Relationship between aortic valve sclerosis and different vascular damage markers: an observational study

Aort kapak sklerozu ile damarsal hasarı gösteren farklı parametreler arasındaki ilişki: Gözlemsel bir çalışma

Levent Korkmaz, Mustafa Tarık Ağaç, Ayça Ata Korkmaz[1], Hakan Erkan, Zeydin Acar, Şükrü Çelik

Clinic of Cardiology, Ahi Evren Cardiovascular and Thoracic Surgery Training and Research Hospital, Trabzon-*Turkey*
[1]Department of Radiology, Akçaabat State Hospital, Trabzon-*Turkey*

ABSTRACT

Objective: Although aortic valve sclerosis (AVS) and atherosclerosis may share same atherosclerotic process, there is still a controversy whether AVS may be related to atherosclerotic and nonatherosclerotic processes. The purpose of present study was to investigate this relation.
Methods: In this cross-sectional and observational study, we enrolled 60 patients diagnosed with AVS and risk factor matched 76 subjects without AVS. Applanation tonometry was applied to assess the augmentation index and aortic pulse-wave velocity (PWV). Control and AVS group were examined by B-mode ultrasound to measure the intima-media thickness (IMT). Continuous variables were compared using unpaired t-test and Mann-Whitney U test. Logistic regression analysis was performed in order to find independent predictors of AVS.
Results: PWV and augmentation index did not differ between control and AVS groups (11.2±3.6 vs 12±3.2, p=0.18 and 26±7.6 vs 27±9.8, p=0.2 respectively). But IMT was significantly higher in AVS group than in control one (0.76 mm±0.17 vs 0.6 mm±0.16; p<0.001). There was a significant positive bivariate correlation between the presence of AVS, IMT (r=0.43, p<0.001), male gender(r=0.31, p<0.001), augmentation index (r=0.17, p:0,04), and age (r=0.36, p<0.001). Logistic regression analysis demonstrated that only IMT (OR: 1.46, 95% CI: 1.1-1.9, p=0.009) and age (OR: 1.1, 95% CI: 1.01-1.16, p=0.013) were independent predictors of AVS.
Conclusion: Increased IMT but not PWV in subjects with AVS compared to control group may suggest that, AVS is probably a multifactorial disease, related to the both atherosclerotic and nonatherosclerotic processes. *(Anadolu Kardiyol Derg 2013; 13: 452-6)*
Key words: Aortic valve sclerosis, intima media thickness, pulse-wave velocity, regression analysis

ÖZET

Amaç: Aort kapak sklerozu (AKS) ile atheroklerosis arasında bir ilişki olduğu düşünülse de AKS'nin patogenezinde nonaterosklerotik procesin rol alıp almadığı konusunda yeterli bilgi bulunmamaktadır. Çalışmanın amacı bunu test etmekti.
Yöntemler: Gözlemsel ve kesitsel çalışmamımızda AKS'si olan 60 hasta ve kardiyovasküler risk faktörleri eşleştirilmiş 76 kontrol grubu çalışmaya alınmıştır. Aplanasyon tonometri ile puls-dalga hız (PWV) ve augmentasyon indeksi değerlendirildi. B-mode ultrasound ile intima-medya kalınlığı (İMK) değerlendirildi. Eşleştirilmemiş t / Mann-Whitney U testleri ve lojistik regresyon analiz yapıldı.
Bulgular: Kontrol ve AVS grubları arasında augmentasyon indeksi ve PWV açısından bir fark yoktu (11,2±3,6-12±3,2, P=0,18 ve 26±7, 6-27±9,8, P=0,2, sırasıyla). Fakat İMK AVS'li grupta anlamlı olarak yüksek bulundu (0,76 mm±0,17-0,6 mm±0,16; P<0,001). AKS ile yaş (r=0,36, p<0,001), augmentasyon indeksi (r=0,17, p:0,04), IMT (r=0,43, p<0,001) ve erkek cinsiyet (r=0,31, p<0,001) arasında anlamlı bir ilişki gözlemlenirken logistik regresyon analizde İMK (OR: 1,46, %95 CI: 1,1-1,9, p=0,009) ve yaş (OR: 1,1, %95 CI: 1,01-1,16, p=0,013) AKS'nin bağımsız prediktörleri olarak bulundu.
Sonuç: AKS'li hastalarda kontrol gruba göre artmış İMK ve normal PWV AKS'nin değil arteriyal stiffnes`in aterosklerotik ve ateroskleroz dışı parametrelerden etkilendiğini gösterebilir. *(Anadolu Kardiyol Derg 2013; 13: 452-6)*
Anahtar kelimeler: Aort kapak sklerozu, intima mediya kalınlığı, puls-dalga hızı, regresyon analizi

Address for Correspondence/Yazışma Adresi: Dr. Levent Korkmaz, Ahi Evren Göğüs Kalp ve Damar Cerrahisi Eğitim ve Araştırma Hastanesi, Kardiyoloji Kliniği, Trabzon-*Türkiye* Phone: +90 462 231 41 14 Fax: +90 462 231 24 20 E-mail: l.korkmaz@yahoo.com
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Introduction

Aortic valve sclerosis (AVS) is defined by echocardiography as thickening and calcification of the normal tri-leaflet aortic valve without obstruction to the left ventricular outflow. Recent studies have suggested that AVS is a manifestation of the atherosclerotic process and presence of AVS was independently associated with an increased risk of death from cardiovascular causes (1-5). However, it remains unclear whether AVS is merely a marker of coexistent cardiovascular risk factors or atherosclerotic and non-atherosclerotic processes are involved in the pathogenesis of AVS.

Pulse wave velocity (PWV) and carotid intima- media thickness (IMT) are well accepted noninvasive surrogate markers of subclinical atherosclerosis. In a previous study, it was found that IMT was significantly greater in subjects with AVS than in those without AVS and AVS was considered as a new surrogate marker of subclinical atherosclerosis (6).

On the other hand, we have not found any association between AVS and PWV in a very similar patient population mentioned above (7).

Therefore, the aim of present study was to try to clarify whether AVS and PWV reflect different aspects of vascular status in subclinical atherosclerosis or AVS is a multifactorial disease, related to both atherosclerotic and nonatherosclerotic processes.

Methods

Study design

It is an observational and cross- sectional study.

Study population

The study population, including two groups who had AVS and cardiovascular risk factors matched without AVS, was prospectively selected from the subjects referred to the echocardiography laboratory at Karadeniz Technical University, School of Medicine, Department of Cardiology, Trabzon, Turkey between 01.01.2009 and 01.05.2009. Patients with aortic stenosis (transaortic flow velocity >2.5 m/sec), rheumatic valvular disease prosthetic valves, bicuspid aortic valves, congenital heart disease, bacterial endocarditis, atrial fibrillation, or hypertrophic obstructive cardiomyopathy, as well as those who had suffered from symptomatic vascular disease such as stroke, transient ischemia, coronary heart disease, congestive heart failure, and intermittent claudication, were excluded from the study. Coronary heart disease was defined by: (1) self-reported myocardial infarction, angina, or use of nitroglycerin; and (2) self-reported history of coronary angioplasty or coronary artery bypass surgery. Cerebrovascular disease was defined by self-reported stroke, transient ischemic attack, or carotid endarterectomy.

An informed consent was obtained from all subjects.

Ethical commitee approved the study.

Study protocol

After routine echocardiography examination, patients and control subjects underwent examination of IMT and PWV.

Assessment of cardiovascular risk factors

In addition to questions about the symptoms of ischemic heart disease, peripheral vascular disease, and stroke, data on the cardiovascular risk factors, diabetes mellitus, arterial hypertension and smoking habits were obtained. Patients were considered to be hypertensive if they had a systolic blood pressure >140 mmHg and/or diastolic pressure >90 mmHg or were using antihypertensive drugs. Subjects with fasting glucose ≥126 mg/dL and/or use of pharmacological treatment were considered as having diabetes. Smoking was defined as "current smokers" or "nonsmokers." Obesity was defined as a body mass index (BMI) ≥30 kg/m^2. Hypercholesterolemia was defined as total cholesterol >200 mg/dL (8).

Arterial stiffness measurements

Peripheral artery pressure waveforms were evaluated noninvasively using applanation tonometry. The measurement of aortic PWV was performed with the SphygmoCor system (AtCor Medical, Sydney, Australia) after an overnight fast and 24 hours off any antihypertensive medications. Subjects were asked to omit caffeine beverages, smoking, and alcohol for at least 12 hours before the assessment. All measurements were performed in a quiet, temperature-controlled room. After 10-15 minutes with the participant resting in the supine position, the aortic PWV was measured by sequential recordings of the arterial pressure waveform at the carotid and femoral arteries with a hand-held micromanometer-tipped probe on the skin at the site of maximal arterial pulsation. Gating of the recordings at these two sites to the electrocardiogram (ECG) allowed the PWV to be measured. The distances from the carotid sampling site to the suprasternal notch and from the suprasternal notch to the femoral artery were measured. The aortic PWV (in meters per second) was calculated automatically as the distance between the suprasternal notch and the femoral artery minus the distance between the carotid sampling site and the suprasternal notch divided by the time interval between systolic R-wave and femoral systolic upstroke minus the time interval between systolic R-wave and carotid systolic upstroke. The aortic PWV was determined as the mean of at least three consecutive beats recorded during 10 seconds of data acquisition.

To measure the augmentation index (AIx), an ascending aortic pressure waveform was derived from the radial artery waveforms recorded at the wrist using applanation tonometry with a high-fidelity micromanometer. The aortic augmentation pressure was calculated as the difference between the first and second systolic peaks of the ascending aortic waveform, and AIx was expressed as a percentage of the central pulse pressure (the difference between the central systolic and diastolic pressures). All measurements were performed by the same investigator who was unaware of the clinical and echocardiographic data. For reliable results, only high-

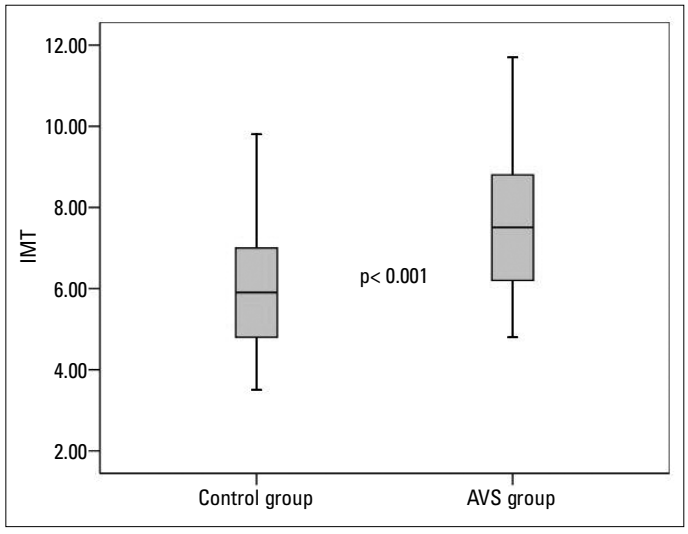

Figure 1. Intima-media thickness in patients with AVS and controls: significant difference is observed (p<0.001)
AVS - aortic valve sclerosis, IMT - intima-media thickness

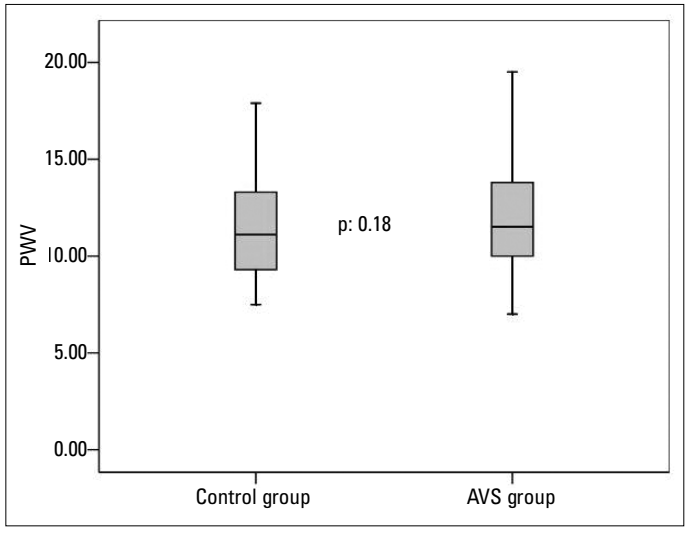

Figure 2. Pulse wave velocity in patients with AVS and controls: no significant difference is observed (p=0.18)
AVS - aortic valve sclerosis, PWV - pulse-wave velocity

quality recordings were included in the analysis. These were defined as an acceptable curves on visual inspection and in-device quality index of >80% derived from an algorithm including average pulse height, pulse height variation, diastolic variation, and the maximum rate of rise of the peripheral waveform.

Carotid ultrasonography

Ultrasonography was performed with a Vivid 7 system (GE Vingmed Ultrasound, Horten, Norway) equipped with a 7.5 MHz linear array imaging probe. The right common carotid artery (CCA) was examined with the patient lying supine, the head directed away from the side of interest, and the neck extended slightly. The transducer was manipulated so that the near and far walls of the CCA were parallel to the transducer footprint, and the lumen diameter was maximized in the longitudinal plane. A region 1 cm proximal to the carotid bifurcation was identified, and the IMT of the far wall was evaluated as the distance between the lumen–intima interface and the media–adventitia interface. The IMT was measured on the frozen frame of a suitable longitudinal image, with the image magnified to achieve a higher resolution of detail. The IMT measurement was obtained from four contiguous sites at 1 mm intervals, and the average of the four measurements was used for analyses.

Statistical analysis

Statistical analysis was done by using SPSS 14.0 statistical software (SPSS Inc., Chicago, IL, USA). Continuous variables were expressed as mean±standard deviation (SD) and categorical variables were expressed as percentage. An analysis of normality of the continuous variables was performed with the Kolmogorov-Smirnov test. A comparison of the categorical variables between the groups was performed using a chi-square test. Continuous variables were compared using unpaired t-test and Mann-Whitney U test. The Spearman and Pearson correlation analyses were used for assessing univariate correlations between AVS and all variables. Logistic regression analysis was performed in order to find independent predictors of AVS. A p value of <0.05 was considered statistically significant.

Results

Baseline characteristics

The baseline clinical characteristics and cardiovascular risk factors for AVS patients and controls are shown in Table 1. There were no statistically significant difference between the groups with regard to age, gender, smoking, diabetes, total cholesterol, high-density lipoprotein and low-density lipoprotein cholesterol, triglycerides and cardiovascular medications.

Vascular markers of AVS

For hemodynamic parameters (Table 2), only central systolic blood pressure was higher in patients with AVS compared to the control group (p=0.04). IMT was significantly higher in AVS group than control (0.76±0.17 versus 0.6±0.16; p<0.001) (Fig. 1). But PWV (11.2±3.6 and 12±3.2, p: 0.18) and AI_X (26±7.6 vs 27±9.8, p=0.20) values were very similar in both groups and they did not reach statistical significance (Fig. 2).

There was a significant positive bivariate correlation between the presence of AVS, IMT (r=0.43, p<0.001), male gender (r=0.31, p<0.001), AI_X (r=0.17, p=0.04), and age (r=0.36, p<0.001). Logistic regression analysis demonstrated that only IMT (OR: 1.46, 95% CI: 1.1- 1.9, p= 0.009) and age (OR: 1.1, 95% CI: 1.01- 1.16, p=0.013) were independent predictors of AVS.

Discussion

In present study, we found increased IMT but not PWV in subjects with AVS compared to the control group. It may suggest

Table 1. Clinical and laboratory characteristics in AVS patients and controls

Variables	Control n=76	AVS n=60	*p
Age, years	66±6	67±7	0.42
Male gender, n (%)	51 (67)	44 (73)	0.10
Hypertension, n (%)	38 (50)	31 (51)	0.12
Diabetes, n (%)	16 (21)	14 (23)	0.13
Smoking, n (%)	9 (11)	11 (18)	0.56
BMI, kg/m^2	30.5±5.4	29.9±4.5	0.51
LDL, mg/dL	126±30	128±38	0.49
HDL, mg/dL	37±8	39±6	0.53
Triglyceride, mg/dL	158±81	177±76	0.43
Cholesterol, mg/dL	186±47	193±51	0.35
Cardiovascular medication			
ACE inhibitors, n (%)	14 (18)	14 (23)	0.68
Calcium channel blockers, n (%)	8 (10)	8 (13)	0.73
Beta-blocker, n (%)	10 (13)	7 (12)	0.09
Cholesterol -lowering drugs, n (%)	13 (17)	11(18)	0.71
ASA, n (%)	22 (28)	14 (23)	0.31

Data are presented as the number (%) of patients or mean value±SD.
*Chi - square, unpaired t and Mann-Whitney U tests
ACE - angiotensin converting enzyme, ASA - acetylsalicylic acid, AVS - aortic valve sclerosis, BMI - body mass index, HDL - high-density lipoprotein, LDL - low-density lipoprotein

Table 2. Hemodynamic and laboratory characteristics in AVS patients and controls

Variables	Control	AVS	*p
Peripheral SBP, mmHg	138±19	142±36	0.34
Peripheral DBP, mmHg	74±12	75±15	0.84
Peripheral PP, mmHg	62±15	72±30	0.34
Central SBP, mmHg	126±17	134±23	0.04
Central DBP, mmHg	75±12	76±15	0.84
Central PP, mmHg	50±11	58±26	0.3
Heart rate, beats/minute	69±11	71±12	0.24
CIMT, mm	0.6±0.16	0.76±0.17	<0.001
Augmentation index (%)	26±7.6	27±9.8	0.20
Aortic PWV, m/sec	11.2±3.6	12±3.2	0.18

Values are expressed as mean±SD
*Unpaired t - test and Mann-Whitney U test
AVS - aortic valve sclerosis, CIMT - carotid intima - media thickness, DBP - diastolic blood pressure, PP - pulse pressure, PWV - pulse wave velocity, SBP - systolic blood pressure

that various subclinical atherosclerosis marker may demonstrate different part of vascular involvement or damage. Also, AVS but not PWV may share similar atherosclerotic process.

Several reports have demonstrated an independent association between AVS and atherosclerosis risk factors or clinical atherosclerosis (1-3, 9, 10). Furthermore, multiple lines of evidence suggest common pathologic mechanisms of AVS and atherosclerosis (4, 11). In a recently published study, AVS predicts all - cause and cardiovascular mortality (12).

IMT is now widely used as a surrogate marker for atherosclerotic disease and increased IMT has been shown to be associated with elevated levels of coronary artery risk factors in several studies (13-15). The correlation between IMT and cardiovascular risk factors was demonstrated in studies performed in the general population and in different groups of patients, especially in the elderly, but also in young subjects (16, 17).

Carotid-femoral pulse wave velocity (PWV), a measure of large artery stiffness, is an important predictor of cardiovascular events. Pulse wave velocity is strongly associated with age and blood pressure. However, findings with regard to its relation with other risk factors have been inconsistent. Cecelja et al. (18) performed a systematic review cross-sectional published literature in order to determine independent predictors of PWV. They found consistently independently association between PWV and age and blood pressure. But no independent association between PWV and sex, total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglycerides, smoking, or body mass index were noted. Therefore, they reached to the conclusion that the contribution of risk factors other than age and blood pressure to PWV is small or insignificant.

A few researcher investigated relation between AVS and IMT. They demonstrated increased IMT values in AVS patients (6) and positive correlation between AVS and IMT (19). They concluded that there was a close correlation between IMT and AVS, therefore they recommended that AVS should be regarded as a surrogate marker of subclinical atherosclerosis and increased cardiovascular risk. Given that there was meaningful association between AVS and subclinical atherosclerosis, we had used PWV as a subclinical atherosclerotic marker and aimed to demonstrate increased PWV value in AVS patients in our first study (7). In contrary to these studies proving AVS as a subclinical atherosclerotic marker, we could not find increased PWV in AVS compared to the control group. In present study, we measured PWV in a very similar patient population like in our previous study and also used a second subclinical atherosclerosis marker, IMT, to be sure whether our population had subclinical atherosclerosis. Although IMT was statistically higher in AVS group meaning that AVS group had subclinical atherosclerosis, we did not find any differences in PWV values among AVS and control group. Although sample size is modest, this is the first study investigating two subclinical atherosclerosis markers in patients with aortic valve sclerosis.

We think that arterial stiffness and intima media thickness are two different independent markers of subclinical vascular damage. Furthermore, we assume that common atherosclerotic risk factors and pathogenetic mechanism may be much more involved in aortic valve sclerosis and intima media thickness than pulse wave velocity and we agree with Ceceja et al. (18) that the prognostic value of PWV may relate to a process of arterial ageing unrelated to classic risk factors other than hypertension.

Study limitations

Sample size is the major limitation of study. Parameters other than traditional cardiovascular risk markers were not evaluated. They may be cause of increased PWV in control subjects.

Conclusion

We could not demonstrate increased arterial stiffness in patients with aortic valve sclerosis. According to the present study, AVS is a probably a multifactorial disease, related to the both atherosclerotic and nonatherosclerotic process.

Conflict of interest: None declared.

Peer-review: Externally peer-reviewed.

Authorship contributions: Concept - L.K., Ş.Ç.; Design - L.K., A.A.K.; Supervision - L.K., H.E., Z.A., M.T.A., A.A.K., Ş.Ç.; Data collection&/or Processing - L.K., H.E., M.T.A., A.A.K., M.T.A., Z.A.; Analysis &/or interpretation - L.K., M.T.A., H.E., Ş.Ç., Z.A.; Literature search - L.K., A.A.K.; Writing - L.K.; Critical review - A.A.K., M.T.A., H.E., Z.A., Ş.Ç.

References

1. Stewart BF, Siscovick D, Lind BK, Gardin JM, Gottdiener JS, Smith VE, et al. Clinical factors associated with calcific aortic valve disease: Cardiovascular Health Study. J Am Coll Cardiol 1997; 29: 630-4. [CrossRef]
2. Agmon Y, Khandheria BK, Meissner I, Sicks JR, O'Fallon WM, Wiebers DO, et al. Aortic valve sclerosis and aortic atherosclerosis: different manifestations of the same disease? Insights from a population based study. J Am Coll Cardiol 2001; 38: 827-34. [CrossRef]
3. 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; 341: 142-7. [CrossRef]
4. Otto CM, Kuusisto J, Reichenbach DD, Gown AM, O'Brien KD. Characterization of the early lesion of 'degenerative' valvular aortic stenosis. Histological and immunohistochemical studies. Circulation 1994; 90: 844-53. [CrossRef]
5. O'Brien KD, Kuusisto J, Reichenbach DD, Ferguson M, Giachelli C, Alpers CE, et al. Osteopontin is expressed in human aortic valvular lesions. Circulation 1995; 92: 2163-8. [CrossRef]
6. Yamaura Y, Nishida T, Watanabe N, Akasaka T, Yoshida K. Relation of aortic valve sclerosis to carotid artery intima-media thickening in healthy subjects. Am J Cardiol 2004; 94: 837-9. [CrossRef]
7. Çelik S, Durmuş I, Korkmaz L, Gedikli O, Kaplan S, Örem C, et al. Aortic pulse wave velocity in subjects with aortic valve sclerosis. Echocardiography 2008; 25: 1112-6. [CrossRef]
8. Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). Circulation 2002; 106: 3143-421.
9. Pohle K, Maffert R, Ropers D, Moshge W, Stilianakis N, Daniel WG, et al. Progression of aortic valve calcification: association with coronary atherosclerosis and cardiovascular risk factors. Circulation 2001; 104: 1927-32. [CrossRef]
10. Adler Y, Levinger U, Koren A, Tanne D, Fink N, Vaturi M, et al. Relation of nonobstructive aortic valve calcium to carotid arterial atherosclerosis. Am J Cardiol 2000; 86: 1102-5. [CrossRef]
11. O'Brien KD, Shavelle DM, Caulfield MT, McDonald TO, Olin-Lewis K, Otto CM, et al. Association of angiotensin-converting enzyme with low-density lipoprotein in aortic valvular lesions and in human plasma. Circulation 2002; 106: 2224-30. [CrossRef]
12. Völzke H, Haring R, Lorbeer R, Wallaschofski H, Reffelmann T, Empen K, et al. Heart valve sclerosis predicts all-cause and cardiovascular mortality. Atherosclerosis 2010; 209: 606-10. [CrossRef]
13. Howard G, Sharrett AR, Heiss G, Evans GW, Chambless LE, Riley WA, et al. Carotid artery intimal–medial thickness distribution in general populations as evaluated by B-mode ultrasound. ARIC Investigators. Stroke 1993; 24: 1297-304. [CrossRef]
14. Grobbee DE, Bots ML. Carotid artery intima–media thickness as an indicator of generalized atherosclerosis. J Intern Med 1994; 236: 567-73. [CrossRef]
15. Salonen R, Salonen JT. Determinants of carotid intima–media thickness: a population-based ultrasonography study in eastern Finnish men. J Intern Med 1991; 229: 225-31. [CrossRef]
16. Davis PH, Dawson JD, Riley WA, Lauer RM. Carotid intimal-media thickness is related to cardiovascular risk factors measured from childhood through middle age: The Muscatine Study. Circulation 2001; 104: 2815-9. [CrossRef]
17. Cuomo S, Gaeta G, Guarini P, Tudisca G, De Michele M, Gene Bond M, et al. Increased carotid intima-media thickness in healthy young subjects with a parental history of hypertension (parental hypertension and vascular health). Heart 2007; 93: 368-9. [CrossRef]
18. Cecelja M, Chowienczyk P. Dissociation of aortic pulse wave velocity with risk factors for cardiovascular disease other than hypertension: a systematic review. Hypertension 2009; 54: 1328-36. [CrossRef]
19. Antonini-Canterin F, Di Bello V, Di Salvo G, La Carrubba S, Bellieni G, Benedetto F, et al. Relation of carotid intima-media thickness and aortic valve sclerosis (from the ISMIR study ["Ispessimento Medio Intimale e Rischio Cardiovascolare"] of the Italian Society of Cardiovascular Echography). Am J Cardiol 2009; 103: 1556-61. [CrossRef]