

Five-Year Follow Up of the ATS Mechanical Heart Valve

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Background and aim of the study: Between January 1, 1997 and December 31, 2001, a total of 342 patients underwent aortic valve replacement (AVR) or mitral valve replacement (MVR) with the ATS Medical prosthesis. The initial three-year phase of this study took place under a United States Food and Drug Administration-approved investigational device exemption study. The study aim was to determine the incidence of valve-related events in up to five years of follow up after valve implantation, and to assess patient disturbance from valve noise.

Methods: Patients were consecutively enrolled to undergo AVR or MVR with the ATS prosthesis. Follow up studies were conducted by patient questionnaire and/or telephone call. Follow up was 96% complete. AVR was conducted in 246 patients (80 with coronary bypass), and MVR in 96 patients (29 with coronary bypass).

Results: The overall operative mortality was 2.6% (n = 9; AVR 3.2%, n = 8; MVR 1.0%, n = 1), with two deaths being valve-related (0.6%). In 878 patient-years (pt-yr) of follow up (613 pt-yr for AVR; 265 pt-yr for MVR) there were an additional 22 deaths. Five

deaths (0.6%/pt-yr) were valve-related: two were neuroembolic (both MVR), one from endocarditis (AVR), and two from bleeding events (both AVR). Late valve-related complications (>30 days) included 17 episodes of major bleeding (11 AVR, 1.8%/pt-yr; six MVR, 2.3%/pt-yr), five permanent neuroembolic events (four AVR, 0.7%/pt-yr; one MVR, 0.4%/pt-yr); 16 transient neuroembolic events (10 AVR, 1.6%/pt-yr; six MVR, 2.3%/pt-yr); three transient peripheral emboli (two AVR, 0.3%/pt-yr; one MVR, 0.4%/pt-yr); four paravalvular leaks (two AVR, 0.3%/pt-yr; two MVR, 0.8%/pt-yr); and one episode of valve thrombosis (MVR, 0.4%/pt-yr; AVR, 0%/pt-yr). Reoperation was required in two patients: one AVR (paravalvular leak, 0.2%/pt-yr) and one MVR (replacement due to thrombosis, 0.4%/pt-yr).

Conclusion: These results indicate that intermediate-term results with the ATS mechanical prosthesis continue to be excellent, though further long-term follow up is warranted.

The Journal of Heart Valve Disease 2004;13:231-238

The ATS™ (ATS Medical Inc., Minneapolis, MN, USA) open-pivot bileaflet cardiac valve prosthesis has encompassed developments in pyrolytic technology coating, which include the ability to coat convexities on the valve housing. The convexities thus formed by pyrolytic carbon coating allow the feasibility of a different leaflet arrangement or open-pivot design. This permits the leaflets to slide before closing, thereby creating a more silent prosthetic valve. In addition, with the absence of concavities there is no stasis at any point in the cardiac cycle, so that trans-cyclic washing is complete. The present authors' initial experience with

the ATS Medical valve at one center in the United States Food and Drug Administration investigational device exemption trial was reported previously (1), followed at a later date by the results of a multi-center international experience (2). Subsequently, the use of this valve prosthesis has continued, and the current report updates the original series of patients with the addition of patients having isolated aortic valve replacement (AVR) or mitral valve replacement (MVR), with or without coronary artery bypass grafting (CABG), to an experience of five years.

Clinical material and methods

Patient data acquisition

The names and pertinent demographic data on all patients having ATS valve implantation by Cardiac

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Table I: Patient demographics.

Parameter	AVR	AVR+ CABG	AVR+ Other	MVR	MVR+ CABG	MVR+ Other	Total
Patients (n)	161 (47.1)	75 (21.9)	10 (2.9)	60 (17.5)	28 (8.2)	8 (2.3)	342 (100.0)
Age (years)*	60 ± 1.24	71 ± 8.4	64 ± 20.6	62 ± 12.3	65 ± 9.6	63 ± 4.9	63 ± 14.1
Gender							
Male	49 (30)	50 (67)	5 (50)	29 (48)	19 (68)	4 (50)	156 (46)
Female	112 (70)	25 (33)	5 (50)	31 (52)	9 (32)	4 (50)	186 (54)
Follow up (years)							
Total	416	175	22	165	77	24	878
Average per patient	2.6	2.3	2.2	2.8	2.7	2.9	2.6
Mortality							
Operative	5 (3)	3 (4)	0 (0)	0 (0)	0 (0)	1 (12)	9 (2.6)
Late	8 (5)	6 (8)	0 (0)	3 (5)	5 (18)	0 (0)	22 (6.4)
Valve-related	4 (2)	1 (1)	0 (0)	1 (2)	1 (4)	0 (0)	7 (2.0)

Values in parentheses are percentages.

*Values are mean ± SD.

AVR: Aortic valve replacement; CABG: Coronary artery bypass grafting; MVR: Mitral valve replacement.

Surgical Associates surgeons were maintained on a database through the Cardiac Surgical Research Foundation (CSRF), a private, non-profit section of Cardiac Surgical Associates, P.A. This database was accessed for all patients having AVR or MVR surgery using the ATS Medical cardiac valve prosthesis, with or without concomitant cardiac procedures, between January 1, 1997 and December 31, 2001.

The primary objective of this study was to document valve-related events in an up to five-year experience in a single surgical group practice. Patient follow up was conducted by questionnaire and telephone contact

with the patient or primary care physician if relevance warranted or valve-related complications occurred. Clinical study documents, questionnaires from prior patient studies, and office medical records were also reviewed to insure the proper identification of adverse events (1,2). Follow up was conducted from June 2002 to February 2003.

Details of the surgical techniques employed have been published previously (1), and have been maintained throughout this current study. Consistent with the prior study guidelines, only single-valve replacement patients were included, with or without con-

Table II: Valve distribution in AVR patients (n = 246) and MVR patients (n = 96).

Valve size (mm)	Aortic: Standard valve (n = 108)	Advanced Performance (n = 138)	Mitral: Standard valve (n = 96)
16	0	3	0
18	3	14	0
19	2	0	0
20	10	43	0
21	5	0	0
22	1	48	0
23	22	0	0
24	5	28	0
25	43	0	1
26	0	2	0
27	16	0	6
29	1	0	40
31	0	0	31
33	0	0	18

comitant procedures. The target INR throughout this study was 1.8-2.5 after AVR, and 2.5-3.5 after MVR. If atrial fibrillation was present, the target INR was 3.5-4.5, and this was recently redefined to account for patient risk factors. Low-dose aspirin has also been added throughout the surgery period. Operative data were entered into the CSRF database, modified from the STS model, to meet CSRF requirements. Data were collected in accordance with standards described by Edmunds et al. (3) and the FDA document for Replacement of Heart Valve Guidance 1994 (4).

Statistical analysis

Continuous variables were reported as mean ± SD. Survival rates were calculated using non-parametric actuarial Kaplan-Meier calculations. Linearized rates were expressed in percentage per patient-year (pt-yr). The SPSS statistical software package (SPSS, Chicago, IL, USA) was used for data analysis.

Results

Over the 60-month study period, 342 patients underwent valve replacement with the ATS Medical prosthesis. In total, 246 patients (72%) underwent AVR, and 96 (28%) underwent MVR procedures. Patient demographics and details of the operative procedures performed, in addition to operative mortality and patient follow up, are listed in Table I. The distribution of valve sizes used is shown in Table II. It should be noted that in 138 patients the advanced performance (AP) sizes were used. In this modification, the materials used in the primary design and manufacture of the standard valve were unchanged, but the device was redesigned to reduce the external sewing cuff bulk, thus permitting a valve of larger size with a greater geometric orifice area to be implanted into any given annulus diameter. This translates into an increase in effective orifice area and a theoretically lower pressure gradient across the valve (1). The operative data were similar to those published previously, and are there-

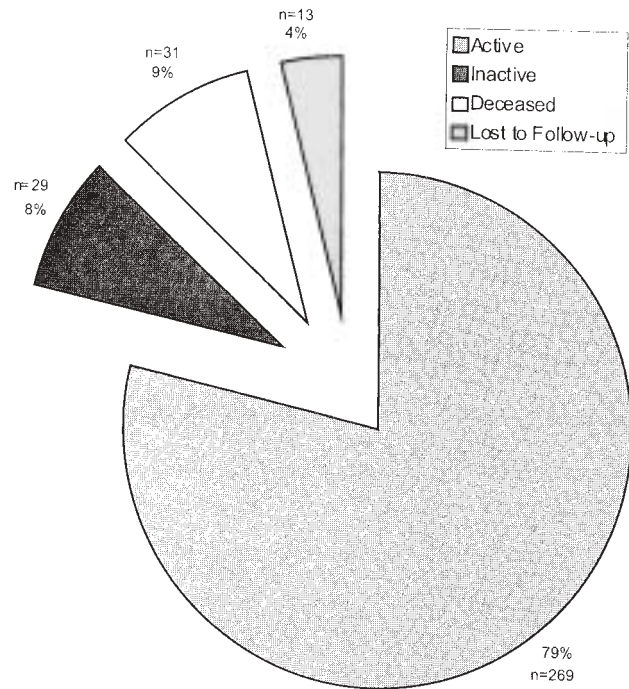


Figure 1: Follow up summary of patients undergoing aortic valve replacement (AVR) or mitral valve replacement (MVR) with the ATS Medical cardiac valve prosthesis

fore not included. The total operative mortality was 2.6% (n = 9), and mortality over five years was 9% (n = 31), as delineated per procedure in Table I.

The total patient follow up was 878 pt-yr (613 pt-yr for AVR; 265 pt-yr for MVR). The average follow up was 2.5 years for AVR, and 2.8 years for MVR. Follow up was 96% complete in the following categories (Fig. 1): Active 79%; deceased 9%; alive but refused to participate in the questionnaire or follow up 8%; and lost to follow up 4% (minimum of three attempts to contact patient). NYHA classification in active patient participants is shown in Table III (average pt-yr of follow up). Valve-related events are discussed under the follow up subsections.

Table III: Preoperative and postoperative NYHA functional classification in active patient participants (n = 269).

NYHA class	Aortic (n = 192)		Mitral (n = 77)	
	Preop.	Postop.*	Preop.	Postop ⁺
I	20 (10)	139 (72)	6 (8)	60 (78)
II	84 (44)	50 (26)	32 (42)	12 (16)
III	49 (26)	3 (2)	26 (34)	5 (7)
IV	39 (20)	0 (0)	13 (17)	0 (0)

Values in parentheses are percentages.

*Average 2.85 years.

⁺Average 3.02 years.

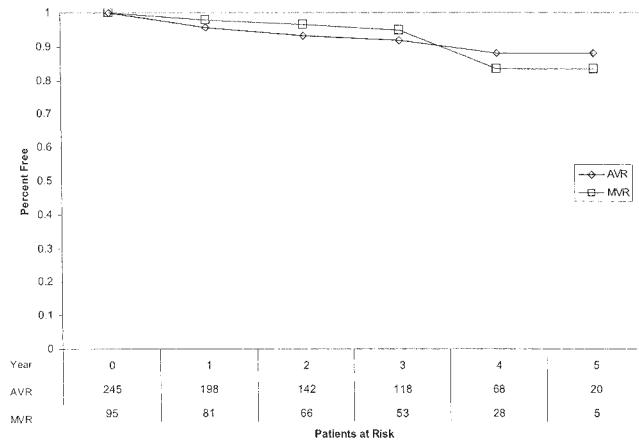


Figure 2: Kaplan-Meier actuarial freedom from all mortality in patients undergoing aortic valve replacement (AVR) or mitral valve replacement (MVR) with the ATS Medical mechanical valve prosthesis.

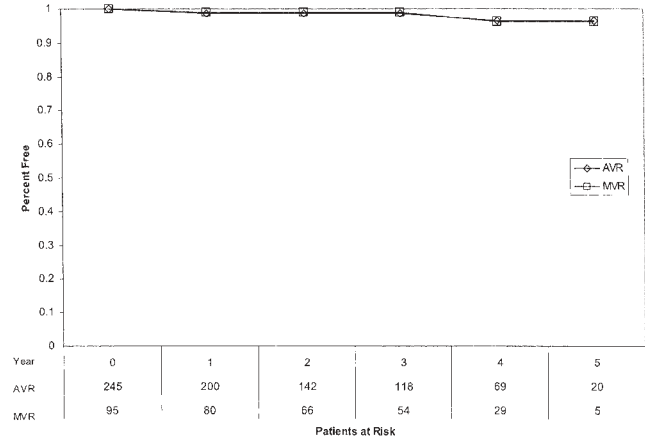


Figure 3: Kaplan-Meier actuarial freedom from valve-related mortality in patients undergoing aortic valve replacement (AVR) or mitral valve replacement (MVR) with the ATS Medical mechanical valve prosthesis.

Mortality

There were nine operative deaths which occurred between 0 and 57 days postoperatively. Two deaths were valve-related and due to prosthetic valve endocarditis (postoperative day 18) and multi-system failure following reoperation for paravalvular leak (day 57) in patients having AVR and AVR+CABG, respectively. Other causes of mortality included cardiogenic shock (days 0, 2 and 5), aortic rupture (day 1), aortic atheromatous embolus (day 1), multi-system organ failure (day 5), and pneumonia and respiratory failure (day 10). Valve-related operative deaths per procedure are shown in Table IV.

Late mortality occurred in 22 patients (6%; eight after MVR, 14 after AVR) at between 98 and 1,841 days following surgery. Five of these deaths were determined to be valve-related (see Table IV). Other causes of patient death included: cardiac in six cases (myocardial infarction, congestive heart failure), systemic sep-

sis in four, vascular in two (ruptured abdominal aortic aneurysm), pulmonary in two (pneumonia), cancer in one case, and other causes in two cases.

Freedom from mortality over the five-year study period for all AVR deaths was $0.88 \pm 0.05\%$, and for AVR valve-related deaths was $0.96 \pm 0.04\%$. Over the same period, freedom from mortality for all MVR deaths was $0.84 \pm 0.10\%$, and for MVR valve-related deaths was $0.96 \pm 0.06\%$ (Figs. 2 and 3).

Anticoagulant-related hemorrhage

Major bleeding events occurring after 30 days (as per the FDA document) occurred in 11 AVR patients (incidence $1.8\% / \text{pt-yr}$) and six MVR patients ($2.3\% / \text{pt-yr}$). These 17 events ($1.9\% / \text{pt-yr}$) are listed in Table V, along with the incidence of each event. It should be noted that five (30%) of the events were related to the surgical procedure. Freedom from major bleeding events is shown graphically over the five-year study period in Figure 4. Data indicating the INR at the time

Table IV: Summary of valve-related patient mortality.

Valve position	Time to death (days)	Cause of death
AVR	18	Prosthetic valve endocarditis
AVR + CABG	57	Multi-system organ failure, postoperative repair paravalvular leak
MVR + CABG	98	Neuroembolism
AVR	104	Bleeding event
AVR	1,315	Subarachnoid bleed
MVR	1,424	Neuroembolism
AVR	1,427	Prosthetic valve endocarditis

AVR: Aortic valve replacement; CABG: Coronary artery bypass grafting; MVR: Mitral valve replacement.

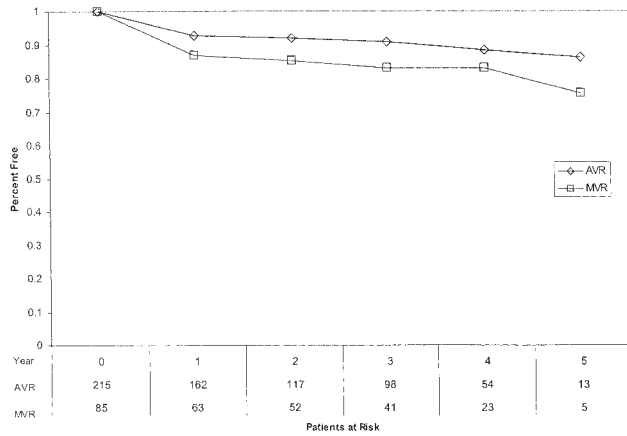


Figure 4: Kaplan-Meier actuarial freedom from anticoagulant-related hemorrhage in patients undergoing aortic valve replacement (AVR) or mitral valve replacement (MVR) with the ATS Medical mechanical valve prosthesis.

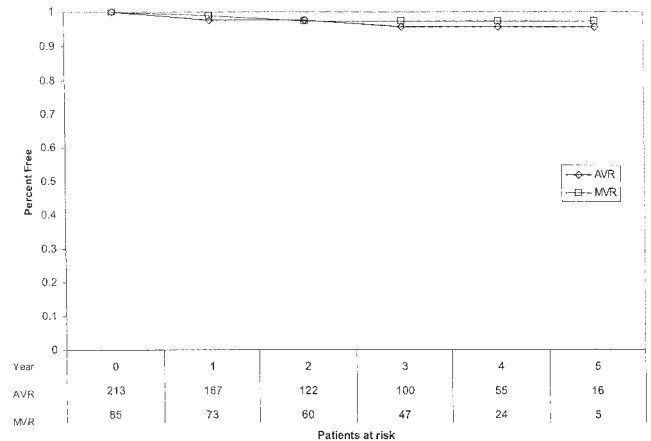


Figure 5: Kaplan-Meier freedom from permanent thromboembolic events in patients undergoing aortic valve replacement (AVR) or mitral valve replacement (MVR) with the ATS Medical mechanical valve prosthesis.

Table V: Linearized rates for valve-related complications: Late events occurring >30 days (postoperative) after hospital discharge.

Complication	AVR (n = 246)		MVR (n = 96)		Total (n = 342)	
	Events (n)	% / pt-yr	Events (n)	% / pt-yr	Events (n)	% / pt-yr
Total follow up (pt-yr)	613		265		878	
Major bleeding	11	1.8	6	2.3	17	1.9
Gastrointestinal bleed	8	1.3	2	0.8	10	1.1
Pericardial effusion	1	0.2	2	0.8	3	0.3
Subdural hematoma	1	0.2	0	0.0	1	0.1
Lower-leg hemorrhage	1	0.2	0	0.0	1	0.1
Retroperitoneal bleed	0	0.0	1	0.4	1	0.1
Postop. surgery site hematoma	0	0.0	1	0.4	1	0.1
Thromboembolic events	16	2.6	8	3.0	24	2.7
Transient neuroembolism	10	1.6	6	2.3	16	1.8
Major permanent neuroembolism	4	0.7	1	0.4	5	0.6
Transient peripheral emboli	2	0.3	1	0.4	3	0.3
Permanent peripheral emboli	0	0.0	0	0.0	0	0.0
Paravalvular leak	2	0.3	2	0.8	4	0.5
Major	1	0.2	0	0.0	1	0.1
Minor	1	0.2	2	0.8	3	0.3
Endocarditis	0	0.0	1	0.4	1	0.1
Prosthetic valve thrombosis	0	0.0	1	0.4	1	0.1

AVR: Aortic valve replacement with or without concomitant procedure(s); MVR: Mitral valve replacement with or without concomitant procedure(s).



Figure 6: Patient interpretation of level of valve sound disturbance after aortic valve replacement (AVR) or mitral valve replacement (MVR) with the ATS Medical mechanical valve prosthesis.

of these events were not available.

Valve thrombosis

One case of valve thrombosis was reported after MVR (0.04%) and none after AVR (0.00%).

Thromboembolism

A total of 24 thromboembolic events occurred, 16 after AVR (2.6% /pt-yr) and eight after MVR (3.0% /pt-yr), for a total incidence of 2.7% /pt-yr (Table V). It should be noted that transient neurological and peripheral events occurred in 12 of the 16 AVR patients, and in seven of the eight MVR patients, thus reducing the incidence of a permanent thromboembolic event to 0.7% /pt-yr for AVR, to 0.4% /pt-yr for MVR, and a total of 0.6% /pt-yr. Freedom from permanent thromboembolic events is shown graphically in Figure 5.

Paravalvular leak

In total, paravalvular leak occurred in four patients (0.5% /pt-yr), including 0.3% /pt-yr after AVR and 0.8% /pt-yr after MVR. Only one AVR patient required reoperation (0.2% /pt-yr), with the remainder showing asymptomatic echocardiographic findings (see Table V).

Endocarditis

At 30 days after surgery, prosthetic valve endocarditis occurred in only one patient (MVR, 0.4% /pt-yr), who required reoperation (see Table V).

Prosthetic valve dysfunction

There was no incidence of valve failure or dysfunction in 878 pt-yr of follow up.

Valve sounds

As part of the questionnaire, patients were asked to assess the level of sound disturbance produced by the implanted heart valve. Of those patients who responded, 84% could not hear the valve or were never bothered, 15% were occasionally bothered, and 1% constantly bothered by valve sounds (Fig. 6).

Discussion

This report, which is a continuation of the previous initial report (1), reveals ongoing excellent performance of the ATS mechanical prosthesis. The current follow up over the intermediate term indicates continued durability, a low incidence of valve-related events, and excellent hemodynamics. The patients' quality of life was also improved (see Fig. 6). Thromboembolism of major impact occurred at a rate of 0.6% per pt-yr, though two late deaths were related to neuroembolic events. This patient population is small and has been closely and continuously followed under FDA guidance, so that transient events which otherwise might have been missed were captured - hence the relatively high total thromboembolism rate of 2.7% per pt-yr, including transient episodes. Cross-checking of patient follow up data from previous reports also provided assurance that a minimum of events might be missed (1,2). Bleeding events were the most common serious complications, and the present authors - as do others - recommend low-level anticoagulation (5). The paucity of permanent thromboembolic events, however, indicates that the recommended INR could be further lowered, especially if patient risk factors are taken into

Table VI: Anticoagulation regimen after aortic valve replacement (AVR) and mitral valve replacement (MVR).

Risk factor	AVR	MVR
No major risk for TE	INR 1.8-2.5 Aspirin 81 mg	INR 2.0-3.0 Aspirin 81 mg
1-3 major risks for TE	INR 2.0-3.0 Aspirin 81 mg	INR 2.5-3.5 Aspirin 81 mg
Atrial fibrillation	INR 3.5-4.5 Aspirin 81 mg	INR 3.5-4.5 Aspirin 81 mg

INR: International Normalized Ratio; TE: Thromboembolism.

account. As thromboembolism and bleeding account for more than 75% of all complications related to valve replacement with a mechanical prosthesis, the INR target range and anticoagulant monitoring become paramount (6).

Patient-related risk factors are likely more important for valve-related events than the presence of a mechanical valve prosthesis per se (7). Emery et al. noted that 247 patients under the age of 50 years, and with no recorded risk factors, had a minimal event rate at follow up of up to 20 years (8). In fact, many pediatric patients in the absence of atrial fibrillation are managed at three months after surgery by using aspirin alone, without an increased risk of thromboembolism or valve thrombus (9). The results of a recent prospective randomized study have shown similar early valve-related event rates with three different bileaflet prosthetic heart valves (10). Butchart et al. recently defined non-traditional risk factors for valve-related events which included - but were not limited to - IgA antibodies to *Chlamydia pneumoniae*, previous cancer history, postoperative infection and Factor VII, despite a warfarin level >90 IU/dl, in addition to traditional risk factors such as atrial fibrillation, age, regional wall motion abnormalities, depressed ejection fraction and coronary disease which impact upon the incidence of events (11). These authors correlated thromboembolic events with the number of risk factors, and recommended increasing INR target levels with the increase in risk factors. This is in agreement with the present experience with the ATS and other mechanical valve prostheses, and is a very reasonable suggestion (1,12). The present authors' current recommendations (Table VI) to patients are more conservative than those of Butchart et al., but target a lower INR level than was recommended by the Ad Hoc Committee of the Working Group on Valvular Heart Disease, or that recommended by the Gelia 4 Database (13,14). Based on the findings of Stein et al., low-dose aspirin has been added to all patient anticoagulant regimens (15).

Improvements in the incidence of valve-related events have recently been shown to be due to an improved management of anticoagulant status rather than to improvements in the cardiac valve prosthesis.

Home anticoagulant monitoring, compared to office-monitored INR, lowers bleeding complications and maintains a higher percentage of patients within the target therapeutic range (16). Valve-related events occur most commonly when the INR varies from the therapeutic range (17). When the target INR was further lowered in the face of home monitoring, the thromboembolism rate was unchanged at 0.21%, yet anticoagulant-related hemorrhage rates decreased by half, from 0.91% in ESCAT I to 0.56% in the ESCAT II study of self-anticoagulation as conducted by Koertke

et al. (17). In order to further significantly reduce valve-related events, home monitoring should be recommended and taught to patients having valve replacement with a mechanical prosthesis. The cost of self-monitoring in valve replacement patients is specifically covered by American Medicare, and is less expensive than the cost of the higher rates of valve-related events in office-managed patients.

Currently, increasing attention is being paid to the sound produced by mechanical heart valves, and the impact that this sound has on a patient's quality of life. While controversy exists over the best way to measure valve sound, there is no doubt that valve sound is an issue for many patients. Past studies have shown a significant number of patients who indicated they were disturbed by the sound produced by their mechanical heart valve, or who wished that they could have a quieter valve (18,19). When compared to the St. Jude Medical (SJM) mechanical valve, these studies showed the ATS Medical valve to be significantly quieter and less bothersome to the patient than the SJM valve (19). In fact, in a recent study only 6% of the ATS Medical valve recipients reported that they can hear their valve all the time, compared to 46% of SJM patients (20). Only two patients (0.7%) stated that they were bothered continuously by their valve sound. The current study showed excellent results with regard to the level of sound reported by patients (see Fig. 6), and none of the patients felt that the sound of their valve interrupted their daily routine.

The aforementioned studies have also indicated complaints regarding other people's ability to hear the valve. Blome-Eberwien et al. reported that 14% of the ATS patients reported that their valve was loud enough to be heard by other people, compared to 86% of SJM valve recipients (18). This parameter was not assessed in the current study.

Study limitations

Limitations of the present study included a lack of patient randomization, and patient participation was voluntary and consecutive. While follow up was closely managed and the patient study surveys cross-checked, patient remembrance of events may have been at fault. The follow up period was short (up to five years), but the data were consistent with prior intermediate results obtained for the St. Jude Medical valve over a similar time frame, both by the present authors and by others (21).

In conclusion, the ATS Medical mechanical valve prosthesis continues to perform with minimal significant valve-related events and - to date - is proving to be durable. Due to differences in patient populations, investigators must be sure to compare like patient

groups, risk factors and anticoagulant regimens when investigating outcomes in patients with mechanical valve prostheses. Ongoing, longer follow up studies of the ATS valve are warranted.

Acknowledgements

These studies were supported in part by an educational grant from ATS Medical, Inc. to Cardiac Surgical Associates Research Foundation.

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