Published in final edited form as:

Mol Genet Metab. 2012 February ; 105(2): 198–202. doi:10.1016/j.ymgme.2011.10.017.

Aortic Stenosis and Vascular Calcifications in Alkaptonuria

Hwaida Hannoush¹, Wendy J. Introne², Marcus Y. Chen¹, Sook-Jin Lee^{1,a}, Kevin O'Brien^{2,3}, Pim Suwannarat^{4,b}, Michael A. Kayser^{4,c}, William A. Gahl^{2,4}, and Vandana Sachdev¹

¹Cardiovascular and Pulmonary Branch, National Heart Lung and Blood Institute, NIH, Bethesda, MD

²Office of the Clinical Director, National Human Genome Research Institute, NIH, Bethesda, MD

³Office of Rare Disease Research, Office of the Director, NIH, Bethesda, MD

⁴Medical Genetics Branch, National Human Genome Research Institute, NIH, Bethesda, MD

Abstract

Alkaptonuria is a rare metabolic disorder of tyrosine catabolism in which homogentisic acid (HGA) accumulates and is deposited throughout the spine, large joints, cardiovascular system, and various tissues throughout the body. In the cardiovascular system, pigment deposition has been described in the heart valves, endocardium, pericardium, aortic intima and coronary arteries. The prevalence of cardiovascular disease in patients with alkaptonuria varies in previous reports. We present a series of 76 consecutive adult patients with alkaptonuria who underwent transthoracic echocardiography between 2000 and 2009. A subgroup of 40 patients enrolled in a treatment study underwent non-contrast CT scans and these were assessed for vascular calcifications. Six of the 76 patients had aortic valve replacement. In the remaining 70 patients, 12 patients had aortic sclerosis and 7 patients had aortic stenosis. Unlike degenerative aortic valve disease, we found no correlation with standard cardiac risk factors. There was a modest association between the severity of aortic valve disease and joint involvement, however, we saw no correlation with urine HGA levels. Vascular calcifications were seen in the coronaries, cardiac valves, aortic root, descending aorta and iliac arteries. These findings suggest an important role for echocardiographic screening of alkaptonuria patients to detect valvular heart disease and cardiac CT to detect coronary artery calcifications.

Keywords

alkaptonuria; aortic stenosis; cardiovascular; calcification

Address correspondence to: Vandana Sachdev, MD 10 Center Drive, CRC, 5NE-room 1436 Bethesda, MD 20892-1650 Phone: 301-496-3015; sachdevv@nhlbi.nih.gov Fax: 301-435-8886.

^aCurrent Address: Cardiology Division, Sejong General Hospital, Sosa District, City of Bucheon, Kyungki Province, South Korea

^bCurrent Address: Genetics Department, Kaiser Permanente, San Francisco, CA

^cCurrent Address: Warren Clinic Center for Genetic and Center for Genetic Testing at St. Francis, Tulsa, OK

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

5. CONFLICT OF INTEREST STATEMENT None of the authors have a conflict of interest to disclose.

1. INTRODUCTION

Alkaptonuria is a rare disorder of tyrosine metabolism due to deficiency of homogentisic acid dioxygenase, the third enzyme in the tyrosine degradation pathway, resulting in the accumulation of homogentisic acid (HGA)(1). Gram quantities of HGA are excreted in the urine; however, remaining circulating HGA and its oxidation products polymerize and deposit in cartilage and connective tissues. The three main features of the disease are darkening of the urine upon standing, ochronosis (dark pigmentation of connective tissue), and degenerative arthritis. Cardiovascular involvement has been described in numerous case reports (2–7) and ochronosis has been shown to involve the heart valves, the endocardium, pericardium, aorta and coronary arteries (7–10). Aortic stenosis is the most commonly reported cardiac abnormality, with many patients requiring valve replacement. In a previous report on the natural history of 58 patients with alkaptonuria, we noted that 3 patients over the age of 50 had undergone aortic valve replacement (11). Previous treatments for alkaptonuria have failed to show a significant clinical benefit. Recent trials of nitisinone, a potent inhibitor of the second enzyme in the tyrosine pathway, demonstrated dramatic reductions in plasma HGA levels although measures of musculoskeletal function did not show improvement (11–13). There is insufficient data to determine whether nitisinone has any effect on the progression of aortic valve disease.

In the current study, we define the prevalence of valvular heart disease in a large group of patients with alkaptonuria followed at the National Institutes of Health (NIH). We retrospectively evaluated echocardiographic studies in order to determine the prevalence and severity of valvular heart disease. We also evaluated the presence of cardiac and vascular calcifications seen incidentally on CT scans performed in a subgroup of 40 alkaptonuria patients enrolled in a nitisinone treatment study.

2. METHODS

2.1 Study subjects

Seventy-nine NIH patients with alkaptonuria (51 men, 28 women; age range 20 to 85 years) had at least one echocardiogram and were enrolled in this study. Alkaptonuria natural history and treatment protocols were approved by the National Human Genome Research Institute and the National Institute for Child Health and Human Development; all patients gave written, informed consent. The diagnosis of alkaptonuria was confirmed by elevated urinary HGA levels. Urinary HGA was measured using the standard gas chromatography/mass spectrometry methodology at Mayo Laboratory in Rochester, MN. Samples were taken from 24-hour urine collections. There were three patients with a diagnosis of bicuspid aortic valve who were excluded.

2.2 Echocardiography

Transthoracic 2-dimensional and Doppler echocardiograms were performed using commercially available systems. Standard views were obtained with patients in the left lateral recumbent position and images were stored digitally and on VHS videotapes. Cardiac measurements were performed according to the American Society of Echocardiography (ASE) guidelines (14). Aortic sclerosis was defined as thickened valve leaflets with a peak aortic velocity of 2.0–2.4 m/s, and mild, moderate, and severe aortic stenosis were defined according to ASE recommendations (15). Aortic valve area was calculated by the continuity equation.

2.3 CT scans

A subgroup of 40 patients enrolled in a treatment study of nitisinone underwent chest/abdominal/pelvis non-contrast CT scans. These were performed according to standard clinical protocols on multislice equipment (Definition, Siemens Medical, Malvern, PA; Brilliance 64, Philips Medical, Cleveland, OH; Lightspeed, General Electric Healthcare, Milwaukee, WI). If the heart was included in the field of view, calcification scores were calculated using the Agatston scoring technique(16) with commercially available software (VitreaFX, Vital Images, Minnetonka, MN). The calcification was assessed in three separate distributions: coronary, intracardiac (aortic and mitral valves), and aorta (ascending and descending).

2.4 Statistical Analysis

Categorical variables, presented as numbers and percentages, were compared using the Chi-square and Fisher exact tests. Continuous variables were expressed as means $\pm$ standard deviations and were compared by use of the Student unpaired t-test and ANOVA. Statistical significance was a p value of <0.05 . Progression of aortic stenosis was assessed by change in aortic peak velocities over time, in meters per second per year (m/sec/year). Analyses were performed with SPSS, version 17 (Chicago, IL).

3. RESULTS

3.1 Prevalence of aortic valve disease

Of 76 alkaptonuria patient who underwent echocardiograms between 2000 and 2009, 6 (8%) had undergone aortic valve replacement. There were 12 patients with aortic sclerosis (16%) and 7 patients with aortic stenosis (9%). Four patients had mild, 2 had moderate, and 1 had severe aortic stenosis. Figure 1 gives the overall prevalence of aortic valve disease in different age groups. Among patients under age 65 years, seven of 64 patients (11%) had aortic stenosis or had undergone valve replacement. Among patients 65 years and older, 6 of 12 patients (50%) had aortic stenosis or had undergone valve replacement.

Among the seven patients with native aortic valve stenosis, aside from age, there was no significant difference in their cardiac risk factors or lipid values compared with the remaining subjects (Table 1). Among patients with aortic stenosis, the average peak velocity was 2.9 ± 0.6 m/sec, the average mean gradient was 19.9 ± 11 mmHg, and the aortic valve area was 1.25 ± 0.17 cm². Echocardiographic images from a representative patient with severe aortic stenosis are shown in Figure 2.

3.2 Other cardiac findings

Echocardiographic findings (Table 2) are compared between patients with and without aortic stenosis. Mild aortic regurgitation was present in 12 patients. Mitral regurgitation of moderate degree or greater was present in one patient. Moderate or greater tricuspid regurgitation was seen in two patients. Two patients (one in each group) had criteria for left ventricular hypertrophy. There were two patients with LV dysfunction (both in the non-AS group). Aortic root dilatation, indexed to body surface area, was noted in seven patients.

3.3 Progression of aortic valve disease

At least one follow-up echocardiogram was performed in 46 patients. The average rate of progression for all groups was 0.08 ± 0.1 m/sec/year (range -0.11 to 0.30 m/sec/year). Using the earliest available echo as the baseline, there was no statistically significant difference in the rate of progression among normal (0.07 m/sec/year, n=34) or sclerotic (0.08 m/sec/year, n=8) valves. Although not statistically significant, mildly stenotic valves

progressed at a rate nearly twice that of normal or sclerotic valves (0.15 m/sec/year, $n=4$, p value vs. normal=0.07).

3.4 Cardiovascular calcifications

Of the 40 patients undergoing CT scans, 17 scans included coverage of the heart suitable for evaluation of coronary or valvular calcification. The mean age of patients undergoing these scans was 55 ± 7 years. Three (18%) patients had evidence of significant coronary calcification (Agatston score >100 or >75 th percentile for age, gender and ethnicity)(17). Valvular calcification was present in 8 (47%) with 3 (18%) having severe calcification (Agatston score >1000). By the age of 60, 100% of individuals had evidence of significant intracardiac calcification. In the aorta, 26 patients (65%) had evidence of significant vascular calcification with a range of Agatston scores from 117 to 21,810. The calcifications predominately involved the aortic root, descending aorta and iliac arteries. The overall prevalence of calcifications increased significantly with advancing age (Figure 3). An example of severe coronary and aortic calcification in an alkaptonuria patient who has undergone aortic valve replacement is shown in Figure 4.

3.5 Correlation with other disease markers

Among the subgroup of 40 patients enrolled in the nitisinone treatment study, there was a modest relationship between the number of joints replaced per patient and the peak aortic valve velocities ($r=0.51$, $p=0.0008$, Figure 5). We found no statistical evidence that patients with aortic stenosis had higher HGA levels at baseline (4.6 ± 2.7 grams/day in no AS group vs 6.8 ± 4.1 grams/day in AS group, $p=0.38$).

4. DISCUSSION

Patients with alkaptonuria exhibit a high frequency of aortic valve involvement, acquiring it in the sixth or seventh decades of life, similar to degenerative calcific aortic stenosis. In contrast to calcific aortic stenosis(18), however, there is no correlation with standard cardiovascular risk factors in our series. Vascular calcifications are common, but the correlation between the extent of calcifications and valvular heart disease remains unknown.

Numerous previous reports have documented aortic valve disease in alkaptonuria. The largest case series include our previous natural history study(11) of 58 alkaptonuria patients, 3 of whom underwent aortic valve replacement, and a recent series by Pettit et al(19) of 16 patients showing a 25% prevalence of significant aortic stenosis. In this group, there were 2 patients with aortic sclerosis, two with mild aortic stenosis, and two with mixed aortic stenosis and regurgitation. The current study of 76 patients further delineates our previous findings with an overall 17% prevalence of aortic stenosis or aortic valve replacement. Our study confirms findings of the Pettit series regarding the infrequent presence of significant disease of the mitral, tricuspid or pulmonic valves.

Most published case reports of alkaptonuria patients describe significant aortic valve disease in the sixth and seventh decades of life. This is similar to studies of aortic valve disease in the general population although the prevalence in alkaptonuria is clearly higher. The Cardiovascular Health Study was a large population based study of valvular heart disease in men and women ages 65 and older. The overall prevalence of aortic sclerosis in that population was 26%. The prevalence of aortic stenosis (peak velocity ≥ 2.5 m/s) was 2%, and 0.4% of the population had valve replacement(18). Our series includes 12 patients age 65 and older and among this group, 25% had aortic sclerosis, 25% had aortic stenosis, and 25% had undergone valve replacement.

In the Helsinki Aging Study, the prevalence of moderate or severe aortic stenosis in subjects over the age of 75 was about 8% and within subgroups, the prevalence increased with advancing age(20). Our series included only two patients over the age of 75. One patient had undergone aortic valve replacement and the other patient had only aortic sclerosis, suggesting that further studies of these patients will be necessary to identify predictors of the development of valvular heart disease.

Aortic valve calcification is a common finding in the elderly. In a population based sample of patients in the MESA study(21), the prevalence was found to be 8% in women and 14% in men. Alkaptonuria patients in our series had a significantly higher rate of aortic valve calcifications seen on CT scans (47%). The presence of thoracic aortic calcification was also examined in the MESA study(22) and was seen in 28% of subjects. In our series of alkaptonuria patients, we found a much higher prevalence of aortic calcifications, i.e. 65% of patients. Although our study included both the thoracic and abdominal aorta, it is likely that we underestimated the degree of calcification on these clinically indicated scans. Since the CT scans were not ECG gated or optimized for cardiac imaging, cardiac motion may have blurred the coronary or vascular calcifications resulting in significant underestimation of the degree of calcification.

We noted some overlap between aortic valve disease and cardiovascular calcifications in a few patients, but prospective evaluations with larger patient numbers are needed to further explore this relationship. Although alkaptonuria patients develop aortic valve disease later in life, it is known that the orthopedic complications result in large joint destruction in the forties and fifties (11). We saw a modest correlation between valvular heart disease and joint involvement suggesting that the same metabolic defect is likely contributing to both complications. Although patients with higher baseline levels of HGA did not seem predisposed to developing valvular heart disease, the variability in these levels and the small sample size makes it difficult to assess their contribution. The mechanism of aortic stenosis remains unknown, but prior studies of alkaptonuria patients have shown pigment deposition in various tissues throughout the body. HGA is oxidized to pigmented benzoquinones, which polymerize and deposit in the joints, cardiovascular system, kidney and skin. In the heart, intense pigment deposition is often seen within the aorta, particularly the aortic root, and the base of the aortic valve. Other sites of pigment deposition include the mitral annulus, the ventricular endocardium and atherosclerotic plaques within epicardial vessels (9,10). This pattern of pigmentation in areas of increased pressure or turbulence suggests that microvascular damage introduces a ideal focus for HGA deposition. Pigment-related damage appears to predispose tissues to dystrophic calcification although the mechanisms leading to this are not well understood.

In our recently reported, randomized therapeutic trial (13), baseline and follow-up echocardiographic data were available in 18 control patients and 18 patients treated for 3 years with nitisinone. In the control group, 4 patients had a significant increase in their baseline aortic valve velocities (≥ 0.3 m/s) while only 1 patient in the treated group had a significant increase in aortic valve velocity. This patient had moderate aortic stenosis with a peak aortic valve velocity of 3.7 m/s at baseline that increased to 4.3 m/s after three years of treatment. Although it is difficult to draw conclusions from this study about treatment of the aortic stenosis in alkaptonuria patients, the results do suggest that early initiation of treatment, before the onset of significant calcification, may be important. An analogous situation is the use of statin therapy for calcific aortic stenosis. This appeared promising in several retrospective studies but did not show efficacy in a large randomized prospective study(23) leading many to conclude that therapy with statins failed because it was given too late in the progression of the disease. Thus, future studies of treatments for alkaptonuria will

also need to consider that therapy for the cardiovascular complications of alkaptonuria may be more effective at an early stage.

In conclusion, in our series of 76 patients with alkaptonuria, there was a 17% prevalence of significant aortic valve disease and a high prevalence of vascular calcifications. Our patients developed aortic valve disease in their fifties and sixties. Cardiovascular disease appears to have some relationship with the extent of joint involvement. In our patients, we recommend baseline echocardiographic screening after the age of 40 to detect valvular heart disease and cardiac CT to detect coronary artery calcifications. Prospective studies are ongoing to further evaluate the presence and extent of calcifications in the cardiovascular system.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

This research was supported by the Intramural Research Program of the National Human Genome Research Institute and the National Heart Lung and Blood Institute, NIH, DHHS.

REFERENCES

1. La Du BN, Zannoni VG, Laster L, Seegmiller JE. The nature of the defect in tyrosine metabolism in alcaptonuria. *J Biol Chem.* 1958; 230:251–60. [PubMed: 13502394]
2. Wilke A, Dapunt O, Steverding D. Image of the month. Bluish-black pigmentation of the sclera and the aortic valve in a patient with alkaptonuric ochronosis. *Herz.* 35:41. [PubMed: 20140788]
3. Wauthy P, Seghers V, Mathonet P, Deuvaert FE. Cardiac ochronosis: not so benign. *Eur J Cardiothorac Surg.* 2009; 35:732–3. [PubMed: 19211256]
4. Brueck M, Bandorski D, Kramer W, Schoenburg M, von Gerlach S, Tillmanns H. Aortic valve stenosis due to alkaptonuria. *J Heart Valve Dis.* 2008; 17:127–9. [PubMed: 18365580]
5. Roser M, Moller J, Komoda T, Knosalla C, Stawowy P. Alkaptonuric aortic stenosis. *Eur Heart J.* 2008; 29:444. [PubMed: 17901078]
6. Kovacevic M, Simic O, Medved I, Lucin K, Padovan M. Ochronosis of the aortic valve and aorta. *J Heart Valve Dis.* 2006; 15:730–2. [PubMed: 17044384]
7. Ffolkes LV, Brull D, Krywawych S, Hayward M, Hughes SE. Aortic stenosis in cardiovascular ochronosis. *J Clin Pathol.* 2007; 60:92–3. [PubMed: 17213354]
8. Helliwell TR, Gallagher JA, Ranganath L. Alkaptonuria--a review of surgical and autopsy pathology. *Histopathology.* 2008; 53:503–12. [PubMed: 18336562]
9. Butany JW, Naseemuddin A, Moshkowitz Y, Nair V. Ochronosis and aortic valve stenosis. *J Card Surg.* 2006; 21:182–4. [PubMed: 16492283]
10. Kragel AH, Lapa JA, Roberts WC. Cardiovascular findings in alkaptonuric ochronosis. *Am Heart J.* 1990; 120:1460–3. [PubMed: 2248197]
11. Phornphutkul C, Introne WJ, Perry MB, et al. Natural history of alkaptonuria. *N Engl J Med.* 2002; 347:2111–21. [PubMed: 12501223]
12. Suwannarat P, O'Brien K, Perry MB, et al. Use of nitisinone in patients with alkaptonuria. *Metabolism.* 2005; 54:719–28. [PubMed: 15931605]
13. Introne WJ, Perry MB, Troendle J, et al. A 3-year randomized therapeutic trial of nitisinone in alkaptonuria. *Mol Genet Metab.*
14. Lang RM, Bierig M, Devereux RB, et al. Recommendations for chamber quantification: a report from the American Society of Echocardiography's Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. *J Am Soc Echocardiogr.* 2005; 18:1440–63. [PubMed: 16376782]

15. Baumgartner H, Hung J, Bermejo J, et al. Echocardiographic assessment of valve stenosis: EAE/ASE recommendations for clinical practice. *Eur J Echocardiogr.* 2009; 10:1–25. [PubMed: 19065003]
16. Agatston AS, Janowitz WR, Hildner FJ, Zusmer NR, Viamonte M Jr, Detrano R. Quantification of coronary artery calcium using ultrafast computed tomography. *J Am Coll Cardiol.* 1990; 15:827–32. [PubMed: 2407762]
17. McClelland RL, Chung H, Detrano R, Post W, Kronmal RA. Distribution of coronary artery calcium by race, gender, and age: results from the Multi-Ethnic Study of Atherosclerosis (MESA). *Circulation.* 2006; 113:30–7. [PubMed: 16365194]
18. Stewart BF, Siscovick D, Lind BK, et al. Clinical factors associated with calcific aortic valve disease. Cardiovascular Health Study. *J Am Coll Cardiol.* 1997; 29:630–4. [PubMed: 9060903]
19. Pettit SJ, Fisher M, Gallagher JA, Ranganath LR. Cardiovascular manifestations of Alkaptonuria. *J Inherit Metab Dis.*
20. Lindroos M, Kupari M, Heikkila J, Tilvis R. Prevalence of aortic valve abnormalities in the elderly: an echocardiographic study of a random population sample. *J Am Coll Cardiol.* 1993; 21:1220–5. [PubMed: 8459080]
21. Katz R, Wong ND, Kronmal R, et al. Features of the metabolic syndrome and diabetes mellitus as predictors of aortic valve calcification in the Multi-Ethnic Study of Atherosclerosis. *Circulation.* 2006; 113:2113–9. [PubMed: 16636166]
22. Takasu J, Budoff MJ, Katz R, et al. Relationship between common carotid intima-media thickness and thoracic aortic calcification: the Multi-Ethnic Study of Atherosclerosis. *Atherosclerosis.* 209:142–6. [PubMed: 19782983]
23. Elmariah S, Mohler ER 3rd. The Pathogenesis and treatment of the valvulopathy of aortic stenosis: Beyond the SEAS. *Curr Cardiol Rep.* 12:125–32. [PubMed: 20425167]

Highlights for “Aortic Stenosis and Vascular Calcifications in Alkaptonuria”

- This is a case series of 76 patients with alkaptonuria.
- There is an overall 17% prevalence of significant aortic valve disease.
- Cardiovascular calcifications are common and may have some relationship with the extent of joint involvement.
- Alkaptonuria patients should undergo screening with echocardiography and cardiac CT after age 40 to detect cardiovascular involvement.

Figure 1. Prevalence of Aortic Valve Disease by Percent of Age Group

Alkaptonuria patients under age 40 do not show evidence of aortic valve disease. Aortic sclerosis and aortic stenosis develop in their 40s and 50s. By their 60s, approximately one quarter of patients have undergone aortic valve replacement.

Figure 2. Echocardiographic Images from an Alkaptonuria Patient With Severe Aortic Stenosis

2a. This echocardiographic image, obtained in the apical long-axis view, shows the mitral valve (MV) and a heavily calcified aortic valve (AV). A movie image of this view is available in Supplementary on-line videos at xxx site.

2b. This is a short-axis view of the aortic valve from the subcostal window showing limited systolic opening. A movie image of this view is available on-line at XXX site.

2c. Doppler of the aortic valve shows a peak systolic gradient of 75mmHg consistent with severe aortic stenosis.

Figure 3. Prevalence of Cardiovascular Calcifications by Percent of Age Group

Vascular calcification was only assessed in patients over age 40. The extent of aortic, intracardiac, and coronary calcification increased with increasing age. Several patients had calcification of more than one type of vessel.

Figure 4. CT scan image of Severe Coronary and Aortic Calcifications

4a. Non-contrast CT image demonstrating severe calcification of the left anterior descending coronary artery (arrows) in an alkaptonuria patient with prior aortic valve replacement. 4b. Coronal view of a 3D volumetric rendering from a non-contrast CT highlighting the severe descending aortic and bilateral iliac calcification.

Figure 5. Relationship Between Number of Joints Replaced and Peak Aortic Velocities
There is a modest, yet significant, correlation between the number of joints replaced per patient and the peak aortic velocities on echocardiogram.

Table 1

Clinical Characteristics of Alkaptonuria Patients With and Without Aortic Stenosis

Parameter	No aortic stenosis (n=63)	Aortic stenosis (n=7)	p value
Age (years)	52 ± 10	59 ± 7	0.03
Male gender n (%)	41 (65%)	5 (57%)	0.68
Body surface area (m ²)	1.9 ± 0.2	1.9 ± 0.2	0.72
Body mass index (kg/m ²)	28.6 ± 5.4	29.5 ± 3.8	0.6
History of smoking n (%)	12 (19%)	2 (29%)	0.55
Diabetes Mellitus n (%)	3 (5%)	0 (0%)	0.55
Hyperlipidemia n (%)	26 (41%)	3 (43%)	0.94
Hypertension n (%)	23 (37%)	4 (57%)	0.29
Total cholesterol (mg/dL)	176 ± 42	166 ± 38	0.54
Triglycerides (mg/dL)	136 ± 77	97 ± 47	0.09
LDL (mg/dL)	106 ± 35	101 ± 30	0.69
HDL (mg/dL)	46 ± 12	48 ± 8	0.71
Creatinine Clearance (ml/min) [§]	131 ± 39	157 ± 64	0.38

* Patients with valve replacement not included

[§] calculated as (24 hour urine creatinine * volume)/serum creatinine * 1000

Table 2

Echocardiographic Data in Alkaptonuria Patients With and Without Aortic Stenosis

Parameter	No aortic stenosis (n=63)	Aortic stenosis (n=7)	p value
Peak aortic velocity (m/s)	1.6 ± 0.4	2.9 ± 0.6	<0.001
Mean aortic gradient (mmHg)	5 ± 3	20 ± 11	0.01
Aortic valve area (cm ²)	2.4 ± 0.7	1.3 ± 0.2	<0.001
LV mass index (g/m ²)	71 ± 17	87 ± 20	0.07
LV ejection fraction (%)	63 ± 7	63 ± 4	0.7
Aortic regurgitation n (%)	9 (14%)	3 (43%)	0.06
Mitral regurgitation n (%)	1 (2%)	0	0.74
Tricuspid regurgitation n (%)	2 (3%)	0	0.63
Aortic root diameter (mm)	35 ± 4	35 ± 5	0.84

* Patients with valve replacement not included