. It is considered a compensatory mechanism of the heart caused by high afterload pressures. The widely accepted theory is that left ventricular hypertrophy is caused by the need of the heart to keep normal wall stress. Subsequently the expansion of the left ventricle is associated with altered systolic function and establishment of heart failure. Over time, clinicians and studies have observed different types of cardiac remodelling associated or not with hypertrophy. Concentric remodelling is the initial step in geometric remodelling of the left ventricle and it induces a high cardiovascular risk in presenting patients.

Keywords: hypertension, hypertrophy, cardiac remodelling, concentric remodelling, myocardial mass, wall thickness, geometric remodelling, echocardiography

Cardiac remodelling is represented by the totality of molecular, cellular and interstitial changes that can induce alterations in size, mass, geometry and function after cardiac tissue injury (3, 4).

In the early 30's, Barksdale and Chanutin (1) have observed in their study that cardiac remodelling is caused renal hypertension (in patients with partial nephrectomy). In the next decades, Linzbach describes in a study done at the Marburg pathologic institute the basic principles of cardiac remodelling. He describes

concentric hypertrophy in patients with high pressures in the left ventricle such as we see in hypertension and aortic stenosis.

The main trait of this type of hypertrophy is that the volume of the ventricular cavity remains unchanged.

Later in the 80's, Hochman and Bulkley describe consecutive ventricular expansion after heart attacks as an early form of postnecrotic remodelling of the left ventricle. A theory confirmed later by Janice and Michael Pfeffer (5).

In the case of essential hypertension, cardiac remodelling represents a complex alteration of the left ventricular cavity as an answer to pressure overload as a consequence of ventricular expansion and/or ventricular hypertrophy (7, 18, 19, 22).

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In order to understand how the ventricle reacts to arterial hypertension we need to define the next term: relative wall thickness (RWT). This term is firstly described by Lincoln Ford in 1976 (16). The author suggests that a normal cardiac muscle develops under a linear relation between systolic hypertension values and the ratio between wall thickness and the cavity radius of the left ventricle. The normal value, given by invasive studies is 0.32-0.44.

It is widely considered that the ventricular response to high blood pressure is concentric hypertrophy as it maintains normal parietal wall stress by increasing the thickness of the ventricular walls.

The onset of left ventricular expansion represents a late stage in cardiac remodelling followed by systolic contractile dysfunction that will later generate heart failure.

In reality, ventricular remodelling caused by high blood pressure is a more complex mechanism. Ganau and Devereaux (19) estimate by use of cardiac echography the myocardial mass of the left ventricle and its relative wall thickness (RWT). RWT is defined as the ratio between the diastolic thickness of the LV or the thickness of the interventricular septum and the radius of the cavity of the LV.

With the purpose of describing ventricular cavity remodeling in relation with arterial hypertension the authors have used two echocardiographic parameters to describe four different types of hypertrophy. The first one is defined by a normal cavity of the LV, with a RWT value less than 0.44 and a mass of 95g/m² for women and 115 g/m² for men. The second type of concentric remodelling is defined by a normal myocardial mass and a RWT value higher than 0.44. The third type is defined by a RWT higher than 0.44 and a high myocardial mass index, this 3rd type is considered concentric hypertrophy. The 4th type, defined as eccentric hypertrophy has a RWT less than 0.44 and a high myocardial mass index.

People with concentric hypertrophy, in the earlier mentioned author's study have presented the lowest systolic volumes, with a spheric like shape of the LV and patients with eccentric hypertrophy have presented the highest values systolic volume, with an elliptic shape of the ventricle.

The relation between concentric hypertrophy and high blood pressure is a highly contested theory, both

from the author's point of view and also other studies and clinicians.

The onset and development of concentric remodelling, secondary to high arterial blood pressure implies many cellular and molecular mechanisms (6). From an anatomical standpoint, the main characteristic of concentric remodeling is represented by an elevated RWT, with reduced enlargement of the interventricular septum but with normal myocardial mass. A high RWT describes onset of ventricular hypertrophy, it is a genetic mediated cellular process and is triggered by the stretching of the contractile units; sarcomeres, secondary to overload and induces protein synthesis and as consequence, contractile units; sarcomeres. Continuous synthesis of sarcomeres in concentric hypertrophy induces enlargement of cell diameters. Current evidence suggests that the heart isn't a post mitotic organ and as such development of left ventricular hypertrophy represents a consequence of hyperplasia, that is, continuous synthesis of myocardial and non-myocardial cells (11, 15).

Coupled with ventricular hypertrophy in this initial stage of hypertensive remodelling we also find structural anomalies like: accelerated synthesis of fibrous tissue, change in coronary blood flow and increase in extracellular matrix turnover and apoptosis. It is important to note that myocardial cells develop a high rate of cell death programed in the initial stages of hypertensive remodelling; it's consequence are progressive loss of contractile mass and onset of ventricular failure.

Growth of fibrous tissue by increase in fibrous tissue by increase in fibroblastic synthesis leads to collagen type 1 and 3 build-up in interstitial and perivascular spaces. Consequently, this leads to diastolic dysfunction, reduction in coronary blood flow and can lead to arrhythmias and finally, systolic dysfunction (11).

Recent studies suggest that there is no relation between brachial arterial pressure and ventricular mass although we cannot neglect the impact of high blood pressure on the ventricular cavity. There are however relationships between 24-hour blood pressure monitoring and development of ventricular hypertrophy. From the perspective, myocardial mass is better correlated with aortic pressure and arterial pressure of the lower limbs.

Moreover, some studies have analysed concentric remodelling from the perspective of clinical and physiopathological variables. One example is the Sundstrom (23) study that has analyzed a group of 475 men, of which 157 had high blood pressure, the study concluded that there is a link between concentric remodeling and insulin resistance syndrome; the trophic effect of insulin precursors and heightened sympathetic activity lead to ventricular hypertrophy. In diabetes there are multiple mechanisms of developing hypertrophy, most known of these are hyperinsulinemia, heightened oxidative stress and activation of the renin angiotensin aldosterone system. Sadly, these processes we just mentioned do not explain ventricular remodeling because, in diabetes we find both concentric and eccentric remodelling (25).

The importance of the renin angiotensin aldosterone system in concentric remodelling has been proven in many clinical studies. The LIFE trial (27) studies the geometric remodelling of the left ventricle in 937 patients that suffer from atrial hypertension on a period of 4.8 years after losartan or atenolol treatment. From the baseline 70% of the participants presented ventricle remodelling. At the end of the follow-up period 82% of them had concentric remodelling with normal geometry. Superior results were registered in patients with losartan treatment, both for patients with concentric hypertrophy and concentric remodelling which proves the importance of the renin angiotensin aldosterone system in the concentric remodeling process.

Most of the studies do not report a gender difference in concentric remodeling development (26). Recent data (25) proves the role of various metabolic factors, environmental comorbidities, genetics in the type of cardiac remodelling in essential hypertension.

The importance of concentric remodeling in cardiovascular risk prediction in hypertensive patients was evaluated in several trials (13, 18, 20, 21). One of which is a study by Ganau and Devereaux that has analysed different types of ventricular remodeling (19). There were 165 hypertensive patients included in this study and both RWT index and MMI were measured. The results showed normal values of both parameters in 52% of patients. 13% of them had high RWT index and normal MMI. The rest, 27%, had high MMI and normal RWT. Only 8% had both high MMI and high RWT and as such presented concen-

tric hypertrophy. Patients that had concentric ventricular remodeling presented high blood pressure, low cardiac index and high peripheral resistance. Also, RWT was moderate (but significantly higher) in this group of patients compared to those with normal blood pressure or hypertensive patients with normal ventricular activity.

Another significant study in the quest for understanding ventricular remodelling was published by Koren et al in 1991 (18). The purpose was to evaluate the link between the mass and geometry of the left ventricle and cardiovascular risk in hypertensive patients (18). For this endpoint the authors have included 280 patients that have been monitored for a follow-up period of 10.2 years. 27% of them had presented diagnostic criteria for concentric ventricular remodeling. The highest risk of cardiovascular mortality, 14%, was associated with concentric hypertrophy and the lowest 0.2% with normal MMI and normal RWT. Patients with geometric remodelling presented a rate of cardiovascular events of 4.2% compared to a rate of 1.8% in patients with a normal left ventricle.

In the Framingham Heart Study (21), Krumholz studies the outcome of geometric remodeling in a group of patients without prior cardiovascular disease. The follow-up period was of 7.7 years and the authors conclude that there is a small but insignificant difference between patients with geometric remodeling of the left ventricle and those with a normal cavity. Sadly, this study consists mostly of normotensive subjects and only a quarter of the total number of patients were treated for hypertension. For this reason, we cannot extend these findings for patients with hypertension.

Another more recent study led by Pierdomenico and Mezzetti (24), studies, in a follow-up period of 4.7 ± 2 years the occurrence of fatal and non-fatal cardiovascular events in 1088 patients with moderate hypertension.

A recent study analyzes "after a 12 years follow-up period" the correlation in between the geometric remodeling of LV and the risk of dementia and cognitive impairment. the study includes a multiethnic population, without cardiovascular disease. The conclusions of the trial show that the concentric remodeling and left ventricular hypertrophy were independently associated with dementia and cognitive impairment.

Biochemic diagnosis

The early diagnosis of concentric remodeling of the left ventricle cavity in hypertension is possible due to the presence of inflammation and fibrosis markers in the plasma.

The main processes encountered in remodeling such as inflammation, the increased extracellular matrix turnover and fibrosis, mentioned above, may associate the increase of appropriate biological markers in plasma. One of the first markers used in early diagnosis is the atrial natriuretic hormone whose rapidity in use has prompted an ample interest. The significant biological variability of the two forms of natriuretic peptide, B and N terminal has a low specificity and therefore a reduced utility in the clinical practice. The association in between the high levels of this marker with impaired cardiac diastolic function and concentric remodeling is one of the main criterias for the preserved ejection fraction cardiac failure diagnosis.

Proinflammatory cytokines have proven their utility in the early diagnosis of concentric remodelling (10). Interleukin 6 (IL 6) and Interleukin 8 (IL 8), monocytic chemotactic protein 1 (MCP-1) and tumor necrosis factor alpha (TNF- α) have been detected by immunodetection methods. Of all the markers specific to fibrosis, the most studied was Procollagen I C-terminal Propeptide (PICP), it was detected by ELISA method. Other markers specific to fibrosis are Procollagen I N-terminal Propeptide (PINP) and Procollagen III N-terminal Propeptide (PIIINP) and Collagen I telopeptide (CITP). The increased turnover of the extracellular matrix was evidenced by dosing matrix metalloproteinases 2(MMP2), matrix metalloproteinases 9 (MMP9) and tissue inhibitors of metalloproteinases 1(TIMP1) in blood plasma.

In a study that consecrated the use of these markers, the linear regression analyses correlated with the left atrial index greater than 34ml/m² and high matrix metalloproteinases 9 (MMP9) values in asymptomatic hypertensives. The increased values of the mentioned markers in the context of the LA which suggests the asymptomatic onset of the preserved ejection fraction heart failure. Monitoring this biomarker levels in plasma could allow the detection of concentric remodeling heart failure progression.

Troponin T highly specific presents elevated plasma values in correlation with the concentric remodeling

of the LV in hypertensives. The cardiomyocytes injury produced by the postprandial overload and excessive apoptosis response would explain the troponin T high levels in LV concentric remodeling.

The mentioned biological and neurohormonal markers present a high sensitivity but a low specificity in the medical cases, characterized by multiple comorbidities which create difficulties in their interpretation.

Imagistic diagnosis

Imagistic diagnosis of concentric remodeling is mainly based on M and 2D transthoracic echocardiography techniques, Spectral Doppler tissue Doppler, as well as modern techniques such as STRAIN, SPECKLE TRACKING.

The main diagnosis criteria for the concentric remodeling are the absence of myocardial mass and a higher than 0.42 value of the relative thickness index.

Myocardial mass is calculated using the Deveaux formula, then indexing the obtained values to gender and body surface area:

$$MM=0.8\{[1.04(LVEDD+IVSD+PWD)^3-LVEDD^3]\}+0.6$$

MM = myocardial mass

LVEDD= left ventricular end-diastolic pressure

IVSD= interventricular septal thickness at diastole

PWD= posterior wall thickness at diastole

Interpretation of myocardial mass values face some difficulties in the medical practice. First of all, it is recommended to index the myocardial mass to the body surface and the genre of the patient. Secondly, this recommendation is limited by the nonlinear regression formula which adjusts the myocardial mass to height without the same accuracy in subjects with extreme anthropometric data. The consequences are reflected in the overestimation of myocardial mass and LVH in the short patients and underestimating it in tall patients (8).

When echocardiography is involved we have to be mindful to follow standard measuring practices to get the most accurate result. It is recommended that when measuring in M mode the ultrasound waves have to fall perpendicular to the ventricular septum and posterior wall. When M mode is not available we should use 2D bidimensional mode to measure wall thickness at the end of diastole (marked by the R wave on our EKG reading).

Table 1 (Adapted from 8).

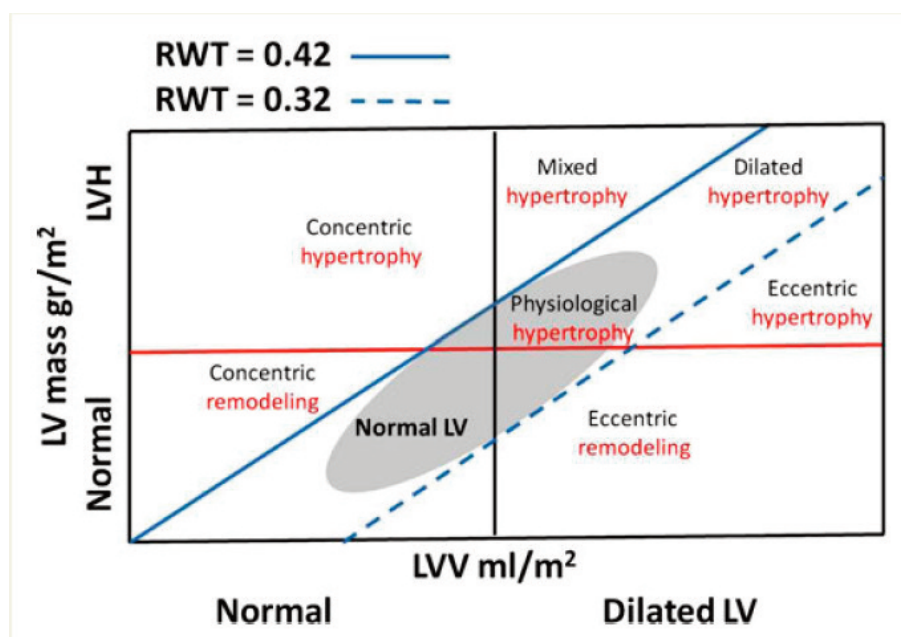
Characterization of LV geometry based on LVM (vertical axis), LV volume (horizontal axis), and RWT, measured using 2D-directed M-mode			
LV geometric pattern	LV volume index (mL/m ²)	LVM index (g/m ²)	RWT
Normal ventricle	≤75	≤115 (men) or ≤95 (women)	0.32–0.42
Physiological hypertrophy	>75	>115 (men) or >95 (women)	0.32–0.42
Concentric remodelling	≤75	≤115 (men) or ≤95 (women)	>0.42
Eccentric remodelling	>75	≤115 (men) or ≤95 (women)	<0.32
Concentric hypertrophy	≤75	>115 (men) or >95 (women)	>0.42
Mixed hypertrophy	>75	>115 (men) or >95 (women)	>0.42
Dilated hypertrophy	>75	>115 (men) or >95 (women)	0.32–0.42
Eccentric hypertrophy	>75	>115 (men) or >95 (women)	<0.32

By defining the normal values (8) for RWT of 0.32–0.42 and the threshold value of 75ml/m² for the left ventricle either by hypertrophy or dilation, there are 7 types of geometric remodeling in patients that suffer from hypertension (see Table 1).

We distinguish four additional patterns: physiological hypertrophy, eccentric remodeling, hypertrophy by dilation and mixed hypertrophy. In accordance to these findings, we must redefine the diagnosis criteria for

concentric remodeling by a systolic stroke volume of the left ventricle lower than 75 ml/m², normal myocardial mass and a RWT higher than 0.42 (graph 1).

Conventional echocardiographic diagnosis for concentric remodeling is supplemented by measuring left ventricular function in systole and diastole. To these means spectral and tissular Doppler scans are made to measure mitral velocities by getting an accurate E/A reading. The above-mentioned parameters are useful



Graph 1: Different types of geometric remodeling of the left ventricle dependent on ventricular mass, volume and RWT. Adapted from (8).

in classification diastolic dysfunction, the most frequent being type 1 “delayed relaxation”. Once cardiac remodeling in the hypertensive disease is progressing the left ventricular filling pressure is rising and the diastolic dysfunction is increasing, this result in systolic dysfunction, especially in untreated patients.

New techniques such as strain echography, speckle-tracking, and 3D mode generate important information in early diagnosis of concentric remodeling. Speckle tracking echocardiography for example, measures the torsion angle of the left ventricle in hypertensive patients. A recent study that uses the torsion indices analyses left ventricular displacement angle in hypertensive patients with geometrical remodeling compared to healthy patients. The authors found out that the torsion angle is increased in patients with concentric remodeling, the highest values being found in concentric hypertrophy. The study concluded that left ventricular torsion amplification is a compensatory phase in the initial stages of left ventricle geometric remodeling in patients suffering from hypertension. Tridimensional speckle-tracking studies showed longitudinal and global changes in this group of patients.

Tissular Doppler gives useful information that helps characterize myocardial tissue. Examination of the myocardial parenchyma using the backscatter technique can find increased density. This method initially was considered to have low reliability because its dependence on the insonation angle, recently though, new advances in technology have considerably diminished the insonance angle influence. Therefore, the reflection of the ultrasound beam, dependent on the position of myocardial fibers (serial or parallel fibers) can generate different results depending on the incidence used. In the initial stage of concentric remodeling, the detected changes with this method allows early diagnosis of the structural modification of the septum in hypertensive patients.

Using MRI we can get tridimensional imaging of the left ventricle without a preexisting geometrical model of the cavity, and as such this represents an advantage in early evaluation of concentric remodeling. Late acquisitions using radioactive gadolinium shows binding in more than half of patients in left ventricular hypertrophy. IRM techniques are probably the most sensible method used to detect the geometric shape of the left ventricle and also in the diagnosis of concentric remodeling. This is sustained not only by its superior

capability but also by the variation in the density and thickness of the cavity walls, where conventional echocardiography shows its limits.

Recent data describes gadolinium induced renal fibrosis so this method is used with caution in patients suffering from renal failure. The high cost of the procedure and the reduced quantitative information in concentric remodeling does not allow for frequent use of this type of imaging in clinical practice.

Conclusion

Concentric remodeling secondary to arterial hypertension represent the initial geometric change in the left ventricular cavity. Studies inform on the increased cardiovascular risk for patients that present this type of remodeling comparing with those with a normal cavity, but lower than those with concentric hypertrophy. Early diagnosis of concentric remodeling allows pharmacological intervention that will limit its progression to systolic dysfunction and heart failure.

Conflicts of interest

The authors confirm that there are no conflicts of interest. All authors have equal contribution to this paper.

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