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RESEARCH

Clinical events and echocardiographic lesion progression rate in subjects with mild or moderate aortic regurgitation

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Abstract

Background: The rate of progression of aortic regurgitation (AR) is not well described. Current guidelines state that asymptomatic patients with mild AR should be followed up every 3–5 years and 1–2 yearly for moderate AR. This study describes the lesion and clinical based progression of mild and moderate AR in a population of patients undergoing systematic follow-up.

Methods and results: 341 patients with either mild or moderate AR were included. The rates of clinical events (death, aortic valve replacement and cardiac hospitalization) and progression of AR are reported.

341 patients were included; mean age was 71.1 years (IQR 66–80 years) and the median follow-up period was 4.6 (IQR 2–6.7) years. 292 patients did not have any events during follow-up. 3 patients required aortic valve replacement (2 of these due to severe aortic stenosis and 1 due to severe mitral regurgitation and co-existent moderate AR). 44 patients required cardiac hospitalization. 9 patients died during follow-up and 35 patients (10%) showed a progression of AR during follow-up with an average time of 4.0 ± 2.6 years. 8 patients (2.3% of the total) progressed to severe AR.

Patients with mixed valvular pathology showed a greater increase in AR progression (27 (15%) vs 8 (5%); $P = 0.004$).

Conclusions: Over medium term systematic follow-up progression and clinical events in patients with AR is rare, regardless of etiology. Patients who suffered from AR as an isolated valve pathology were less likely to show AR progression over time.

Key Words

- AR
- valvular heart disease
- echocardiography

Introduction

The prevalence of heart valve disease increases with age and therefore represents an increasing public health problem (1). Aortic regurgitation (AR) remains a very common heart valve lesion with an overall prevalence

in the Framingham study of 4.9% (2). The prevalence may vary with ethnicity and occurred in 10% of middle aged American Indians in the Strong Heart Study (3). The recently published OxVALVE study found a prevalence of mild AR in 13.6% and moderate-to-severe AR in 1.6%, in a cohort of predominantly Caucasian individuals aged 65 and over (4). AR can be caused by malcoaptation of the valve leaflets due to abnormalities of the leaflets themselves, their supporting structures (aortic root or annulus) or both. In Western Europe and North America, the main cause of chronic AR is degenerative calcific valve disease (5), while congenital bicuspid aortic valve, with a prevalence of 1% (6) and secondary dilatation of the aortic root and annulus (7) are also implicated. Outside of these, the etiology of milder degrees of AR is not always clear but because the lesion is not haemodynamically important, more extensive characterization is not warranted.

The natural history of severe AR and its effect on left ventricular remodeling is well defined with a gradually progressive clinical course leading to eccentric hypertrophy, fibrosis and ultimately, cardiac failure (8). The natural history of lesser grades of AR at both the lesion and on clinical outcomes is poorly described (9, 10, 11).

The current AHA guidelines for surveillance echocardiography suggest re-testing every 1–2 years for patients with moderate AR, and every 3–5 years for patients with mild AR (12) while the ESC guidelines suggest that patients with mild-to-moderate aortic regurgitation should be reviewed on a yearly basis and echocardiography performed every 2–3 years (13).

The objective of this investigation is to describe the rate of clinical and echocardiographic progression in a well-defined cohort of patients with mild and moderate AR (whether as a lone lesion or in association with another valve lesion requiring surveillance) followed up systematically in a physiologist-led valve clinic.

Methods

This was a retrospective cohort study of consecutive patients under follow-up in the dedicated physiologist-led valve clinic at Eastbourne District General Hospital. The clinic serves a town with a predominantly elderly Caucasian population with little population mobility. The heart valve clinic was established in 2005 (14).

AR severity was graded at the initial echocardiogram. All patients were enrolled between August 2001 and December 2014, if they had at least mild but not severe AR and who underwent at least one follow-up echocardiogram. Patients were under follow-up for primary (degenerative) AR and for AR secondary to a bicuspid aortic valve and aortic root dilatation. Both patients with lone AR and those with mixed aortic valve disease or co-existing valve lesions including primary mitral valve disease or following mitral valve replacement or repair, were included. In cases where patients suffered from dual valvular pathology, the valve with the greatest severity was considered the primary reason for follow-up.

At each visit, echocardiography was undertaken and an assessment of symptoms was made. The Specific Activity Scale questionnaire (15) was used to determine NYHA class. Patients would be referred back to their cardiologist if there was any deterioration of symptoms or decline in left ventricular function.

This study was approved by the local institutional audit board (East Sussex Healthcare NHS Trust).

Exclusion criteria

Patients with a history of aortic valve replacement or trans-catheter aortic valve implantation (TAVI) on their baseline valve clinic echo were excluded. Patients who had only received 1 echocardiogram were excluded, as no follow-up could be determined. Patients who were found to have trivial or severe AR on echocardiography were excluded.

Echocardiographic measurements

All echocardiographic examinations were performed using the GE Vivid 7, GE Vivid E9 or the Phillips IE33 echo platforms. A physiologist accredited in echocardiography by the British Society of Echocardiography performed all echocardiograms. The echocardiograms were re-analyzed for consistency by an experienced echo cardiologist (SB). The minimum dataset for a standard transthoracic echocardiogram was collected for every scan (16). Left ventricular function assessment was divided into five categories: hyperdynamic function (LVEF >70%), normal function (LVEF: 55–69%), mild impairment (LVEF: 45–54%), moderate impairment (LVEF: 36–44%) and severe impairment (LVEF ≤35%).

AR severity was defined by an integrated echocardiography assessment that included visual assessment, the AR jet width at the aortic valve and the jet height in the left ventricular outflow tract, the strength of the AR CW signal and the pressure half time. The presence of

pan-diastolic flow reversal in the proximal descending aorta was taken as indicating severe AR. Volumetric assessment was not performed in the majority of cases because this can be much more challenging to perform in patients with less severe AR (as the PISA shell is less well defined) and because it was not introduced as a means of assessing AR in the clinic at the beginning of the assessment period. AR severity was graded as mild, moderate and severe.

Definition of events during follow-up

Cardiac events were primarily established by the investigators. Progression of aortic regurgitation was defined as a sustained increase in recorded AR grade over at least two subsequent visits. Hospitalization was defined as an admission that lasted at least 24 h. Deaths were classified as cardiac and non-cardiac, and these were verified by review of the medical records and death certificates. Aortic valve intervention was verified from the clinical and surgical notes. Independent adjudication of events was undertaken by an experienced cardiologist (SS). The initial adjudication involved the clinical details only scored for each case on the following basis: on balance likely caused by AR, on balance not caused by AR or insufficient information to score. For those in whom there was insufficient information or it was felt that AR was the cause, these procedures were repeated with the echo images and report as scored in a binary way.

Statistical analysis

Continuous data are expressed as interquartile ranges, as data were not normally distributed. Categorical data are expressed as percentages and absolute values. Differences between datasets were determined using the Mann–Whitney *U* test. To determine the differences between categorical data, the chi-squared test was used.

A Kaplan–Meier analysis was used to describe the event-free survival and the log-rank test to describe the differences between the primary reason of follow-up in AR progression. All statistical analyses were performed using Statistical Package for the Social Sciences (SPSS, version 20.0; SPSS). A *P* value of <0.05 was considered significant.

Results

A total of 341 patients with mild or moderate AR were identified. The median follow-up was 4.6 years (IQR: 2–6.7 years). A total of 1930 echocardiograms were performed, averaging a follow-up of 5.7 echocardiograms per patient, and 1.3 echocardiograms per patient per year. Patient demographics and baseline echocardiographic data are shown in Table 1. The primary reason for follow-up according to valvular lesion is shown in Table 2. Of the 341 patients, 189 patients had mild AR and 152 moderate AR.

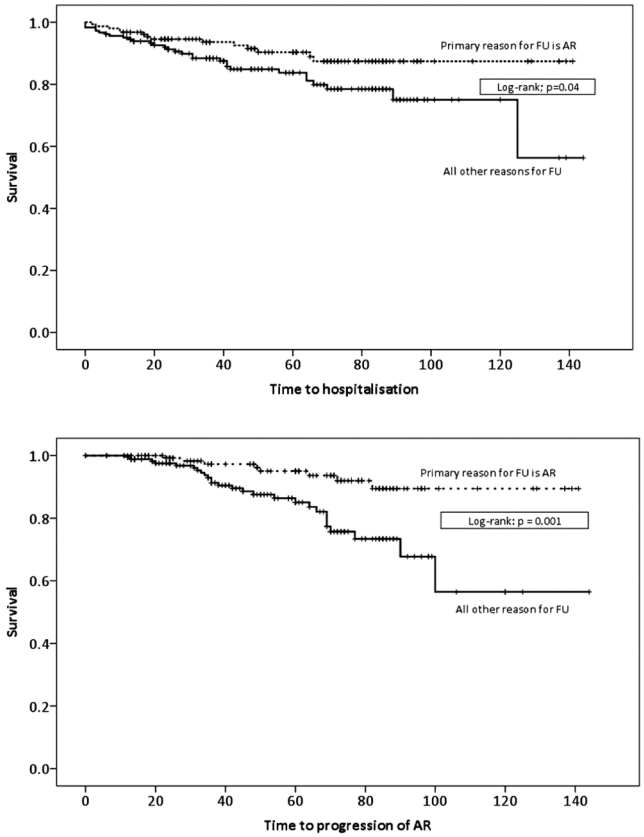

Figure 1
Kaplan–Meier curves comparing hospitalization (top) and progression (bottom) for patients primarily followed up for primary AR ($n=157$) vs all other pathologies ($n=184$).

Progression

A total of 35 patients (10% – 8 patients with lone AR, 11 with mixed aortic valve disease and 13 with multi-valve disease) showed a progression of at least one AR grade during follow-up. The average time to progression of these patients was 4.0 ± 1.9 years (Fig. 1). Patients followed up for mixed aortic valve disease (including aortic stenosis, bicuspid aortic valve disease and dilated aortic root ($n=250$)) were less likely to show progression of AR

Table 1 Patient demographics and baseline echocardiographic data: $n=341$.

Demographics	
Age (years)	71.1 (IQR: 66–80)
Gender (male)	161 (47%)
Hypertension	109 (32%)
Diabetes	16 (5%)
Symptoms at first valve clinic visit	
Asymptomatic	146 (43%)
Dyspnea	81 (24%)
Chest pain	32 (9%)
Palpitations	24 (7%)
Other (pre-syncope, syncope, fatigue)	15 (4%)
Multiple symptoms	31 (9%)
Unknown	12 (4%)
NYHA class	
I	238
II	78
III	8
IV	1
Echocardiographic data	
LVEDD (cm)	4.9 (IQR: 4.4–5.3)
LVESD (cm)	3.0 (IQR: 2.7–3.4)
Aortic root (cm)	3.1 (IQR: 2.8–3.5)
Patients with aortic root >4 cm	25 (7%)
LV ejection fraction at first valve clinic visit	
Hyperdynamic (LVEF >70%)	58 (17%)
Normal (LVEF 55–69%	256 (75%)
Mildly impaired (LVEF 45–54%)	18 (5%)
Moderately impaired (LVEF 36–44%)	6 (2%)
Severely impaired (LVEF <35%)	2 (1%)

compared to those followed up for all other pathologies (8% vs 18%). Patients exclusively followed up for AR were less likely to progress compared to patients followed up for all other pathologies (5% vs 15% respectively $P=0.004$; Table 3). This was statistically significant when comparing lone AR with all other lesions. In the whole cohort, 8 (2.3%) progressed from any grade to severe AR.

No associations were observed for AR progression and gender, age, symptoms, NYHA class, hypertension or diabetes. Neither an aortic root greater than 4 cm ($n=25$) nor bicuspid aortic valve ($n=16$) was associated with progression of AR. Patients who showed progression of AR had a greater LV end diastolic dimension on first echocardiogram than those who did not show worsening in AR grade (5.1 ± 0.6 vs 4.8 ± 0.6 cm; $P=0.03$). Patients with mild aortic regurgitation were more likely to show echocardiographic progression in AR grade compared to those with moderate AR (29 vs 6, 15% vs 4%, $P=0.001$; Table 4).

Table 2 Primary reason for valve clinic follow-up: $n=341$.

Reason for follow-up	Number of patients
Aortic regurgitation (degenerative)	157 (46%)
Bicuspid aortic valve	16 (5%)
Dilated aortic root	13 (4%)
Mixed aortic valve disease	64 (19%)
Mitral valve disease	39 (11%)
MVR/MV repair	22 (6%)
Double valve disease (aortic and mitral regurgitation)	30 (9%)

Clinical events

Out of the total 341 patients, 44 patients (13%) had a cardiac admission. 22 patients were admitted with a cardiac arrhythmia, 10 with chest pain and 3 with heart failure related symptoms. 9 patients were admitted with breathlessness and pre-syncope; however, these symptoms were found to be non-cardiac in nature. 9 patients (3%) died (6 non-cardiac related, 2 cardiac related, 1 unknown cause); independent adjudication judged that none of these deaths were related to AR. 3 patients (1%) underwent aortic valve replacement during follow-up (2 due to severe aortic stenosis and 1 due to severe mitral regurgitation and moderate AR; Table 3). No patients underwent a TAVI procedure, and no patients underwent aortic valve replacement for primary AR.

There were no differences in clinical events (cardiac hospitalization, death, AVR) between those followed up primarily for AR ($n=157$) or for those with additional lesions (Fig. 1). Patients with mixed aortic valve disease suffered the same number of events as those with pure AR. The event rate was similar between those with mild and moderate AR.

Of the patients followed up predominantly for AR, 55 patients suffered from mild AR and 102 patients from moderate AR (Table 5). A total of 14 (6%) patients were hospitalized, 4 (3%) patients died and none required AVR during follow-up. There were no significant differences in events between patients followed up for mild AR compared to patients with moderate AR (Table 5).

Discussion

This data demonstrates that over a medium term follow-up period, progression and clinical events in patients with mild and moderate AR that relate to the regurgitant lesions are very rare, regardless of etiology. Those who did experience either clinical events or echocardiographic progression were more likely to have either dual aortic valve pathology or be followed up primarily for an alternative valve lesion. Over 5 years no aortic valve replacements and no events primarily related to AR were

Table 3 End points comparing patients followed up for aortic regurgitation vs all other pathology: $n = 341$.

	Total ($n = 341$)	**AR as main valve pathology** ($n = 157$)	**All other pathology** ($n = 184$)	***P* value**
Progression	35 (10%)	8 (5%)	27 (15%)	0.004
Cardiac hospitalization	44 (13%)	14 (9%)	30 (16%)	0.04
Death (cardiac and non-cardiac)	9 (3%)	4 (3%)	5 (3%)	0.9
AVR	3 (1%)	0 (0%)	3 (2%)	0.10

observed. A small proportion of patients (8 out of the total of 341 (2.3%)) progressed from any grade of aortic regurgitation to severe AR.

In contrast to aortic stenosis and severe AR, there is only very limited data available regarding the long-term progression and follow-up of patients with mild and moderate AR. Patients with severe AR have significantly increased mortality and morbidity compared to the general population, and highly symptomatic patients e.g. in NYHA class III and IV symptoms have been shown to have an annual mortality of approximately 25% (17). A further study showed that mortality may be as high as 10–20% at one year in patients with symptoms (9). In asymptomatic patients with chronic severe AR and normal LV function, if the LVESD is greater than 50 mm, then the probability of death, symptoms or LV dysfunction is reported to be 19% (9, 10, 17). Asymptomatic patients with AR may not develop symptoms for many years. 490 asymptomatic patients in seven studies with chronic moderate to severe AR and normal LV function were followed up for a mean of 6.4 years. The rate of progression to symptoms and/or LV dysfunction was less than 6% per year, the rate of progression to asymptomatic LV dysfunction was less than 3.5% per year, and the rate of sudden death was less than 0.2% per year (9, 11, 18, 19, 20). Patients with rheumatic AR may exhibit a rapid downhill course and die unexpectedly (21).

Broch *et al*. sought to investigate the mechanisms of left ventricular contraction patterns in asymptomatic patients with moderate to severe AR and preserved ejection fraction, using speckle tracking. Despite a normal LVEF, global longitudinal strain (GLS) was markedly reduced and global circumferential strain (GCS) was increased in these patients compared with controls and athletes. These findings suggest that in the clinical course of chronic AR a prolonged phase of stability, during which the left ventricle adapts to the volume and pressure overload and patients remain asymptomatic, LVEF is preserved, but the true myocardial performance may be markedly reduced, as reflected by the low GLS (22).

Mild AR may be physiological rather than pathological and valvular regurgitation of a trivial or mild degree is a frequent finding in normal subjects (23). One study reported an increasing prevalence of AR with advancing age in apparently healthy subjects (24). In contrast to severe lesions, there are no published papers that describe follow-up and progression of mild and moderate AR. The available data is in the form of conference abstracts. Patel *et al*. (25) included 4128 patients, where 3266 patients had at least mild and 862 patients had at least moderate AR. 95% of patients with at least mild AR on the initial echocardiogram had no change over a mean interval of 4.2 years. 90% of patients with at least moderate AR had no change over the follow-up period, implying that the rate of progression of aortic regurgitation is extremely slow. Our results are comparable with this study. Fujimoto and coworkers in a study of 600 patients with mild-to-moderate AR demonstrated that 88% of patients had no change in severity of aortic regurgitation. Only 0.8% progressed to severe AR (26). In our study, we found a progression to severe AR of 2.3% of patients with mild or moderate AR on initial echocardiogram. In a smaller study of 262, patients with moderate AR and no more than mild aortic stenosis were followed for a mean of 42 ± 31 months. Progression to severe AR occurred in 6.9% of patients (18 patients), an average progression rate of 1.9% per year. Patients in whom the main pathology was aortic root dilatation had a significantly higher rate of progression to severe AR, compared to those patients with leaflet pathology (3.7% per year compared to 1.4% per year). 3 patients were

Table 4 Progression of aortic regurgitation in all patients: $n = 341$.

	Total ($n = 341$)	**Mild AR** ($n = 189$)	**Moderate AR** ($n = 152$)	***P* value**
Progression	35 (10%)	29 (15%)	6 (4%)	0.001
Cardiac hospitalization	44 (13%)	28 (15%)	16 (11%)	0.2
Death (cardiac and non-cardiac)	9 (3%)	6 (3%)	3 (2%)	0.5
AVR	3 (1%)	2 (1%)	1 (1%)	0.7

Table 5 Patients followed up primarily for aortic regurgitation: $n = 157$.

	Total ($n = 157$)	**Mild AR** ($n = 55$)	**Moderate AR** ($n = 102$)	***P* value**
Progression	8 (5%)	4 (7%)	4 (4%)	0.4
Cardiac hospitalization	14 (6%)	5 (9%)	9 (9%)	0.9
Death (cardiac and non-cardiac)	4 (3%)	2 (4%)	2 (2%)	0.5
AVR	0 (0%)	0 (0%)	0 (0%)	

referred for AVR (aortic root dilatation) and there were 26 deaths. These findings suggest slow progression and a low event rate (27). A study by Vaturi and coworkers showed that in 131 patients with rheumatic heart disease at the time of mitral valve surgery, 58 had mild AR. 90% of these remained stable after a mean follow-up period of 13 ± 7 years (28).

A recent study sought to establish the role of regurgitant volume on the likelihood of developing cardiac dysfunction in patients with moderate and severe aortic and mitral regurgitation (29). Over a 3-year follow-up period, the left ventricular dimensions and function deteriorated in the patients with severe AR, whereas in patients with moderate AR, the left ventricular volumes, ejection fraction and contractility parameters did not significantly change. These data suggest that these patients do not require frequent echocardiography unless there is a change in clinical condition. Detaint and coworkers sought to define the link between aortic regurgitation quantitation and clinical outcome in 251 asymptomatic patients with mild, moderate and severe AR and left ventricular ejection fraction ≥50%. The results showed that regurgitant volume, effective regurgitant orifice and end systolic volume index are independent and superior predictors of clinical outcome (30). This carries clinical implications as patients with any of these criteria should be carefully monitored for progression of AR and left ventricular remodeling (31).

Our study confirms that the echo follow-up intervals mandated in the AHA and ESC guidelines are over burdensome for sole AR but better calibrated for those with mixed valve disease. The rate of events and progression of AR was very low and no patients followed up primarily for mild or moderate AR underwent aortic valve replacement. Interestingly, patients with mild AR were more likely to show progression than patients of moderate severity. Why should this be? As the means of assessment was clinical, it could be that a physiologist undertaking the investigation would be happier to upgrade from mild to moderate, rather than from moderate to severe where intervention would potentially be required. The event rate in our population was high, reflecting the age and co-morbidities of the population. Because of this, each case was independently adjudicated for the likelihood that the AR contributed, and in all cases, the regurgitation was felt to be non-contributory.

Study limitations

This was a retrospective study, although all records were collected in a single valve clinic database, meaning follow-up was comprehensive. Current guidelines recommend Quantitative American Society of Echocardiography (QASE) thresholds for AR assessment (32). The assessment of AR was using integrated echocardiographic assessment with the final adjudication by the cardiac physiologist rather than quantitate assessment including regurgitant volume and EROA. This is a well-established methodology where comprehensive quantitative assessment is not available in all patients. The study was carried out in a largely Caucasian population, without ethnic or socioeconomic diversity. The findings may therefore be difficult to generalize to other communities.

Conclusions

The proportion of patients with mild and moderate lone aortic regurgitation that show progression in AR severity is very low, over a 5-year follow-up period regardless of etiology. No patients with primary AR underwent AVR during the follow-up period. Current follow-up guidelines may therefore be excessively burdensome, and it may be for milder degrees of AR follow-up is simply not required. Patients with dual pathology were, more likely to show a progression of AR, and closer follow-up in these cases, in line with current guidance is warranted.

Declaration of interest
The authors declare there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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