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Aortic valve calcification in hypertensive patients: prevalence, risk factors and association with transvalvular flow velocity ☆

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Abstract

Background: The important role of the "nonobstructive" aortic valve calcification (AVC) in cardiovascular morbidity and mortality has recently been emphasized. The present work had two goals: (1) to analyze the prevalence and factors determining the extent of AVC in hypertensive patients; (2) to investigate a possible association between the extent of AVC and flow velocity across the aortic valve. *Methods*: This was a prospective study performed in a university hospital. The sample included 263 consecutive patients (139 men and 124 women), mean age 65 ± 6, who underwent echo-Doppler. The upper quartile of peak flow velocity across the aortic valve (>130 mm/s in our population) was defined as augmented flow velocity. *Results*: There were 31 (12%) patients in the advanced AVC group and 122 (46%) without any calcified deposits (the no AVC group). The remaining 110 (42%), who did not meet criteria for advanced AVC, comprised the trivial AVC group. Peak flow velocity was significantly higher in patients with advanced vs. trivial AVC and no AVC groups: 135 ± 45, 116 ± 23 and 113 ± 23 cm/s, respectively; $p = 0.0002$. Prevalence of augmented transvalvular aortic flow was significantly higher ($p = 0.01$) among patients with advanced AVC (41.9%) vs. trivial (20.9%) and no AVC (20.5%). Multivariate analyses identified age as the only independent variable associated with advanced AVC [OR 1.6 (CI 1.2–2.3), 5 years increment]. Advanced AVC and female gender were identified as independent variables for augmented transvalvular aortic flow with OR 2.9 (CI 1.3–6.4) and 2.5 (CI 1.4–4.6), respectively. *Conclusions*: Prevalence of AVC among hypertensive patients is high and clearly age-related. Female gender and advanced (but not trivial) AVC are associated with augmented aortic transvalvular peak flow. Our results stress the role of protruding calcium deposits in augmentation of rest flow velocity across the aortic valve regardless of visible restriction of leaflet opening.

Keywords: Aortic valve; Blood flow; Calcium; Echocardiography

1. Introduction

Aortic valve calcification (AVC) represents a common degenerative process that occurs mainly in the elderly and may result in serious valve stenosis [1]. This degenerative mechanism may accelerate when mechanical stress on the valvular apparatus is increased, as is the case in hypertension [2–4]. Recently, the important role of the "non-obstructive" AVC and aortic sclerosis in cardiovascular morbidity and mortality was emphasized [5,6]. The factors determining the extent of AVC and its interrelationship with flow velocity across the aortic valve are scarce and discordant [2,7–11] and focus primarily on patients with established aortic stenosis. The present work had two goals: (1) to analyze the factors determining the extent of AVC in hypertensive patients; (2) to investigate a possible association between the extent of AVC and the presence of a relatively augmented rest flow velocity across the aortic valve in patients without established aortic stenosis.

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2. Materials and methods

2.1. Patients

Over the course of 18 months, a total of 356 consecutive patients, who were recruited to The International Nifedipine GITS Study of Intervention as a Goal in Hypertension Treatment (INSIGHT) Trial study in our region, were enrolled in the present analysis and underwent echo-Doppler examination as well as fast (dual mode) spiral computed tomography (FSCT) of the heart. The design of the INSIGHT study as well as the major inclusion and exclusion criteria and the ethical guidelines have been previously reported [12,13].

For the purpose of the present analysis, the patients with bicuspid aortic leaflets, aortic stenosis (defined in accordance with Otto et al. [7] as thickened leaflets with reduced systolic opening and an increased velocity across the aortic valve ≥ 2.5 mm/s) or aortic regurgitation (more than mild), and patients with inadequate echocardiographic examination or uncompleted clinical data were excluded. The final study sample comprised 263 patients (139 men and 124 women, age ranged 52–79 years, mean 65 ± 6 years).

Echo-Doppler two-dimensional echocardiography was performed with a Hewlett-Packard ultrasound imaging system SONOS 2500, 4500 and 5500 models. Standard images were obtained during rest condition from the left parasternal (long and short axis view), apical (long, two chamber and four chamber) and subcostal views.

The calcified deposit into the aortic valve was defined as the presence of a bright dense echo structure located at the aortic valve leaflet [4]. A calcified deposit of <2 mm in its highest thickness in the short axis parasternal view was defined as minimal, a deposit ranging from 2 to 5 mm thickness was defined as mild and a calcified deposit of ≥ 5 mm, as significant. Advanced AVC was defined as follows: (a) presence of at least one significant calcified deposit or (b) presence of two or more mild calcified deposits (Fig. 1). There were 31 patients in the advanced AVC group. Patients without any calcified deposits into the aortic valve comprised the no AVC group (122 patients). The remaining patients with AVC who did not meet criteria of the advanced AVC comprised the trivial AVC (Fig. 2) group (110 patients).

Using steerable continuous wave Doppler, peak and mean flow velocity across the aortic valve were assessed from the apical five-chamber view. All measurements of the transaortic valve velocity were taken from three cycles and averaged for results. For the purpose of this study, the upper quartile of peak flow velocity (>130 cm/s in our population) was defined as augmented flow velocity.

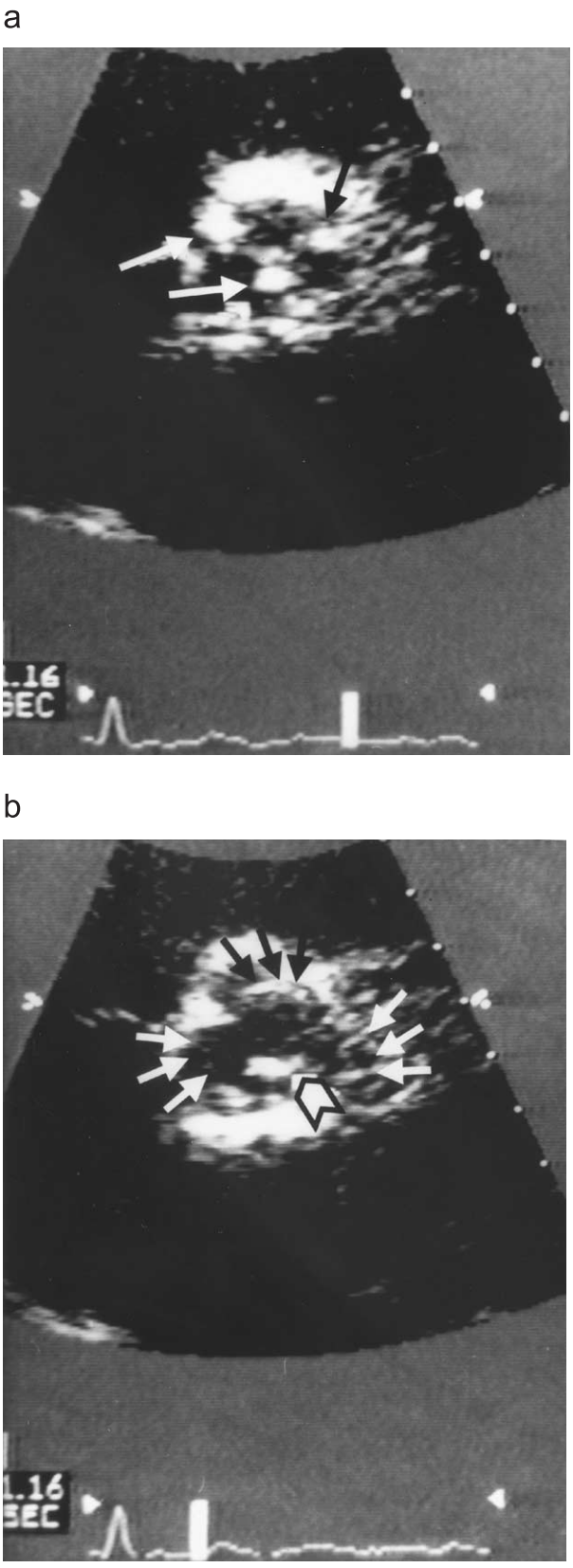
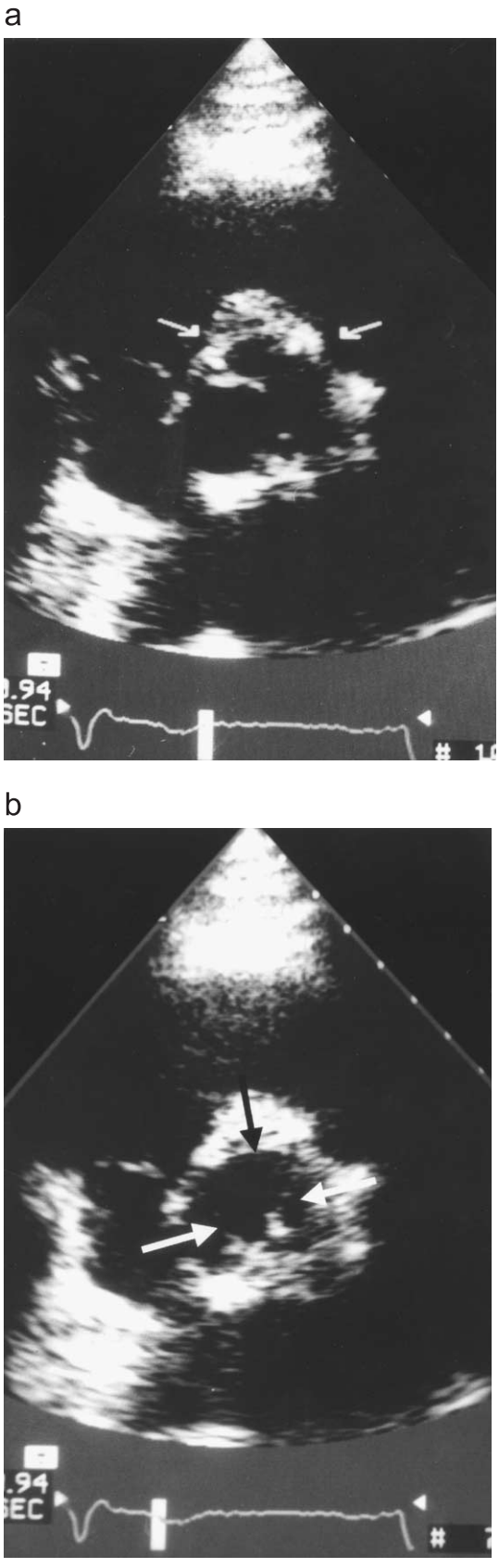


Fig. 1. Advanced aortic valve calcification, short axis parasternal view. (a) Diastolic frame. Significant calcified deposits (arrows) can be seen. (b) Systolic frame; unrestricted opening of the valve leaflets (white and black arrows) with protruding significant calcified deposit (arrowhead). The electrocardiogram is displayed on the bottom.



All echocardiographic studies were performed by three examiners with expertise in echocardiography (MM, EZF, AT) using a carefully standardized technique. All studies were recorded on a super-VHS tape and evaluated by two cardiologists. In case of disagreement, a third examiner was consulted. The cardiologists who made the diagnosis of AVC were blinded to the clinical data of the patients and to the aortic flow velocity results.

Intra-(AT) and interobserver (AT, MM) variability for the AVC extent and peak flow velocity across the aortic valve were determined by the reassessment of 20 randomly selected echocardiography studies for each type of variability analyses. There was no intraobserver disagreement in AVC grading (none, trivial or advanced). There was no interobserver disagreement in the determination of the presence or absence of AVC. In one case, there was discordance regarding the grading of AVC (trivial vs. advanced). No statistically significant differences were observed in the mean $\pm$ S.D. peak flow velocity across the aortic valve: 111 ± 28 vs. 113 ± 31 cm/s for intraobserver and 109 ± 34 vs. 105 ± 32 cm/s for interobserver variability analyses.

2.2. Clinical data and other variables

In order to search for possible predictors of the extent of AVC the following additional clinical variables were recorded: age, sex, diabetes mellitus (known diabetes treated with drugs or a fasting blood glucose ≥ 7.8 mmol/l), coronary artery disease (documented myocardial infarction or disease established on coronary angiography), hypercholesterolemia (drug treatment or total cholesterol level ≥ 6.5 mmol/l), body mass index (BMI), smoking status and duration of hypertension. Left ventricular hypertrophy (LVH) was defined as interventricular septum or posterior wall thickness >12 mm on the echocardiography. FSCT for coronary calcium detection was performed according to a previously described protocol [14,15] using a commercially available double-helical scanner (CT Twin; Elscint, Haifa, Israel) and spiral scanning mode (without injection of contrast material).

2.3. Statistical analysis

Data were analyzed using SAS software [16,17]. Continuous variables were presented as mean value $\pm$ S.D. Comparisons between groups were made using chi-square tests for discrete variables and Student's *t*-test for continuous variables. The Mantel–Haenszel chi-square statistic was used to assess linear trends in proportions. Linear trend for continuous variables was tested using general linear model

Fig. 2. Trivial aortic valve calcification, short axis parasternal view. (a) Diastolic frame. Mild calcified deposits (arrows) can be seen. (b) Systolic frame; unrestricted opening of the valve leaflets (white and black arrows) without protruding calcified deposits. The electrocardiogram is displayed on the bottom.

Table 1
Clinical characteristics of the study groups

	No AVC	Trivial AVC	Advanced AVC	p for trend
	n = 122	n = 110	n = 31	
Age	63 ± 6	66 ± 6	68 ± 6	0.001
Male gender	66 (54)	57 (52)	16 (52)	0.9
Smoking	20 (16)	18 (16)	5 (16)	0.99
Diabetes mellitus	38 (31)	29 (26)	6 (19)	0.4
Hypercholesterolemia	50 (41)	40 (36)	16 (52)	0.3
Duration of hypertension (years)	11 ± 7	12 ± 8	14 ± 9	0.3
Presence of CC	82 (67)	79 (71)	20 (65)	0.6
Proven CAD	19 (16)	13 (12)	3 (10)	0.6
Myocardial infarction	9 (7)	9 (8)	2 (6)	0.9
BMI	29 ± 4	28 ± 4	29 ± 5	0.2
LVEF	65 ± 6	67 ± 9	66 ± 8	0.1
LVH	16 (54)	65 (59)	15 (48)	0.5

Data are presented as mean ± S.D. or number (percentage) of patients. AVC = aortic valve calcification, BMI = body mass index, CC = coronary calcification, CAD = coronary artery disease, LVH = left ventricular hypertrophy, LVEF = left ventricular ejection fraction.

(GLM) procedure. A p-value of <0.05 was considered statistically significant. Multivariate analysis was performed using logistic regression model. A stepwise selection method was used, with a significance level of 0.05 for entering and removing explanatory variables.

3. Results

3.1. Patient characteristics

There were 122 patients without AVC, 110 patients with trivial AVC and 31 patients with advanced AVC (Table 1). The patients with advanced AVC were older. The were no intergroup differences regarding prevalence of any other variables (gender, diabetes mellitus, smoking, hypercholesterolemia, old myocardial infarction, duration of hypertension, proven coronary artery disease (CAD), presence of coronary calcium, BMI, ejection fraction, LVH).

3.2. AVC and gender

For hypertensive patients of both genders, the prevalence of any AVC (trivial + advanced) was high and similar (Table 2) and ranged between 53% and 55% (men and women, respectively), average 54%. There were no inter-gender differences regarding the prevalence of the advanced AVC: 12% in the both groups.

Table 2
AVC and gender

	No AVC	Any AVC (trivial + advanced)	Advanced AVC	p for trend
Men (n = 139)	66 (47)	73 (53)	16 (12)	
Women (n = 124)	56 (45)	68 (55)	15 (12)	
Total (n = 122)	122 (46)	141 (54)	31 (12)	0.9

Data are presented as number (percentage) of patients.

Table 3
AVC and transvalvular aortic flow velocity (FV)

	No AVC	Trivial AVC	Advanced AVC	p for trend
	n = 122	n = 110	n = 31	
Peak FV (mm/s)	113 ± 23	116 ± 23	135 ± 45	0.0002
Mean FV (mm/s)	74 ± 16	76 ± 17	89 ± 34	0.0004
Presence of augmented transvalvular aortic FV	25 (20)	23 (21)	13 (42)	0.01

Data are presented as mean ± S.D. or number (percentage) of patients.

3.3. Flow velocity across the aortic valve

Peak flow velocity across the aortic valve among all study patients ranged from 65 to 245 cm/s (lower quartile 100 cm/s, median 115 cm/s, upper quartile 130 cm/s). Mean flow velocity ranged from 25 to 195 cm/s (lower quartile 65 cm/s, median 75 cm/s, upper quartile 85 cm/s). The mean ± S.D. transvalvular aortic flow velocity (both peak and mean) was significantly higher in patients with advanced AVC as compared with patients with trivial AVC and no AVC groups (Table 3): respectively, for peak flow velocity 135 ± 45, 116 ± 23 and 113 ± 23 cm/s, $p = 0.0002$; for mean flow velocity 89 ± 34, 76 ± 17 and 74 ± 16 cm/s, $p = 0.0004$.

3.4. AVC and augmented flow velocity across the aortic valve

The prevalence of augmented transvalvular aortic flow (above 130 cm/s) was significantly higher ($p = 0.01$) among patients with advanced AVC (41.9%) in comparison with patients with trivial (20.9%) and no AVC (20.5%) groups (Fig. 3).

Multivariate analysis (Table 4) was performed in order to determine the independent variables associated with ad-

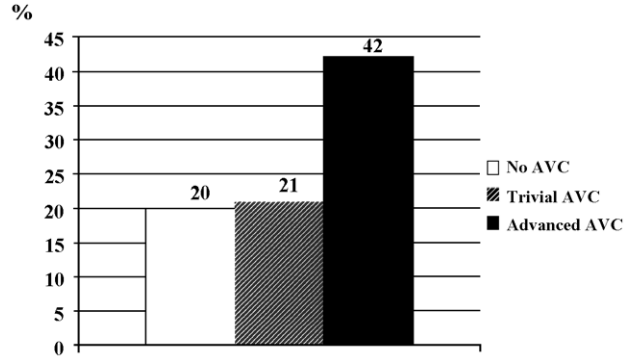


Fig. 3. Prevalence of augmented transvalvular aortic flow velocity among the study patients in accordance with presence and degree of AVC.

Table 4
Multivariate stepwise logistic regression analysis of the variables associated with advanced AVC and augmented peak flow velocity (AFV) across the aortic valve

	Advanced AVC		AFV	
	OR	95% CI	OR	95% CI
Age (5 years increment)	1.6	1.2–2.3	1.05	0.8–1.4
Female sex	1.2	0.7–2.1	2.5	1.4–4.6
Advanced AVC	–	–	2.9	1.3–6.4

CI = confidence interval, OR = odds ratio.

vanced AVC, any AVC (trivial + advanced) and augmented transvalvular aortic flow. The model of the multivariate analysis for AVC included age, gender, hypercholesterolemia, diabetes, duration of hypertension of >5 years, smoking, presence of coronary artery disease, myocardial infarction and coronary calcification, BMI, left ventricular hypertrophy and ejection fraction. To the model for augmented transvalvular aortic flow, advanced and trivial AVC were added. This analysis identified age as only independent variable associated with advanced AVC [OR of 1.6 (CI 1.2–2.3), 5 years increment] and any AVC [OR of 1.5 (CI 1.2–1.9)]. Advanced AVC and female sex were identified as independent variables for augmented transvalvular aortic flow with OR of 2.9 (CI 1.3–6.4) and 2.5 (CI 1.4–4.6), respectively. On further adjustment for concomitant use of medications, results of the multivariate analysis were almost equal.

4. Discussion

The salient findings of our study were: (1) the prevalence of the AVC among elderly hypertensive patients (mean age 65 ± 6 years) is high (more than half of them were affected). The single predictor for the presence of the advanced aortic valve calcification in hypertensive patients is age. (2) The only variables associated with augmented peak flow velocity across the aortic valve were advanced (but not trivial) aortic valve calcification and female gender.

The factors determining the magnitude of AVC and its influence on the development on flow obstruction are still unclear [2,7–11] and focused primary on patients with established aortic stenosis. It appears that, in the elderly, an interaction between two factors play a major role in the flow obstruction development: (1) well-established restriction of leaflet mobility (due to leaflets thickening and calcification) with reduction of opening during systole; (2) less clear direct flow obstruction caused by large protruding aortic valve calcium deposits which lead to reducing of the effective orifice area. In order to elucidate the role of the latter (AVC) on the aortic flow, all patients with established aortic stenosis and reduced systolic opening of the aortic valve were excluded from the current analysis. The results of our study confirmed the important and independent role of advanced AVC with protruding aortic valve calcium deposits in augmentation of the rest flow velocity across the aortic valve in patients without visible restriction of leaflet opening. Obviously, in patients with established aortic stenosis and background restriction of the leaflets opening, the additional impact of advanced AVC (with protruding calcium deposits) on the reduction of the effective orifice area may be even more noticeable. Our findings corresponded with recent studies, which stressed the role of the AVC on the prognosis and natural history of the patients with established aortic stenosis [8,9].

The relation of "nonobstructive" aortic valve sclerosis (defined as focal areas of increased echogenicity and thickening of the leaflets) with increased risk of death was recently reported [5]. The close association of "nonobstructive" AVC with other cardiovascular conditions was also established [1,6,18]. It is unclear whether "nonobstructive" AVC is simply a marker of increased risk or has a direct effect on clinical outcome. Currently, the most popular point of view proposes that AVC is a marker of other forms of cardiovascular disease [6,11,19]. However, more heavily calcified valves showed little or no increase in the aortic valve area during periods of increased flow, whereas the degree of area enlargement is dependent on the inertia of the cusps [19–21]. Thus, transvalvular flow velocity (and pressure gradient) at rest may not correctly reflect possible left ventricular pressure overload during exercise. Since transvalvular gradient increases by the square of the flow, substantial gradients may result during periods of exercise. It is possible that patients with advanced AVC (with protruding calcium deposits, which reduced the effective orifice area) may show greater augmentation of the transvalvular pressure gradient during their daily activities leading to appearance of turbulence and flow instability in the thoracic aorta. Unstable aortic flow (turbulence and vortices along the aortic walls) cause regions of altered shear stress and may be important in atherogenesis in the thoracic aorta [22–24]. The close association between aortic valve calcium on spiral computed tomography and calcification of the thoracic aorta was recently demonstrated [25].

AVC and aortic valve thickening (sclerosis) in the absence of significant rest flow obstruction are common in the elderly, affecting 21–26% of adults over 65 years and up to 48% over 85 years of age [5,26,27]. In the presence of the increased mechanical stress on the valvular apparatus (as is the case in hypertension), the prevalence of AVC significantly raised [2–4]. AVC affected more than half of the hypertensive patients (mean age 65 ± 6 years) in our study group: at least a twofold increase in the prevalence in compared with a general population of the similar age.

The reasons for appearance and different extent of AVC in the elderly are still uncertain. Some reports shown an association of hyperlipidemia and diabetes with AVC [4,11], whereas others have failed to find this association [2,10]. In our study, we also failed to identify clinical variables associated with advanced AVC except age. There are a number of possible explanations for this observation: (1)

AVC and other well known cardiovascular conditions may have partially the same pathogenesis or may reflect the presence of common risk factors. Therefore, they may be not independent variables in the multivariate analysis. (2) Since the impact of established hypertension on prevalence of AVC among our patients was strong, the relative contribution of other variables appears to be diminished. Statistically, the presence of one or more extremely strong and dominating determinants may lead to relative eclipse of other less prominent factors.

Gender predominance in AVC prevalence seems to be less obvious [3] in comparison with mitral annular calcification with strong female [3,28] or coronary calcification with clear male predisposition [29–32]. A gender predominance in AVC prevalence among our patients was not observed. Female gender was associated directly with augmented aortic flow velocity in our study. The same data were reported previously [33]. Women have been shown to have proportionally smaller heart and aorta than men and higher cardiac outputs because of the lower oxygen-carrying capacity of their blood (lower hemoglobin levels as well as lower peripheral oxygen extraction). These physiological differences may lead to higher aortic flow velocities in women as compared to men [34]. In addition, other gender-related mechanisms (such as hormonal influence and elasticity of the aorta) may be suggested.

Further studies designed to explore mechanisms of the AVC development and extent, as well as a potential link between advanced AVC with protruding calcium deposits and flow disturbance during exercise are crucial.

5. Conclusion

The prevalence of AVC among hypertensive patients is high and clearly age-related. Female gender and advanced (but not trivial) AVC are associated with relatively augmented aortic transvalvular peak flow. Our results stress the role of protruding calcium deposits in augmentation of rest flow velocity across the aortic valve regardless of visible restriction of leaflet opening.

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