VENTRICULAR REMODELING IN AORTIC SCLEROSIS

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Abstract

Background and aims. Aortic sclerosis associates an increased risk of cardiovascular morbidity and mortality. Recent studies suggest that aortic sclerosis is able to produce ventricular remodeling through inflammatory, non-hemodynamic mechanisms. Our study aims to evaluate the correlation between ventricular remodeling and aortic sclerosis severity.

Method. 68 patients with aortic sclerosis without other significant associated valvulopathies were examined clinically, biologically and echocardiographic. In 20 patients, we quantified the severity of aortic valve calcification using the backscatter ecographic technique, in parasternal long and short axis view. Backscatter values obtained at the valvular level were calibrated to the blood and pericardium backscatter values.

Results. In the 68 patients group, transvalvular aortic velocity correlates with left ventricular mass (p =0.031), which in turn incline to augment with increasing calcification severity assessed by backscatter. Calcification severity assessed by backscatter corellates with transvalvular aortic velocity in parasternal long axis view (p =0.039 for blood calibrated backscatter, p =0.029 for pericardium calibrated backscatter), and tends to augment with increasing transvalvular aortic velocity in parasternal short axis view. Patients with normal ventricular geometry incline to have lower aortic transvalvular velocities and a lower degree of calcification (evaluated by backscatter) compared to patients with ventricular remodeling.

Conclusions. Aortic sclerosis is not benign, and may lead, in time, to left ventricular remodeling. With the progression of valvular calcifications in aortic sclerosis patients, the prevalence of ventricular remodeling tends to increase.

Keywords: backscatter, aortic sclerosis, ventricular remodeling.
Rezumat

Introducere și obiective. Scleroza aortică asociază un risc crescut de morbiditate și mortalitate cardiovasculară. Studii recente sugerează că scleroza aortică poate produce remodelare ventriculară prin mecanisme inflamatorii, nonhemodinamice. Studiul de față își propune să evaluate corelația dintre remodelarea ventriculară și severitatea sclerozei aortice.

Metoda. Un număr de 68 de pacienți cu scleroză aortică fără alte valvulopatii semnificative asociate au fost examinați clinic, biologic și ecocardiografic. În cazul a 20 de pacienți, severitatea calcificărilor aortice a fost cuantificată prin tehnica ecografică backscatter (parasternal ax lung și scurt). Valorile backscatter obținute la nivel valvular au fost calibrate la valorile backscatter de la nivelul sângeului, respectiv pericardului.

Rezultate. În grupul de 68 de pacienți există o corelație semnificativă statistic între viteza transvalvară aortică și masa ventriculară stângă (p =0,031), care, la rândul său, tende să crească odată cu creșterea severității calcificării valvulare aortice evaluate prin backscatter. Severitatea calcificării evaluate prin backscatter se corelează cu viteza transvalvară aortică (în secțiune parasternal ax lung) (p =0,039 pentru backscatter calibrat la sânge, p =0,029 pentru backscatter calibrat la pericard) și tende să crească odată cu creșterea vitezei transvalvarare aortice (în secțiune parasternal ax scurt). Pacienții cu geometrie ventriculară normală tind să aibă viteze transvalvulare aortice mai mici și un grad mai mic de calcificare (evaluat prin backscatter) comparativ cu pacienții cu remodelare ventriculară.

Concluzii. Scleroza aortică nu este o entitate benignă și poate duce, în timp, la remodelare ventriculară stângă. Odată cu evoluția calcificărilor valvulare la pacienții cu scleroză aortică, prevalența remodelării ventriculare tinde să crească.

Cuvinte cheie: backscatter, scleroza aortică, remodelare ventriculară.
**Introduction**

With a prevalence ranging from 9% in patients with a mean age of 54 years, to 42% in patients with a mean age of 81 years\(^1\), aortic sclerosis is the most common valvular change. Because it has no hemodynamic impact and it is totally asymptomatic, aortic sclerosis was considered until recently totally benign. However, it may lead over time to clinically manifest aortic stenosis, and on the other hand it is associated with a 50% increase in the risk of death from cardiovascular causes and myocardial infarction\(^2\).

Aortic sclerosis presence has been frequently associated with left ventricular hypertrophy, especially in hypertensive patients\(^3\). On the other hand, initial phases of calcific aortic disease represents an inflammatory process with endothelial dysfunction\(^4\), able to lead to ventricular hypertrophy regardless of afterload. Therefore, aortic sclerosis patients may develop, in theory, ventricular hypertrophy regardless the presence / absence of hypertension.

A study performed by Dweck suggests that in patients with moderate-severe aortic stenosis (advanced form of aortic calcific disease, a spectrum including aortic sclerosis), not only hemodynamic factors determine ventricular remodeling\(^5\). Thus, Dweck shows by nuclear magnetic resonance technique that in 91 patients with moderate to severe aortic stenosis there are multiple phenotypes of left ventricular remodeling: concentric remodeling, concentric hypertrophy, normal geometry, eccentric hypertrophy, asymmetric remodeling and asymmetric hypertrophy. In Dweck’s study, the remodeling type was not related to the aortic stenosis severity\(^5\).

Yan shows in a study performed on rats with chronic kidney disease the association between inflammation and heart remodeling\(^6\).

A study enrolling 135 patients with chronic kidney disease in the hemodialysis program shows the association between aortic valve calcifications and left ventricular hypertrophy regardless of pulse pressure, the presence of anemia and hyperhydration\(^7\). In patients undergoing peritoneal dialysis, cardiac valve calcifications are associated with the presence of ventricular hypertrophy\(^8\).

On the other hand, a study that included 79 patients without pre-existing cardiovascular disease and without hypertension did not found a significant difference between LV mass in patients with or without aortic sclerosis. In this study, LV mass was correlated only with systolic blood pressure, increased BMI and male sex\(^9\). However, this study only considered patients with hypertrophic ventricular remodeling, not those with concentric remodeling, so with normal left ventricular mass.

**Aim**

The present study aims to evaluate the correlation between ventricular remodeling and the severity of aortic sclerosis.

**Material and methods**

**Patients and settings**

We conducted a prospective study that included 68 patients with aortic sclerosis and LVEF (left ventricular ejection fraction) ≥50%. Patients with other hemodynamically significant valvulopathies, congenital heart disease or those with aortic bicuspid valve, as well as those with pulmonary hypertension were excluded. For each patient, the associated comorbidities, clinical, biological, ECG and echocardiographic parameters were
analyzed. The quantitative evaluation of the valvular calcifications was performed in 20 patients using backscatter technique\(^{10,11,12}\). The study was approved by the hospital’s Ethics Council, and patients were enrolled after signing the informed consent.

**Echocardiographic examination**

The presence of aortic sclerosis was established using echocardiography (Phillips IE33 system, QLAB software, phased-array 5MHz-1MHz samples) and was defined as a maximum aortic transvalvular velocity between 1.5 m/sec (upper limit of normal aortic valve) and 2.5 m/sec (lower limit from which aortic stenosis is defined). The measurements of IVS (interventricular septum), PWT (posterior wall thickness) and left ventricular dimensions, were performed in parasternal long axis view according the european guidelines recommendations\(^{13}\). The LV (left ventricular) mass was calculated using cube formula\(^{13}\), as follows: 

\[ \text{LV mass} = 0.8 \times 1.04 \times [(\text{IVS} + \text{LVd} + \text{PWT})^3 - \text{LVd}^3] + 0.6 \text{ g.} \]

In this formula, LVd represents left ventricular internal diameter.

The 4 types of ventricular remodeling were established according the recommendations of the same guideline, depending on the ventricular mass and the relative walls thickness (RWT), as follows: Patients with normal LV mass (≤95gm/m\(^2\) in women, ≤115 gm/m\(^2\) in men) present concentric remodeling (normal mass and RWT >0.42) or normal geometry (normal VS mass and RWT ≤0.42). Patients with increased LV mass (>95gm/m\(^2\) in women, 115 gm/m\(^2\) in men) present concentric (RWT >0.42) or eccentric hypertrophy (RWT ≤0.42). RWT was calculated as \(2 \times \text{PWT/LVd}\).

The quantitative evaluation of the valvular calcifications was performed in 20 patients using backscatter technique\(^{10,11,12}\).

For each analyzed area the soft assigned a numerical value, depending on the shade of gray, at standard device settings (gain - 0, compression -55, mechanical index -1.4). The measurements were performed offline, in 3 different cardiac cycles, at the same moment of the cardiac cycle. The ROI (regions of interest) were placed in the bazal, mid and apical level of the 2 visible cusps in parasternal long axis view (figure 1)\(^{10,9}\) and in the middle of each of the 3 cusp in short axis view (figure 2). Backscatter values in the blood respectively in the pericardium were used as a reference.

Blood calibrated backscatter (BCB) and pericardium calibrated backscatter (PCB) were calculated separately for both the long-axis and short-axis ultrasound views. BCB is calculated by subtracting backscatter of blood pool from values obtained on aortic valve. PCB is calculated by subtracting backscatter of aortic valve from values obtained on pericardium.
A study sheet was prepared for each patient to allow comparative processing and data centralization obtained from clinical, biological and echocardiographic examination.

**Figure 1.** Backscatter in parasternal long axis view - 3 ROI placed on the right and on the noncoronary aortic valve (basal / on the valvular ring, middle and apical portion)

**Figure 2.** Backscatter in parasternal short axis view - ROI placed in the middle of the right, noncoronary and left aortic cusps

**Statistical analysis**
Statistical analysis was performed using EpiInfo 7 and IBM SPSS Statistics 20. A value \( p<0.05 \) was considered significant. The strength of statistical correlation was assessed using Spearman’s rho correlation coefficients. The differences between groups were analysed using the Mann-Whitney \( U \) test, ANOVA, or Bartlett’s Test for Inequality of Population Variances.

**Results**

Table 1 summarizes patient characteristics (table 1). In the study group were enrolled 46 women and 22 men, aged between 42 and 95 years, the mean age \( 69.72 \pm 10.738 \) years. Table 2 summarizes the biological and echocardiographic parameters of the analysed patients (table 2).

In the study group of 68 patients Spearman analysis shows a statistically significant correlation between maximum transvalvular aortic velocity and left ventricular mass \( (p=0.031) \) (figure 3). This correlation is maintained when we use left ventricular mass indexed to body surface area \( (p=0.007) \). Thus, patients with high maximum aortic transvalvular velocity often have high ventricular mass. However, aortic transvalvular velocity is not a standardized method for assessing the severity of aortic sclerosis. Therefore, in 20 patients we quantitatively assessed the severity of aortic sclerosis using the backscatter technique.

In patients whose valvular calcifications have been evaluated using backscatter technique, Spearman analysis shows a statistically significant correlation between both long-axis BCB values and aortic transvalvular velocity \( (p =0.039, \text{correlation coefficient } 0.464) \) (Figure 4) and between long-axis PCB values and aortic transvalvular velocity \( (p =0.029, \text{correlation coefficient } 0.476) \) (Figure 5).
correlation coefficient -0.489) (figure 5). This suggests that patients with high aortic transvalvular velocities are more likely to have a high degree of calcification quantified by backscatter values.

In the short axis view, although there is no statistically significant correlation between aortic transvalvular velocity and backscatter values, there is a tendency to increase the aortic transvalvular velocity at more severe calcifications evaluated by backscatter. However, due to anisotropy and due to the different planes arrangement of the aortic valves, in relation to the ultrasound beam, BCB value and PCB in short and long axis view can not be compared with each other.

Patients with normal ventricular geometry have lower BCB (figure 6) and higher PCB values (figure 7) compared to patients with hypertrofic or non-hypertrofic ventricular remodeling. Although this correlation is not statistically significant due to the small number of patients included in the study, these results suggest that the patients with normal ventricular geometry incline to have a lower degree of calcification (evaluated by backscatter) compared to patients with ventricular remodeling.

**Discussions**

In the 68 patients group, left ventricular mass correlates with transvalvular aortic velocity. In the 20 patients group in whom backscatter analysis was performed, backscatter values in parasternal long axis view correlate with the aortic transvalvular velocity and tends to augment with LV mass increase. In contrast, in the short axis view, the backscatter values do not correlate statistically significantly with the aortic transvalvular velocity, and tends to decrease with LV mass decrease. These findings are consistent with previous data suggesting the backscatter measurements for aortic valve are often performed in the long axis section\(^9\), although only 2 cusps are visible, probably due to the anisotropy of backscatter in short axis view\(^9\) but also due to the different planes arrangement of the aortic valves, in relation to the ultrasound beam.

However, in the above mentioned study\(^{18}\), ROI was placed at the myocardial level not at the valvular level, and in our study the small number of patients results in low statistical power. The backscatter definition threshold of sclerosis is different in long and short axis view.

The result of the current study reveals the tendency to associate the magnitude of valvular degenerative lesions with the increase in the prevalence of ventricular remodeling (hypertrophic or non-hypertrophic).

However, all patients included in the study were hypertensive patients.
## Table 1. Patient characteristics

*GRF* - glomerular filtration rate

| Biological parameters | Average ± std deviation | Echocardiographic parameters | Average ± standard deviation |
|-----------------------|-------------------------|-----------------------------|----------------------------|
| Blood glucose         | 120.82 mg/dl ± 51.62 mg/dl | Ao velocity                 | 1.8 ± 0.24 m/sec           |
| Urea                  | 43.67 mg/dl ± 19.06 mg/dl  | LV mass                     | 206.22 ± 51 g              |
| Creatinine            | 1.08 mg/dl ± 0.7 mg/dl    | LV mass indexed to body surface area | 107.81 ± 25.67 g/cm²   |
| GFR                   | 66.34 ml/min ± 20.02 mg/dl | RWT (2PWT/LVd)              | 0.46 ± 0.11 cm             |
| Hemoglobin            | 13.04 g/dl ± 1.59 g/dl    | RWT (IVS + PWT)/LVd        | 0.47 ± 0.11 cm             |
| Platelets             | 239929.03 uL ± 72614.38 uL | EF                          | 60.44 ± 6.98 %            |

### Table 2. Patient biological and echocardiographic parameters

*Ao velocity - transvalvular aortic velocity; LV - left ventricle; RWT - relative wall thickness; PWT - posterior wall thickness; IVS - interventricular septum; LVd - left ventricle measured in diastole; EF - ejection fraction; GFR - Glomerular filtration rate*
The question is whether ventricular remodeling has been caused by high blood pressure or by aortic sclerosis in patients who associate both conditions.

According to literature data, the prevalence of ventricular hypertrophy in hypertensive patients varies as follows: 10-19% in studies including patients in the general population, 19-48% in studies including untreated hypertensive patients, and 58-77% in studies including high-risk hypertensive patients. Moreover, some studies suggest that the most common type of ventricular hypertrophy in hypertensive patients is not concentric hypertrophy, but eccentric hypertrophy.

In the present study, which included mostly hypertensive patients with aortic sclerosis, concentric hypertrophy was present in 38% patients, concentric remodeling in 21%, normal geometry in 26% and eccentric hypertrophy in 15%.

It is very difficult to differentiate between the magnitude of the impact induced by each factor (hypertension and aortic degenerative valve lesions) on the remodeling development and on the type of ventricular remodeling. It is likely that the pathological value of the maximum aortic transvalvular velocity would be the element that leads to ventricular remodeling. In our study, hypertensive patients were on antihypertensive treatment at the time of examination. On the other hand, the LV mass can be influenced by an individual genetic component. This explains, in some cases, the presence of increased LV mass independent of afterload, induced by aortic valve sclerosis or stenosis and explains an exacerbated response to minimal afterload increases in some patients.

According to Cioffi, some patients with mild and moderate aortic stenosis present an inappropriately high left-ventricular mass, unrelated to severity of aortic stenosis or presence of hypertension. In our study, patients with high aortic transvalvular velocities are more likely to associate high ventricular mass, supporting the above mentioned data.

Comparing the literature data on LV mass, there are conflicting results (table 3). Some data obtained from hypertensive patients shows a lower LV mass compared to the present study group with hypertension (in 94.11% of cases) and aortic sclerosis, suggesting that aortic sclerosis leads to further increase in left ventricular mass. However, it is impossible to differentiate the magnitude of each factor impact on ventricular hypertrophy.

A study conducted by Koren on 172 hypertensive patients shows a LV mass index of 107 ±36 g/m², similar with our findings in patients with aortic sclerosis and
Figure 3. Transvalvular aortic velocity and left ventricular mass

Figure 4. Blood calibrated backscatter in long axis view and aortic transvalvular velocity (BCB - blood calibrated backscatter)

Figure 5. Pericardium calibrated backscatter in long axis view and aortic transvalvular velocity (PCB - pericardium calibrated backscatter)
Figure 6. BCB and ventricular remodeling (BCB - blood calibrated backscatter)

Figure 7. PCB and ventricular remodeling (PCB - pericardium calibrated backscatter)
| Trial       | Inclusion criteria                                                                 | Mass calculation formula                  | Trial LV mass         | Current study (left ventricular mass) |
|------------|-------------------------------------------------------------------------------------|--------------------------------------------|-----------------------|--------------------------------------|
| Levy, 1990 | 3220 patients 40 years of age or older, free of clinically apparent cardiovascular disease (Framingham trial) | $1.04\left[(L Vd + IVS + PWT)^3 - (L Vd^3) - 13.6\right]$ | 86.84±27.12 women     | 145.6415±40.42567 women               |
|            |                                                                                     |                                             | 115.58±34.36 men      | 150.182 ±33.34072 men                |
| Kizer, 2004 | 580 hypertensive patients, free of >2 valvular regurgitation or any degree of valvular stenosis, free of overt coronary artery disease (HyperGEN trial) | $0.8 \cdot 1.04 \cdot [(IVS + LVd + PWT)^3 - LVd^3] + 0.6 g$ | 168.2 ± 37.4 g        | 206.22 ±51 g                         |
| Koren, 2002 | 172 hypertensive patients                                                            | $1.04 \cdot [(IVS + LVd + PWT)^3 - LVd^3] - 14 g$ | 107±36 g/m²           | 126.994±31.987 g/m²                  |
| Nightingale, 2011 | 79 subjects without existing cardiovascular disease or previous antihypertensive therapy | Magnetic resonance calculation            | 104.9±24.9 g          | 157.5 g                             |
| Otto, 1999  | Population based study                                                               | None                                       | 157.5 g               | 243.4301 g±63.75043 g                |
| Agno, 2005  | 1624 hypertensive patients                                                           | $1.04 \cdot [(IVS + LVd + PWT)^3 - LVd^3] - 13.6 g$ | 170.0±41.7 g normal aortic valve | 178.8 ± 43.5 g aortic sclerosis      |

Table 3. Regression Analysis of Characteristics of Patients with Pre-and Intraoperatively Detected Tumor Characteristics of Significance for the Percentage of Involved Lymph Nodes

LVd-left ventricle measured in end diastole; IVS - interventricular septum; PWT – posterior wall thickness
hypertension (LV mass index 107.81±25.67 g/m²). This may suggest that aortic sclerosis does not interfere with left ventricular mass. The current study has several limitations. First, the study included a small number of patients, and did not include control patients – backscatter values were compared to backscatter values in literature\(^{(10,11)}\). In addition, as already shown, many patients had hypertension and is difficult to appreciate the impact of each of these factors - arterial hypertension and aortic sclerosis on ventricular remodeling.

Conclusions

Aortic sclerosis is not benign, and may lead, in time, to left ventricular remodeling. With the progression of valvular calcifications in aortic sclerosis patients, the prevalence of ventricular remodeling tends to increase. There are significant differences between the backscatter values in the long axis view, with 2 visible cusps, and short axis view- with 3 visible cusps. This is probably due to the arrangement in different planes of the aortic valves, in relation to the ultrasound beam, and to the anisotropy of backscatter in short axis view\(^{(18)}\). Assessment of aortic calcifications by backscatter technique could be useful in monitoring the progression of aortic calcific disease, from sclerosis to valvular stenosis.

Future perspectives

It would be useful to follow in time the remodeling and the progression of aortic degenerative lesions by backscatter until the transformation of valvular sclerosis into stenosis. This would be necessary to assess the particular response of each patient, and would allow the correction of aggravating factors and treatment initiation. It would also be useful to establish a backscatter cutoff for aortic sclerosis and normal valve definition.

Conflict of interest: none declared.

Bibliography:
1. Coffey S, Cox B, Williams MJ.; The prevalence, incidence, progression, and risks of aortic valve sclerosis: a systematic review and meta-analysis.; J Am Coll Cardiol. 2014 Jul 1;63(25 Pt A):2852-61.
2. Otto CM, Lind BK, Kitzman DW, Gersh BJ, Siscovick DS.; Association of aortic-valve sclerosis with cardiovascular mortality and morbidity in the elderly.; N Engl J Med. 1999 Jul 15;341(3):142-7.
3. Olsen MH, Wachtell K, Bella JN, et al; LIFE substudy.; Aortic valve sclerosis relates to cardiovascular events in patients with hypertension (a LIFE substudy).; Am J Cardiol. 2005 Jan 1;95(1):132-6.
4. Otto CM, Kuusisto J, Reichenback DD, et al; Characterisation of the early lesion of degenerative valvular aortic stenosis histological and immunohistochemical studies; Circulation. 1994;90:844–853.
5. Dweck, M. R., Joshi, S., Murigu, T et al.; Left ventricular remodeling and hypertrophy in patients with aortic stenosis: insights from cardiovascular magnetic resonance. J Cardiovasc Magn Reson. 2012; 14(1): 50.
6. Yan L, Mathew L, Chellan B, et al.; S100/Calgranulin-
mediated inflammation accelerates left ventricular hypertrophy and aortic valve sclerosis in chronic kidney disease in a receptor for advanced glycation end products-dependent manner.;Arterioscler Thromb Vasc Biol. 2014 Jul;34(7):1399-411.

7. Ventura JE, Tavella N, Romero C, et al.;Aortic valve calcification is an independent factor of left ventricular hypertrophy in patients on maintenance haemodialysis.;Nephrol Dial Transplant. 2002 Oct;17(10):1795-801.

8. Yilmaz M, Unsal A, Oztekin E, et al.;The prevalence of hypertension, valve calcification and left ventricular hypertrophy and geometry in peritoneal dialysis patients.;Kidney Blood Press Res. 2012;35(6):431-7. doi: 10.1159/000336946. Epub 2012 Jun 6.

9. Nightingale AK, Sverdlov AL, Rajendran S, et al.;Lack of association between aortic sclerosis and left ventricular hypertrophy in elderly subjects.;Int J Cardiol. 2011 Jul 1;150(1):33-8. doi: 10.1016/j.ijcard.2010.02.024. Epub 2010 Mar 16.

10. Ngo DT, Wuttke RD, Turner S, Marwick TH, Horowitz JD.;Quantitative assessment of aortic sclerosis using ultrasonic backscatter.;J Am Soc Echocardiogr. 2004 Nov;17(11):1123-30.

11. Sgorbini L, Scuteri A, Leggio M, Leggio F.;Association of mitral annulus calcification, aortic valve calcification with carotid intima media thickness.;Cardiovasc Ultrasound. 2004 Oct 8;2:19.

12. Mor-Avi, V., Lang, R. M., Badano, L. P., Belohlavek, M et al; Current and evolving echocardiographic techniques for the quantitative evaluation of cardiac mechanics ASE/EAE Consensus Statement on Methodology and Indications Endorsed by the Japanese Society of Echocardiography.;J Am Soc Echocardiogr. 2011;24(3):277-313. doi:10.1016/j.echo.2011.01.015.

13. Roberto M. Lang, Luigi P. Badano, Victor Mor-Avi et al.;Recommendations for Cardiac Chamber Quantification by Echocardiography in Adults: An Update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging;European Heart Journal – Cardiovascular Imaging (2015) 16, 233-271 doi:10.1093/ehjci/jev014.

14. Daniel Levy, Robert J. Garrison, Daniel D. Savage, et al.;Prognostic Implications of Echocardiographically Determined Left Ventricular Mass in the Framingham Heart Study;N Engl J Med 1990; 322:1561-1566, DOI: 10.1056/NEJM199005312322203.

15. Kizer, J. R., Arnett, D. K., Bella, J. N et al.;Differences in left ventricular structure between black and white hypertensive adults: the Hypertension Genetic Epidemiology Network study.;Hypertension. 2004;43(6):1182-1188.doi:10.1161/ 01.HYP. 00001 28738.94190.9f.

16. Koren Mj, Ulin Rj, Koren At, Laragh Jh, Devereux Rb.;Left ventricular mass change during treatment and outcome in patients with essential hypertension; Am J Hypertens. 2002;15(12):1021-1028. doi:10.1016/s0895-7061(02)03061-3.

17. Agno, F. S., Chinali, M., Bella, J. N., Liu, J. E., Arnett, et al;Aortic valve sclerosis is associated with preclinical cardiovascular disease in hypertensive adults: the Hypertension Genetic Epidemiology Network study.;J Hypertens. 2005;23(4):867-873. doi:10.1097/ 01.hjh.0000163157. 14493.c7.

18. Holland MR, Kovacs A, Posdamer SH, Wallace KD, Miller JG.;Anisotropy of apparent backscatter in the short-axis view of mouse hearts.;Ultrasound Med Biol. 2005 Dec;31(12):1623-9.

19. C Cuspidi 1, C Sala, F Negri, G Mancia, A Morganti, Italian Society of Hypertension;Prevalence of Left Ventricular Hypertrophy in Hypertension: An Updated Review of Echocardiographic Studies; J Hum Hypertens. 2012;26(6):343-349. doi:10.1038/jhh.2011.104.

20. K Wachtell , J N Bella, P R Liebson, et al;Impact of Different Partition Values on Prevalences of Left Ventricular Hypertrophy and Concentric Geometry in a Large Hypertensive Population: The LIFE Study.; Hypertension.2000;35(1Pt 1):6-12.doi:10.1161/01.hyp.35.1.6.

21. Cioffi G, de Simone G, Cramariuc D, Mureddu GF, Gerdts E; Inappropriately high left-ventricular mass in asymptomatic mild-moderate aortic stenosis.;J Hypertens. 2012;30(2):421-428. doi:10.1097/ HJH.0b013 e3283 4f0b00.