Appendix A. *(Continued)*

	19		9.0± 2.0	1.5± 0.3
	21		6.6± 2.9	1.7± 0.4
Cryolife	23		6.0± 2.3	2.3± 0.2
Stentless	25		6.1± 2.6	2.6± 0.2
	27		4.0± 2.4	2.8± 0.3
	21	39.0± 13		
Edwards Duromedics	23	32.0± 8.0		
Bileaflet	25	26.0± 10.0		
	27	24.0± 10.0		
	19		18.2± 5.3	1.2± 0.4
Edwards Mira	21		13.3± 4.3	1.6± 0.4
Bileaflet	23		14.7± 2.8	1.6± 0.6
	25		13.1± 3.8	1.9
	21	18.0± 6.0	12.0± 2.0	
Hancock	23	16.0± 2.0	11.0± 2.0	
Stented porcine	25	15.0± 3.0	10.0± 3.0	
	21		14.8± 4.1	1.3± 0.4
Hancock II	23	34.0± 13.0	16.6± 8.5	1.3± 0.4
Stented porcine	25	22.0± 5.3	10.8± 2.8	1.6± 0.4
	29	16.2± 1.5	8.2± 1.7	1.6± 0.2
	17-19		9.7± 4.2	4.2± 1.8
	19-21			5.4± 0.9
	20-21		7.9± 4.0	3.6± 2.0
	20-22		7.2± 3.0	3.5± 1.5
Homograft	22	1.7± 0.3		5.8± 3.2
Homograft valves	22-23		5.6± 3.1	2.6± 1.4
	22-24			5.6± 1.7
	24-27		6.2± 2.6	2.8± 1.1
	26	1.4± 0.6		6.8± 2.9
	25-28			6.2± 2.5
	19	40.4± 15.4	24.5± 9.3	
	21	40.9± 15.6	19.6± 8.1	1.6± 0.4
Intact	23	32.7± 9.6	19.0± 6.1	1.6± 0.4
Stented porcine	25	29.7± 15.0	17.7± 7.9	1.7± 0.3
	27	25.0± 7.6	15.0± 4.5	
	17	23.8± 3.4		0.9± 0.1
Ionescu-Shiley	19	19.7± 5.9	13.3± 3.9	1.1± 0.1
Stented bovine pericardial	21	26.6± 9.0		
	23		15.6± 4.4	
	19	18.6± 5.0	11.8± 3.3	1.2± 0.1
Labcor Santiago	21	17.5± 6.6	8.2± 4.5	1.3± 0.1
Stented bovine pericardial	23	14.8± 5.2	7.8± 2.9	1.8± 0.2
	25	12.3± 3.4	6.8± 2.0	2.1± 0.3
	21	24.3± 8.1	13.3± 4.2	1.1± 0.3
Labcor Synergy	23	27.3± 13.7	15.3± 6.9	1.4± 0.4
Stented porcine	25	22.5± 11.9	13.2± 6.4	1.5± 0.4
	27	17.8± 7.0	10.6± 4.6	1.8± 0.5
	19	21.3± 10.8	11.8± 3.4	1.5± 0.2
MCRI On-X	21	16.4± 5.9	9.9± 3.6	1.7± 0.4
Bileaflet	23	15.9± 6.4	8.6± 3.4	1.9± 0.6
	25	16.5± 10.2	6.9± 4.3	2.4± 0.6
	23		10.4± 3.1	2.2± 0.3
Medtronic Advantage	25		9.0± 3.7	2.8± 0.6
Bileaflet	27		7.6± 3.6	3.3± 0.7
	29		6.1± 3.8	3.9±0.7
	19		13.0± 3.9	
Medtronic Freestyle	21		9.1± 5.1	1.4± 0.3
Stentless	23	11.0± 4.0	8.1± 4.6	1.7± 0.5
	25		5.3± 3.1	2.1± 0.5
	27		4.6± 3.1	2.5± 0.1

Appendix A. *(Continued)*

Medtronic Hall *Single tilting disc*	20	34.4± 13.1	17.1± 5.3	1.2± 0.5
	21	26.9± 10.5	14.1± 5.9	1.1± 0.2
	23	26.9± 8.9	13.5± 4.8	1.4± 0.4
	25	17.1± 7.0	9.5± 4.3	1.5± 0.5
	27	18.9± 9.7	8.7± 5.6	1.9± 0.2
Medtronic Mosaic *Stented porcine*	21		14.2± 5.0	1.4± 0.4
	23	23.8± 11.0	13.7± 4.8	1.5± 0.4
	25	22.5± 10.0	11.7± 5.1	1.8± 0.5
	27		10.4± 4.3	1.9± 0.1
	29		11.1± 4.3	2.1± 0.2
Mitroflow *Stented bovine pericardial*	19	18.6± 5.3	13.1± 3.3	1.1± 0.2
	19		27.4± 8.8	
	21	27.5± 3.1	20.5± 6.2	
Monostrut Bjork-Shiley *Single tilting disc*	23	20.3± 0.7	17.4± 6.4	
	25		16.1± 4.9	
	27		11.4± 3.8	
Prima *Stentless*	21	28.8± 6.0	13.7± 1.9	1.4± 0.7
	23	21.5± 7.5	11.5± 4.9	1.5± 0.3
	25	22.1± 12.5	11.6± 7.2	1.8± 0.5
Omnicarbon *Single tilting disc*	21	37.4± 12.8	20.4± 5.4	1.3± 0.5
	23	28.8± 9.1	17.4± 4.9	1.5± 0.3
	25	23.7± 8.1	13.2± 4.6	1.9± 0.5
	27	20.1± 4.2	12.4± 2.9	2.1± 0.4
Omniscience *Single tilting disc*	21	50.8± 2.8	28.2± 2.2	0.9± 0.1
	23	39.8± 8.7	20.1± 5.1	1.0± 0.1
	23	32.6± 12.8	22.0± 9.0	1.1± 0.2
Starr Edwards *Caged ball*	24	34.1± 10.3	22.1± 7.5	1.1± 0.3
	26	31.8± 9.0	19.7± 6.1	
	27	30.8± 6.3	18.5± 3.7	
	29	29.0± 9.3	16.3± 5.5	
Sorin Bicarbon *Bileaflet*	19	30.1± 4.5	16.7± 2.0	1.4± 0.1
	21	22.0± 7.1	10.0± 3.3	1.2± 0.4
	23	16.8± 6.1	7.7± 3.3	1.5± 0.2
	25	11.2± 3.1	5.6± 1.6	2.4± 0.3
Sorin Pericarbon *Stentless*	19	36.5± 9.0	28.9± 7.3	1.2± 0.5
	21	28.0± 13.3	23.8± 11.1	1.3± 0.6
	23	27.5± 11.5	23.2± 7.6	1.5± 0.5
St. Jude Medical Haem Plus *Bileaflet*	19	28.5± 10.7	17.0± 7.8	1.9± 0.1
	21	16.3± 17.0	10.6± 5.1)	1.8± 0.5
	23	16.8± 7.3	12.1± 4.2	1.7± 0.5
St Jude Medical Regent *Bileaflet*	19	20.6± 12	11.0± 4.9	1.6± 0.4
	21	15.6± 9.4	8.0± 4.8	2.0± 0.7
	23	12.8± 6.8	6.9± 3.5	2.3± 0.9
	25	11.7± 6.8	5.6± 3.2	2.5± 0.8
	27	7.9± 5.5	3.5± 1.7	3.6± 0.5
St Jude Medical Standard *Bileaflet*	19	42.0± 10.0	24.5± 5.8	1.5± 0.1
	21	25.7± 9.5	15.2± 5.0	1.4± 0.4
	23	21.8± 7.5	13.4± 5.6	1.6± 0.4
	25	18.9± 7.3	11.0± 5.3	1.9± 0.5
	27	13.7± 4.2	8.4± 3.4	2.5± 0.4
	29	13.5± 5.8	7.0± 1.7	2.8± 0.5
St Jude Medical *Stentless*	21	22.6± 14.5	10.7± 7.2	1.3± 0.6
	23	16.2± 9.0	8.2± 4.7	1.6± 0.6
	25	12.7± 8.2	6.3± 4.1	1.8± 0.5
	27	10.1± 5.8	5.0± 2.9	2.0± 0.3
	29	7.7± 4.4	4.1± 2.4	2.4± 0.6

*Modified from Rajani et al.[126]

Appendix B. Normal Doppler Echocardiography Values for Prosthetic Mitral Valves*

Valve	Size	Peak gradient (mm Hg)	Mean gradient (mm Hg)	Peak velocity (m/s)	Pressure half-time (ms)	Effective orifice area (cm^2)
Biocor *Stentless bioprosthesis*	27	13 ± 1				
	29	14 ± 2.5				
	31	11.5 ± 0.5				
	33	12 ± 0.5				
Bioflo pericardial *Stented bioprosthesis*	25	10 ± 2	6.3 ± 1.5			2 ± 0.1
	27	9.5 ± 2.6	5.4 ± 1.2			2 ± 0.3
	29	5 ± 2.8	3.6 ± 1			2.4 ± 0.2
	31	4.0	2.0			2.3
Bjork-Shiley *Tilting disc*	23			1.7	115	
	25	12 ± 4	6 ±2	1.75 ± 0.38	99 ± 27	1.72 ± 0.6
	27	10 ± 4	5 ±2	1.6 ± 0.49	89 ± 28	1.81 ± 0.54
	29	7.83 ± 2.93	2.83 ± 1.27	1.37 ± 0.25	79 ± 17	2.1 ± 0.43
	31	6 ±3	2 ± 1.9	1.41 ± 0.26	70 ± 14	2.2 ± 0.3
Bjork-Shiley monostrut *Tilting disc*	23		5.0	1.9		
	25	13 ± 2.5	5.57 ± 2.3	1.8 ± 0.3		
	27	12 ± 2.5	4.53 ± 2.2	1.7 ±0.4		
	29	13 ± 3	4.26 ± 1.6	1.6 ± 0.3		
	31	14 ± 4.5	4.9 ± 1.6	1.7 ± 0.3		
Carbomedics *Bileaflet*	23			1.9 ± 0.1	126 ± 7	
	25	10.3 ± 2.3	3.6 ± 0.6	1.3 ± 0.1	93 ± 8	2.9 ± 0.8
	27	8.79 ± 3.46	3.46 ± 1.03	1.61 ± 0.3	89 ± 20	2.9 ± 0.75
	29	8.78 ± 2.9	3.39 ± 0.97	1.52 ± 0.3	88 ± 17	2.3 ± 0.4
	31	8.87 ± 2.34	3.32 ± 0.87	1.61 ± 0.29	92 ± 24	2.8 ± 1.14
	33	8.8 ± 2.2	4.8 ± 2.5	1.5 ± 0.2	93 ± 12	
Carpentier- Edwards *Stented bioprosthesis*	27		6 ±2	1.7 ± 0.3	98 ± 28	
	29		4.7 ± 2	1.76 ± 0.27	92 ±14	
	31		4.4 ± 2	1.54 ± 0.15	92 ± 19	
	33		6 ±3		93 ± 12	
Carpentier- Edwards pericardial *Stented Bioprosthesis*	27		3.6	1.6	100	
	29		5.25 ± 2.36	1.67 ± 0.3	110 ± 15	
	31		4.05 ± 0.83	1.53 ± 0.1	90 ± 11	
	33		1.0	0.8	80	
Duromedics *Bileaflet*	27	13 ± 6	5 ± 3	1.61 ± 0.4	75 ± 12	
	29	10 ± 4	3 ± 1	1.40 ± 0.25	85 ± 22	
	31	10.5 ± 4.33	3.3 ± 1.36	1.38 ± 0.27	81 ± 12	
	33	11.2	2.5		85	
Hancock I or not specified *Stented bioprosthesis*	27	10 ± 4	5 ± 2			1.3 ± 0.8
	29	7 ± 3	2.46 ± 0.79		115 ± 20	1.5 ± 0.2
	31	4 ± 0.86	4.86 ± 1.69		95 ± 17	1.6 ± 0.2
	33	3 ± 2	3.87 ± 2		90 ± 12	1.9 ± 0.2
Hancock II *Stented bioprosthesis*	27					2.21 ± 0.14
	29					2.77 ± 0.11
	31					2.84 ± 0.1
	33					3.15 ± 0.22
Hancock pericardial *Stented bioprosthesis*	29		2.61 ± 1.39	1.42 ± 0.14	105 ± 36	
	31		3.57 ± 1.02	1.51 ± 0.27	81 ± 23	
Ionescu-Shiley *Stented bioprosthesis*	25		4.87 ± 1.08	1.43 ± 0.15	93 ± 11	
	27		3.21 ± 0.82	1.31 ± 0.24	100 ± 28	
	29		3.22 ± 0.57	1.38 ± 0.2	85 ± 8	
	31		3.63 ± 0.9	1.45 ± 0.06	100 ± 36	

Appendix B. *(Continued)*

Ionescu-Shiley low profile	29		3.31 ± 0.96	1.36 ± 0.25	80 ± 30	
Stented bioprosthesis	31		2.74 ± 0.37	1.33 ± 0.14	79 ± 15	
Labcor-Santiago	25	8.7	4.5		97	2.2
pericardial	27	5.6 ± 2.3	2.8 ± 1.5		85 ± 18	2.12 ± 0.48
Stented bioprosthesis	29	6.2 ± 2.1	3 ± 1.3		80 ± 34	2.11 ± 0.73
	18			1.7	140	
Lillehei- Kaster	20			1.7	67	
Tilting disc	22			1.56 ± 0.09	94 ± 22	
	25			1.38 ± 0.27	124 ± 46	
	27			1.4	78	
Medtronic- Hall	29			1.57 ± 0.1	69 ± 15	
Tilting disc	31			1.45 ± 0.12	77 ± 17	
	29		3.5 ± 0.51	1.6 ± 0.22		
Medtronic Intact Porcine	31		4.2 ± 1.44	1.6 ± 0.26		
Stented bioprosthesis	33		4 ± 1.3	1.4 ± 0.24		
	35		3.2 ± 1.77	1.3 ± 0.5		
	25		6.9	2.0	90	
Mitroflow	27		3.07 ± 0.91	1.5	90 ± 20	
Stented bioprosthesis	29		3.5 ± 1.65	1.43 ± 0.29	102 ± 21	
	31		3.85 ± 0.81	1.32 ± 0.26	91 ± 22	
	23		8.0			
	25		6.05 ± 1.81	1.77 ± 0.24	102 ± 16	
Omnicarbon	27		4.89 ± 2.05	1.63 ± 0.36	105 ± 33	
Tilting disc	29		4.93 ± 2.16	1.56 ± 0.27	120 ± 40	
	31		4.18 ± 1.4	1.3 ± 0.23	134 ± 31	
	33		4 ±2			
	25	11.5 ± 3.2	5.3 ± 2.1			1.9 ± 1.1
On-X	27-29	10.3 ± 4.5	4.5 ± 1.6			2.2 ± 0.5
Bileaflet	31-33	9.8 ± 3.8	4.8 ± 2.4			2.5 ± 1.1
	25	15 ± 3	5 ± 1	2 ± 0.2	105 ± 29	2.2 ± 0.6
Sorin Allcarbon	27	13 ± 2	4 ±1	1.8 ± 0.1	89 ± 14	2.5 ± 0.5
Tilting disc	29	10 ± 2	4 ±1	1.6 ± 0.2	85 ± 23	2.8 ± 0.7
	31	9 ±1	4 ±1	1.6 ± 0.1	88 ± 27	2.8 ± 0.9
	25	15 ± 0.25	4 ± 0.5	1.95 ± 0.02	70 ± 1	
Sorin Bicarbon	27	11 ± 2.75	4 ± 0.5	1.65 ± 0.21	82 ± 20	
Bileaflet	29	12 ± 3	4 ± 1.25	1.73 ± 0.22	80 ± 14	
	31	10 ± 1.5	4 ± 1	1.66 ± 0.11	83 ± 14	
	23		4.0	1.5	160	1.0
	25		2.5 ± 1	1.34 ± 1.12	75 ± 4	1.35 ± 0.17
St Jude Medical	27	11 ± 4	5 ± 1.82	1.61 ± 0.29	75 ± 10	1.67 ± 0.17
Bileaflet	29	10 ± 3	4.15 ± 1.8	1.57 ± 0.29	85 ± 10	1.75 ± 0.24
	31	12 ± 6	4.46 ± 2.22	1.59 ± 0.33	74 ± 13	2.03 ± 0.32
	26		10.0			1.4
	28		7 ± 2.75			1.9 ± 0.57
Starr- Edwards	30	12.2 ± 4.6	6.99 ± 2.5	1.7 ± 0.3	125 ± 25	1.65 ± 0.4
Caged ball	32	11.5 ± 4.2	5.08 ± 2.5	1.7 ± 0.3	110 ± 25	1.98 ± 0.4
	34		5.0			2.6
Stentless quadrileaflet	26		2.2 ± 1.7	1.6	103 ± 31	1.7
bovine pericardial	28			1.58 ± 0.25		1.7 ± 0.6
Stentless bioprosthesis	30			1.42 ± 0.32		2.3 ± 0.4
Wessex	29		3.69 ± 0.61	1.66 ± 0.17	83 ± 19	
Stented bioprosthesis	31		3.31 ± 0.83	1.41 ± 0.25	80 ± 21	

*modified from Rosenhek, et al. [139]

Circ J 2008; **72:** 1265–1269

Clinical Implication of Energy Loss Coefficient in Patients With Severe Aortic Stenosis Diagnosed by Doppler Echocardiography

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Background The Doppler-derived energy loss coefficient (ELCo), which can take into account the pressure recovery phenomenon and reconcile discrepancies between the aortic valve effective orifice area (EOA) obtained by the Gorlin formula using a catheter (EOA_{cath}) and the EOA obtained by the Doppler continuity equation (EOA_{Dop}), is proposed as an equivalent index to represent EOA_{cath}. Therefore, the purpose of this study was to evaluate the clinical impact of ELCo in patients with severe aortic stenosis (AS).

Methods and Results Thirty-three patients with severe AS were assessed by Doppler examination [EOA obtained by the continuity equation (EOA_{Dop}) ≤1.0 cm^2], and referred to the cardiac catheterization laboratory for evaluation of EOA obtained by the Gorlin formula (EOA_{cath}). Patients with ELCo ≤1.0 cm^2 (n=26) had significantly lower incidence of symptoms related to AS compared with those having ELCo >1.0 cm^2 (n=7) (p=0.002). Superior concordance in severity of AS was demonstrated between EOA_{cath} and ELCo compared with EOA_{cath} and EOA_{Dop} (κ=0.52, and κ=0.32, respectively).

Conclusions In 21% of patients with "severe" AS diagnosed by Doppler echocardiography, the ELCo value indicated moderate rather than severe AS. These patients had significantly lower incidence of symptoms compared with patients who had ELCo ≤1.0 cm^2. (*Circ J* 2008; **72:** 1265–1269)

Key Words: Catheterization; Diagnosis; Echocardiography; Valvular diseases

According to the American College of Cardiology/American Heart Association (ACC/AHA) recommendations, the aortic valve effective orifice area (EOA) can be used to grade aortic stenosis (AS) as severe at ≤1.0 cm^2.[1] In the clinical situation, the EOA is routinely obtained by using either the Gorlin formula (EOA_{cath}) during cardiac catheterization or the continuity equation (EOA_{Dop}) during Doppler echocardiography[2–5] However, discrepancies between EOA_{cath} and EOA_{Dop} in the grading of the severity of AS, mainly because of the pressure recovery phenomenon, are sometimes observed. The concept of the pressure recovery phenomenon is based on fluid mechanics theory: increased static pressure downstream of the stenosis because of reconversion of kinetic energy into potential energy[6–8] Recently, the Doppler-derived energy loss coefficient (ELCo), which can take into account the pressure recovery phenomenon and reconcile discrepancies between EOA_{cath} and EOA_{Dop}, was proposed as an equivalent index to represent EOA_{cath}[9,10] However, the impact of using ELCo in patients with AS has not been clarified, so the purpose of this study was to evaluate the clinical use of ELCo in patients with severe AS.

(Received January 21, 2008; revised manuscript received April 1, 2008; accepted April 9, 2008)

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Methods

Patients

We enrolled a total of 33 patients (mean age 71±8 years; females 20, males 13) with severe AS by Doppler examination (EOA_{Dop} ≤1.0 cm^2), who were referred to the cardiac catheterization laboratory for evaluation of AS. Critical AS is considered to be present when EOA or ELCo is <0.75 cm^2, severe AS when EOA or ELCo is 0.75–1.0 cm^2, and moderate AS when EOA or ELCo is >1.0 cm^2. All patients were in sinus rhythm. We excluded patients with atrial fibrillation, other moderate to severe valvular heart diseases, dialysis and systolic left ventricular (LV) dysfunction (LV ejection fraction <40%). The study protocol was approved by the Ethics Committee of Kawasaki Medical School, and written informed consent was given by all patients.

Table 1 Patients' Characteristics

	Group A (n=26)	*Group B (n=7)*	*p value*
Age (years)	*71±8*	*69±6*	*0.455*
Female sex, n (%)	*15 (58)*	*5 (71)*	*0.419*
Body surface area (m^2)	*1.49±0.18*	*1.42±0.03*	*0.297*
Hypertension (%)	*9 (35)*	*4 (57)*	*0.281*
Diabetes mellitus (%)	*6 (23)*	*1 (14)*	*0.531*
Hyperlipidemia (%)	*6 (23)*	*1 (14)*	*0.531*
Smoking (%)	*2 (8)*	*0 (0)*	*0.616*
Symptoms (dyspnea/angina pectoris/syncope), n (%)	*21 (81)*	*1 (14)*	*0.002*

Table 2 Hemodynamic and Echocardiographic Data

	Group A (n=26)	Group B (n=7)	p value
Hemodynamic data			
LV maximum pressure (mmHg)	197±34	191±25	0.659
LV end-diastolic pressure (mmHg)	20±6	19±5	0.698
Ascending aorta maximum pressure (mmHg)	140±25	161±31	0.061
Ascending aorta minimum pressure (mmHg)	65±12	66±13	0.836
Cardiac index ($L \cdot min^{-1} \cdot m^{-2}$)	3.0±0.9	3.8±1.3	0.107
Pulmonary capillary wedge pressure (mmHg)	13±6	12±3	0.804
Pulmonary artery maximum pressure (mmHg)	32±12	33±9	0.915
Pulmonary artery minimum pressure (mmHg)	15±7	14±3	0.815
Echocardiographic data			
LV diastolic dimension (mm)	44±6	42±6	0.628
LV systolic dimension (mm)	28±7	27±6	0.888
LV mass index (g/m^2)	195±73	180±51	0.626
LV ejection fraction (%)	64±9	61±8	0.445
Aortic cross-sectional area (mm^2)	58±15	55±8	0.631

LV, left ventricular.

Table 3 Comparison of Medications

	Group A (n=26)	Group B (n=7)	p value
ACE-inhibitors	1 (4%)	0 (0%)	0.787
AT1-receptor antagonists	5 (19%)	2 (29%)	0.469
Calcium-channel blockers	7 (27%)	2 (29%)	0.635
α-blockers	1 (4%)	0 (0%)	0.789
β-blockers	0 (0%)	0 (0%)	1.000
Statins	9 (35%)	1 (14%)	0.294

ACE, angiotensin-converting enzyme; AT1, angiotensin II type I.

Table 4 Severity of Aortic Stenosis

	Group A (n=26)	Group B (n=7)	p value
Hemodynamic data			
EOA_{cath} (cm^2)	0.70±0.19	1.13±0.32	<0.001
Peak-to-peak gradient (mmHg)	57±29	27±15	0.019
Echocardiographic data			
EOA_{Dop} (cm^2)	0.63±0.13	0.92±0.05	<0.001
ELCo (cm^2)	0.72±0.16	1.11±0.07	<0.001
Maximum transvalvular aortic gradient (mmHg)	85±21	52±25	0.003

EOA_{cath}, catheter-derived effective orifice area; EOA_{Dop}, Doppler-derived effective orifice area; ELCo, energy loss coefficient.

Cardiac Catheterization

Cardiac catheterization was performed within 10 days of an echocardiographic examination by 2 experienced cardiologists who were unaware of the echocardiographic data. A standard procedure of catheterization was performed via the femoral approach in all patients, including coronary angiography and pressure measurements. The left ventricle could be reached by retrograde advancement of a 5Fr fluid-filled pigtail side-hole catheter. When direct crossing of the aortic valve was not possible with the pigtail catheter, a right Judkins catheter was used to cross the valve. After recording the LV pressure, the catheter was pulled back into the ascending aorta. The peak-to-peak gradient was measured as: LV maximum pressure−ascending aorta maximum pressure, and the EOA_{cath} was determined according to the Gorlin formula, using 44.3 as the coefficient[2] A 6Fr Swan-Ganz catheter was positioned in the pulmonary arteries. Cardiac output was measured by thermodilution, and the pulmonary capillary wedge pressure was also measured.

Echocardiography

All echocardiographic procedures were performed by 3 experienced cardiologists and 2 sonographers. The transvalvular gradients were measured using a continuous wave Doppler technique, and the EOA_{Dop} was computed with the continuity equation, by measuring the area of the LV outflow tract, and the velocity−time integral in the outflow tract and in the vena contracta[4,5] The diameters of the tubular ascending aorta were recorded in the parasternal long-axis view. In order to correct the EOA for the pressure recovery phenomenon, the ELCo equation was used as previously reported: ELCo = (EOA_{Dop} × aortic cross-sectional area)/(aortic cross-sectional area − EOA_{Dop})[9-11] Study patients were grouped according to the ELCo value: Group A (26 patients with ELCo ≤1.0 cm^2) and Group B (7 patients with ELCo >1.0 cm^2). Symptoms related to AS (chest pain, syncope, and dyspnea), hemodynamic and echocardiographic data were compared between the 2 groups.

Statistical Methods

Continuous variables are reported as mean±SD. Unpaired Student's t-test was used to differentiate between 2 sets of data with normal distribution. If normality tests failed, the Mann-Whitney U-test was used. Comparison of the incidence of symptoms and coronary risk factors was performed using Fisher's exact test. Comparison of each parameter was made using linear regression and the Bland-Altman test[12] Agreement in the assessment of severity of AS between EOA_{cath}, EOA_{Dop}, and ELCo was quantified by the κ test of concordance[13] A p-value <0.05 was considered statistically significant.

Results

Table 1 shows the characteristics of the 2 groups; age, gender, and coronary risk factors were similar. Patients in Group B had a significantly lower incidence of symptoms related to AS compared with Group A (p=0.002). The results of hemodynamic and echocardiographic investigtions are summarized in Table 2. There was no significant difference between the 2 groups for medications (Table 3). Table 4 shows the severity of AS assessed by both cardiac catheterization and echocardiography. As expected, EOA was significantly smaller and the pressure gradient was significantly

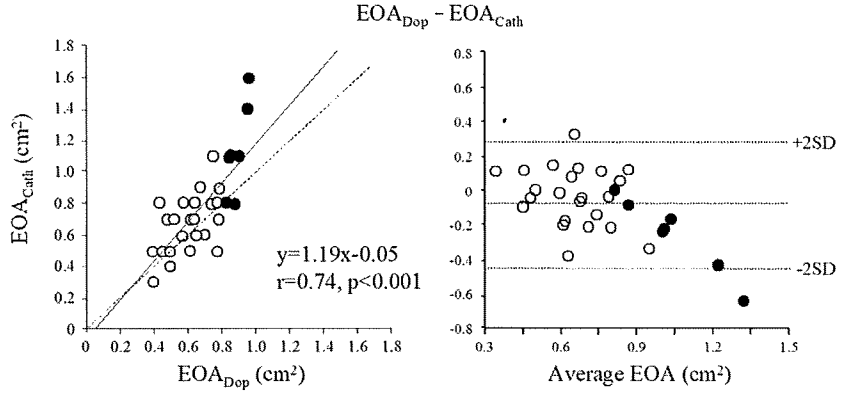

Fig 1. Comparison of the effective orifice area (EOA) measured by a catheter (EOA_{cath}) vs EOA measured by Doppler echocardiography (EOA_{Dop}) (Left) and the Bland-Altman test for EOA_{cath} vs EOA_{Dop} (Right). (●) Patients with ELCo >1.0 cm².

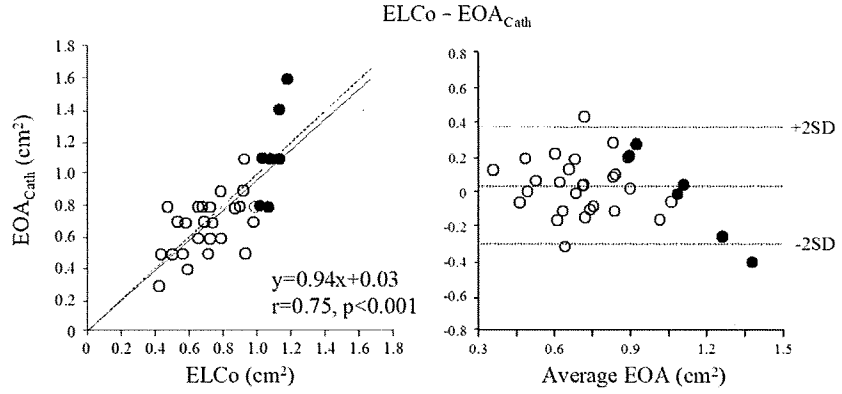

Fig 2. Comparison of the effective orifice area (EOA) measured by a catheter (EOA_{cath}) vs energy loss coefficient (ELCo) (Left) and the Bland-Altman test for EOA_{cath} vs ELCo (Right). (○) Patients with ELCo ≤1.0 cm², (●) patients with ELCo >1.0 cm².

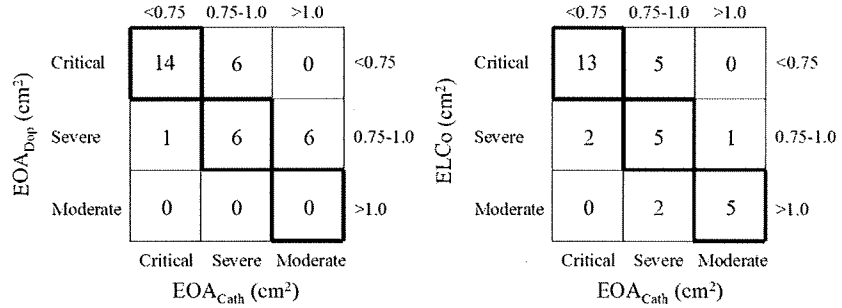

Fig 3. Matrix showing overall severity agreement between effective orifice area (EOA) measured by catheter (EOA_{cath}) and EOA measured by Doppler echocardiography (EOA_{Dop}) (Left), and EOA_{cath} and the energy loss coefficient (ELCo) (Right). Critical aortic stenosis is considered present when EOA or ELCo is <0.75 cm², severe aortic stenosis when EOA or ELCo is 0.75–1.0 cm², and moderate aortic stenosis when EOA or ELCo is >1.0 cm².

greater in Group A than in Group B. There was a significant correlation between EOA_{Dop} and EOA_{cath}, and the Bland-Altman test showed good agreement between EOA_{Dop} and EOA_{cath} (mean difference, 0.08±0.19 cm²) (Fig 1). Six of the 33 patients (18%) had EOA_{cath} >1.0 cm². There was a significant correlation between EOA_{cath} and ELCo, and the Bland-Altman test showed good agreement between EOA_{cath} and ELCo (mean difference: 0.02±0.18 cm²) (Fig 2). There was a better 1-to-1 correspondence between EOA_{cath} and ELCo than between EOA_{Dop} and EOA_{cath} (y=0.94x+0.03 and y=1.19x–0.05, respectively). Seven of the 33 patients (21%) had ELCo >1.0 cm². Superior concordance was demonstrated between EOA_{cath} and ELCo compared with EOA_{cath} and EOA_{Dop} (κ=0.52, and κ=0.32, respectively) (Fig 3).

Discussion

In this study, 6 of 33 patients (18%) with "severe" AS by EOA_{Dop} had EOA_{cath} >1.0 cm², which was classified as moderate AS by the ACC/AHA guidelines. This discrepancy between EOA_{cath} and EOA_{Dop} is thought to be related to the pressure recovery phenomenon[6–8] ELCo, which can take into account the pressure recovery phenomenon, is proposed as an equivalent index representing EOA_{cath}, and in this study patients with ELCo >1.0 cm² (21%) had a significantly lower incidence of symptoms related to AS and a lower transvalvular aortic gradient. To the best of our knowledge, this is the first evaluation of the clinical impact of ELCo in patients with "severe" AS diagnosed by the continuity equation.

The ACC/AHA guidelines for defining AS severity are mainly based on data obtained from catheter measurements, as well as clinical outcomes in relation to those measurements[1,14–16] The same value for severe AS (<1.0 cm²) was extended to echocardiographic data on the assumption that EOA_{Dop} and EOA_{cath} were equivalent parameters, and the aforementioned guidelines do not distinguish between catheter and Doppler measurements. However, it has been reported that discrepancies of up to 20% between EOA_{Dop}

and EOA_{cath} can occur, depending on the pressure recovery phenomenon[9,10] Therefore, measurements made from EOA_{Dop} might result in overestimations of the severity of AS compared with EOA_{cath}, affecting clinical management. On the other hand, there is a strong linear correlation between ELCo and EOA_{cath} compared between EOA_{Dop} and EOA_{cath}. ELCo might be a more exact assessment of AS severity than EOA_{Dop}. In addition, ELCo can be calculated non-invasively from the echocardiogram. Therefore, ELCo might be more appropriate for quantifying AS severity.

The ratio of EOA to the ascending aorta cross-sectional area is a major determinant of the pressure recovery phenomenon![7-19] For example, patients with EOA_{Dop} of 0.9 cm^2 and ascending aorta diameter <3.39 cm would have an ELCo >1 cm^2, shifting the patient's severity from severe to moderate. Similarly, a patient with EOA_{Dop} of 0.8 cm^2 and ascending aorta diameter <2.26 cm would have an ELCo >1 cm^2. Therefore, in patients with severe AS who have EOA_{Dop} of approximately 1.0 cm^2, the evaluation of ELCo, taking into account pressure recovery, is necessary for the assessment of AS severity.

Kadem et al[20] determined the effect of systemic arterial hypertension, induced by banding the distal thoracic aorta in 14 pigs, on the indices of AS severity, including ELCo. They reported that the changes in systemic arterial hemodynamic properties associated with systemic hypertension could cause a decrease in the mean flow rate and thus an increase in ELCo. In the present study, the ascending aorta maximum pressure was greater in Group B than in Group A, although the difference was not statistically significant, but may have affected the ELCo value in this study. On the other hand, hypotension associated with LV dysfunction could cause a decrease in ELCo. Measuring AS severity by calculating ELCo is recommended/should be performed when the patient is normotensive.

Study Limitations

Pressure recovery was not directly measured by invasive technique and usage of standard protocols meant that distal pressure measurements were not obtained at sites where pressure had recovered to the fullest extent. Theoretically, the distance required for full pressure recovery depends on the orifice size and aortic diameter[6,7] However, previous in vitro studies have shown that most pressure recovery occurs within several centimeters and that differences between wall measurements at 5 cm and central measurements at 10–20 cm downstream from the stenosis are small and clinically irrelevant![8,21-23] The distance for the occurrence of pressure recovery increases with the diameter of the aorta, whereas a large diameter aorta precludes clinically significant pressure recovery. In addition, clinical study suggests that all measurable increase of pressure occurs within the ascending aorta![24,25] Therefore, the measurement technique used in this study should reflect pressure recovery to a great extent.

Our study has the inherent limitations of any small, observational series and further large-scale studies are needed to reveal the clinical implications of using ELCo in patients with AS.

Conclusions

In 21% of patients with "severe" AS diagnosed by Doppler echocardiography, the ELCo value indicated moderate rather than severe AS (>1.0 cm^2). These patients had a significantly lower incidence of symptoms related to AS than patients who had ELCo ≤1.0 cm^2. ELCo, which can be calculated non-invasively from the echocardiogram, might be a useful measure for quantifying the severity of AS.

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C-Reactive protein predicts severity, progression, and prognosis of asymptomatic aortic valve stenosis

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Background C-Reactive protein (CRP) has been shown to play a pivotal role in the pathogenesis of atherosclerosis progression. The aim of this study was to assess whether CRP predicts severity, progression, and prognosis of aortic valve stenosis (AS).

Methods One hundred and thirty-five patients with asymptomatic AS were studied. Patients were diagnosed as mild (n = 18, aortic valve area [AVA] $\geq$1.5 cm^2), moderate (n = 57, AVA 1.0-1.49 cm^2), or severe AS (n = 60, AVA <1.0 cm^2) by Doppler echocardiography. Patients with serial (baseline and at 1 year) echocardiographic examination (n = 47) were grouped as either slow (n = 22, ΔAVA <–0.15 cm^2/y) or rapid progression group (n = 25, ΔAVA $\geq$–0.15 cm^2/y). In addition, long-term prognosis was compared between patients with low CRP (n = 68, CRP <0.15 mg/dL) and those with high CRP (n = 67, CRP $\geq$0.15 mg/dL).

Results Baseline CRP was significantly higher in patients with severe AS than in those with mild or moderate AS (mild AS 0.17 ± 0.43, moderate AS 0.22 ± 0.28, severe AS 0.53 ± 0.66 mg/dL, P = .001). By multivariate logistic regression analysis, CRP was an independent predictor of severe AS (odds ratio 3.51, P = .015). Similarly, CRP was significantly higher in the rapid progression group than in the slow progression group (0.56 ± 0.76 vs 0.19 ± 0.25 mg/dL, P = .004). Furthermore, long-term survival was significantly lower in the high CRP group than in the low CRP group (log rank: P < .001).

Conclusion C-Reactive protein predicts severity, progression, and prognosis in patients with asymptomatic AS. (Am Heart J 2008;156:713-8.)

In adults older than 65 years, aortic valve stenosis (AS) is seen at a rate of 2% to 3%.[1,2] Aortic valve disease is still the leading cause of cardiac valve replacement in developed countries.[3] Although several investigators have suggested possible predictors of AS, the exact mechanisms of AS remain unclear.

Inflammation is an important etiologic factor of cardiovascular disease.[4] C-Reactive protein (CRP) has been reported as an independent predictor of the atherosclerosis progression. Increased CRP has also been reported in patients with degenerative AS, suggesting that inflammation may play a pathogenic role in AS.[5-7] However, the relationship between CRP and severity of AS is unclear. Although CRP may be related to progression of AS, its impact on mortality has not been investigated. The aim of this study was to assess whether CRP predicts severity, progression, and prognosis of AS.

Methods

The present study included 135 patients who were suspected AS for cardiac murmur and/or echocardiographic routine assessment to our hospital between January 2004 and March 2006. Patients with bicuspid aortic valves (n = 17), history of ischemic heart disease (IHD, n = 18), systemic inflammatory disease (n = 12), hemodialysis (n = 18), and rheumatic valve disease (n = 2) were excluded.

Echocardiographic assessment was carried out with a Sonos 5500 system (Philips Medical Systems, Bothell, WA) using standardized imaging techniques. The peak velocity across the valve was measured with continuous-wave Doppler from whichever window gave the greatest velocity signal. Aortic valve area (AVA) was calculated by the continuity equation.[8,9] Study patients were diagnosed as mild AS (AVA $\geq$1.5 cm^2), moderate AS (AVA 1.0-1.49 cm^2), and severe AS (AVA <1.0 cm^2). And 47 (35%) of 135 patients who underwent repeat echocardiographic assessment at 1 year later were grouped as slow progression group (n = 22, a decrease in AVA <0.15 cm^2/y) and rapid progression group (n = 25, a decrease in AVA $\geq$0.15 cm^2). The cut-off of AVA value to separate between rapid and slow progression of AS was defined based on the average from previous reports.[10-12]

In addition, study patients were divided into 2 groups based on baseline median of CRP value in this study: low CRP group

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This report was presented in part at the European Society of Cardiology Congress 2008, Munich, Germany.
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doi:10.1016/j.ahj.2008.04.011

Table I. Clinical characteristics and biochemical findings among the 3 study groups

	Mild AS (n = 18)	Moderate AS (n = 57)	Severe AS (n = 60)	P value
Age (y)	71 ± 10	77 ± 9	78 ± 8	.019
Male sex, n (%)	7 (39)	22 (39)	19 (29)	.700
Hypertension, n (%)	8 (44)	20 (35)	23 (38)	.769
Hyperlipidemia, n (%)	1 (6)	19 (33)	17 (28)	.069
Diabetes mellitus, n (%)	1 (6)	8 (14)	10 (17)	.493
Smoking, n (%)	4 (22)	12 (21)	12 (20)	.977
Total cholesterol (mg/dL)	179 ± 38	184 ± 39	180 ± 40	.910
LDL Cholesterol (mg/dL)	124 ± 15	122 ± 28	121 ± 28	.821
CRP (mg/dL)	0.17 ± 0.43	0.22 ± 0.28	0.53 ± 0.66	.001
Medications				
Statin, n (%)	1 (6)	12 (21)	11 (18)	.321
ACE Inhibitor/ AT1 receptor antagonist, n (%)	3 (17)	18 (32)	18 (30)	.429
β-Blocker, n (%)	3 (17)	2 (4)	1 (2)	.068
Calcium blocker, n (%)	7 (39)	13 (23)	16 (27)	.423
Creatinine (mg/dL)	0.87 ± 0.42	0.86 ± 0.32	0.84 ± 0.26	.906
BMI (%)	22.6 ± 3.7	22.0 ± 3.3	21.6 ± 3.3	.543

LDL, Low-density lipoprotein; *AT1*, angiotensin II type 1; *ACE*, angiotensin-converting enzyme; *BMI*, body mass index.

(n = 68, CRP >0.15 mg/dL) and high CRP group (n = 67, CRP ≥0.15 mg/dL).

Left ventricular (LV) mass was calculated with the Devereux formula.[13] Left ventricular mass index was calculated by dividing LV mass by height in meters raised to the power of 2.7. The degree of calcification of the aortic valve was assessed and scored as mild (no calcification or small isolated calcified spots), moderate (multiple large spots), or severe (extensive thickening and calcification of all the aortic valve cusps).[14]

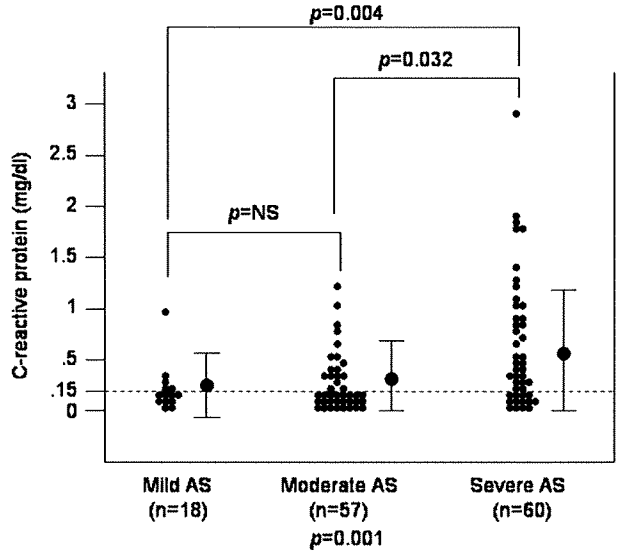
The serum CRP was measured by latex nephelometry (LT Auto Wako CRP, Osaka, Japan). We used latex as the reagent and Hitachi 7500 analyzer (Hitachi, Tokyo, Japan) as the measurement system. The lowest detection CRP limit of this test was <0.02 mg/dL.

Hypertension was defined as a history of systolic blood pressure of ≥140 mm Hg, a diastolic blood pressure of ≥90 mm Hg, or the use of antihypertensive therapy. Hyperlipidemia was defined as a fasting total cholesterol concentration of ≥220 mg/dL or the use of antihyperlipidemic therapy. Diabetes mellitus was defined as a fasting plasma glucose concentration ≥126 mg/dL or the use of antidiabetic therapy. Informed consent was obtained from all patients. Study protocol was approved by the Institutional Review Committee on Human Research at our institution.

Clinical follow-up

To further address the prognostic impact of CRP in patients with AS, long-term clinical events were compared between low-CRP and high-CRP groups. Long-term clinical events included death, hospitalization due to congestive heart failure, and aortic valve replacement.

Figure 1



C-Reactive protein level in patients with mild, moderate, and severe AS. C-Reactive protein in patients with severe AS was significantly higher than in patients with mild or moderate AS.

Statistical analysis

Data are expressed as mean value ± SD. The 2 groups were compared with an unpaired Student *t* test and χ^2 test. Statistical comparison between the 3 groups was performed by 1-way analysis of variance and post hoc multiple comparison, using the Scheffé's test. Logistic regression analysis was used to identify the independent risk factor for severity of AS. Long-term survival was evaluated by Kaplan-Meier survival analysis. A *P* value of <.05 was considered significant.

Results

One hundred and thirty-five patients with mild (n = 18), moderate (n = 57), and severe AS (n = 60) were examined in this study. All patients were asymptomatic at the time of baseline echocardiographic study. Table I summarizes the baseline clinical characteristics data of the 3 study groups. There were significant differences in age and CRP among mild, moderate, and severe AS. Figure 1 shows plots of CRP in patients with mild, moderate, and severe AS. C-Reactive protein in patients with severe AS was significantly higher than in patients with mild or moderate AS ($P = .004$ vs mild AS, $P = .0032$ vs moderate AS, respectively). CRP correlated weakly but significantly with AVA ($r = 0.26$, $P = .003$). Table II shows the echocardiographic findings. There were significant differences in LV ejection fraction (LVEF), degree of calcification, and LV mass index among mild, moderate,

Table II. Echocardiogrphic findings among the 3 study groups

	Mild AS (n = 18)	Moderate AS (n = 57)	Severe AS (n = 60)	*P* value
LV Diastolic dimension (mm)	43.1 ± 6.4	43.1 ± 5.0	42.2 ± 5.1	.650
LV Systolic dimension (mm)	26.3 ± 5.4	26.1 ± 5.0	26.9 ± 5.9	.697
LV Septal wall thickness (mm)	10.9 ± 1.1	11.9 ± 2.4	12.9 ± 2.2	.002
LV Posterior wall thickness (mm)	10.6 ± 1.5	11.8 ± 2.0	12.6 ± 1.9	<.001
LVEF (%)	68.4 ± 5.6	66.0 ± 7.3	62.2 ± 10.0	.009
Aortic valve area (cm^2)	1.70 ± 0.21	1.18 ± 0.14	0.75 ± 0.16	<.001
Peak aortic velocity (m/s)	2.48 ± 0.40	2.74 ± 0.59	3.90 ± 0.90	<.001
Peak pressure gradient (mm Hg)	25.4 ± 7.8	31.6 ± 14.8	63.8 ± 31.1	<.001
Severe calcification, n (%)	5 (28)	18 (32)	33 (55)	.016
LV Mass index (g/m^2)	125.6 ± 40.3	157.4 ± 50.9	169.7 ± 73.4	.028

EF, Ejection fraction.

Table III. Multivariate analysis of variables associated with severe AS

	OR (95% CI)	*P* value
CRP	3.51 (1.27-9.71)	.015
LVEF	0.95 (0.90-1.00)	.047
Severe calcification	2.16 (0.99-4.73)	.054
Age	1.02 (0.98-1.07)	.288
LV Mass index	1.00 (0.99-1.00)	.559

OR, Odds ratio.

and severe AS. Valve calcification and LV mass index were also found to be positively associated with the severity of AS ($r = 0.48$, $P < .001$; $r = 0.23$, $P = .006$, respectively). During the follow-up period, 13 patients (10%) (2 patients with moderate AS, 11 patients with severe AS at baseline) developed symptoms and underwent aortic valve replacement. Baseline CRP was similar in patients with moderate and severe AS who developed symptoms (median 0.23 ± 0.25 and 0.33 ± 0.39 mg/dL) compared with those who were asymptomatic (0.21 ± 0.29 and 0.57 ± 0.70 mg/dL, $P = .679$ and .249, respectively). By univariate analysis, CRP ($P = .001$), LVEF ($P = .009$), age ($P = .019$), calcification ($P = .016$), and LV mass index ($P = .028$) were predictors of severe AS. By multivariate analysis, CRP and LVEF were independent predictors of severe AS (Table III).

Table IV presents a summary of the comparison between the rapid progression group and slow progression group. Although clinical and echocardiographic data were similar, baseline CRP was significantly higher in the rapid progression group than in the slow progression group. By univariate and multivariate analysis, CRP was the only independent predictor of rapid progression (odds ratio 1.91, 95% CI 0.861-4.216, $P = .024$).

During follow-up (mean 23 ± 11 months), 33 deaths (23 cardiac deaths and 10 noncardiac deaths), 25 hospitalization due to congestive heart failure, and 13 aortic valve replacements were documented. Kaplan-Meier survival analysis showed that long-term survival as well as event-free survival was significantly lower in the high CRP group than in the low CRP group (Figures 2 and 3).

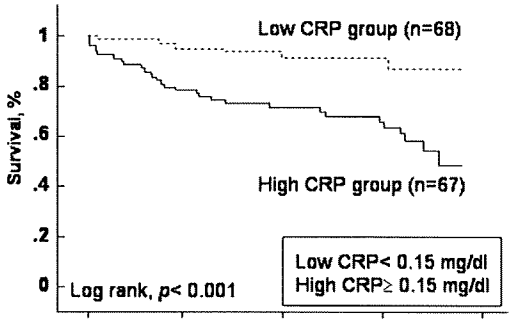
Table IV. Comparison of baseline characteristics of study patients between the rapid progression group and slow progression group

	Rapid progression (n = 25)	Slow progression (n = 22)	*P* value
Age (y)	75 ± 9	75 ± 8	.482
Male SEX, n (%)	9 (36)	7 (32)	.503
CRP (mg/dL)	0.56 ± 0.76	0.19 ± 0.25	.004
Hypertension, n (%)	7 (28)	11 (50)	.106
Hyperlipidemia, n (%)	9 (36)	8 (36)	.601
Diabetes mellitus, n (%)	6 (24)	2 (9)	.167
Smoking, n (%)	6 (24)	4 (18)	.450
Total cholesterol (mg/dL)	189 ± 39	175 ± 35	.200
LDL Cholesterol (mg/dL)	133 ± 24	124 ± 10	.155
Statins therapy, n (%)	4 (16)	5 (23)	.549
AVA (cm^2)	1.08 ± 0.40	1.02 ± 0.37	.309
Peak aortic velocity (m/s)	3.36 ± 0.87	3.01 ± 0.80	.085
Peak pressure gradient (mm Hg)	47.9 ± 23.9	38.5 ± 20.8	.079
LVEF (%)	65.3 ± 11.1	66.6 ± 6.7	.689
Severe calcification, n (%)	11 (44)	7 (32)	.289
AS Grade, n (%)			
Mild	5 (20)	2 (9)	.265
Moderate	8 (32)	11 (50)	.169
Severe	12 (48)	9 (41)	.424

Discussion

To the best of our knowledge, this is the first study demonstrating that baseline CRP is an independent predictor of severe AS. In addition, serial echocardiographic

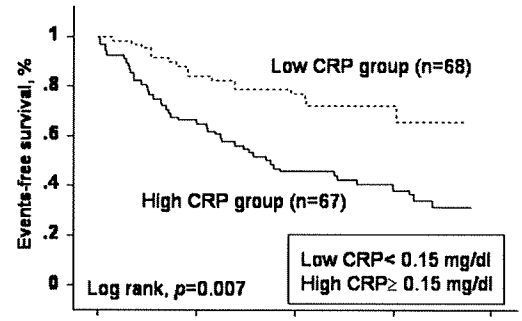
Figure 2



Number of subjects at risk					
Low CRP group	68	65	63	61	61
High CRP group	67	53	49	47	40
Number of events					
Low CRP group	0	3	2	2	0
High CRP group	0	14	4	2	7

Kaplan-Meier plots of all-cause deaths–free survival curves showing a significantly lower survival rate in the high-CRP group than in the low-CRP group.

Figure 3



Number of subjects at risk					
Low CRP group	68	52	44	42	42
High CRP group	67	43	29	25	18
Number of events					
Low CRP group	0	16	8	2	0
High CRP group	0	24	14	4	7

Kaplan-Meier survival plots of event (cardiac death, noncardiac death, hospitalization due to congestive heart failure, and aortic valve replacement)-free survival curves showing a significantly lower survival rate in the high-CRP group than in the low-CRP group.

examination shows that CRP is associated with progression of AS. Furthermore, CRP is related to long-term clinical outcome in patients with asymptomatic AS.

Histologic findings of AS resemble the morphological changes seen in atherosclerosis including calcification, fibrosis, and lipid storage.[15] Microscopically chronic inflammation characterized by infiltration of T lymphocytes and macrophages and by accumulation of plasma lipoproteins such as oxidized low-density lipoprotein and lipoprotein (a) is detected.[16] Skowasch et al[17] reported that CRP has been localized in the valve tissue of both calcific AS and degenerative aortic valve bioprostheses, with a positive correlation between serum CRP and valvular expression. Therefore, it is possible that inflammation plays an important role during the course of aortic valve sclerosis, calcification, and stenosis. Also, it may be inconclusive whether increased CRP is a cause or result of severe AS based on the difference in CRP among patients with mild, moderate, and severe AS.

Aortic valve stenosis tends to progress overtime, and the rate of progression varies in different patients. Otto et al[10] suggested that AVA decreased by 0.10 to 0.12 cm^2/y, and mean gradient increased by 5 to 10 mm Hg/y in patients with asymptomatic AS. Whereas Kume et al reported that the degree of AS progressed more rapidly in patients undergoing dialysis with severe aortic valve calcification (AVA 0.17 cm^2/y, maximum velocity 0.37 m/s per year, respectively) and older than 80 years with mild to moderate AS (AVA 0.10 cm^2/y, maximum velocity 0.11 m/s per year, respectively).[11,12] Moreover, Beppu et al[18] reported the rapidity of progression of aortic stenosis in patients with congenital bicuspid aortic valves (maximum pressure gradient 8 mm Hg/y). In this study, CRP was significantly higher in the rapid progression group than in the slow progression group. These results were concordant with a previous study. Sanchez et al[19] reported that CRP is higher in patients with rapid progression of AS. On the other hand, Novaro et al[20] reported that CRP was not associated with progression of aortic sclerosis. Previous reports suggested that aortic sclerosis and AS are considered different stages in the continuum of calcific aortic valve disease.[21,22] Therefore, CRP may not be associated with early stage of this continuum but with advanced stage of AS.

The relationship between progression of AS and statin therapy is still controversial. Previous studies have suggested that cholesterol lowering by statin therapy may have a salutary effect on the progression of AS.[23-27] However, a recent randomized study by Cowell et al[28] showed a negative result. In the present study, statin was prescribed in a small subset of patient and there was no significant difference in statin use between the rapid and slow progression group. Recent studies consistently showed that statin did lower not only low-density lipoprotein cholesterol but also CRP.[29-31] Therefore, statin may be efficacious in patients with AS with elevated CRP.

In our present study, long-term survival was significantly lower in patients with AS with high CRP level. Previous reports suggested that CRP might be a cardiovascular risk marker in patients with IHD, stroke, metabolic syndrome, and renal disease.[5,6,32-35] Although

high CRP may represent the presence of comorbid condition such as IHD, CRP may be a useful parameter to predict disease progression and prognosis in patients with AS.

Study limitations

First, this is a retrospective analysis of a small number of patients from a single center. Thus, the results need to be confirmed by a large prospective multicenter study. Second, although patients with known history of IHD were excluded, it is possible that occult coronary artery disease was related to the elevated CRP. Although previous studies showed that coronary artery disease was detected in 33% and 45% of patients with AS,[36,37] significant coronary artery disease was detected in <10% of the severe AS at our hospital (data not shown). Therefore, it is unlikely that coronary artery disease affects our results. Third, the percentage of females was high in our study. It might be due to the exclusion of patients with bicuspid valves and ischemic heart disease. In fact, the percentage of males was higher than that of females (male 69%, female 31%) among patients with bicuspid valves and ischemic heart disease. However, we did not observe any sex-specific differences in this study.

Conclusion

C-Reactive protein is associated with the severity and progression of asymptomatic AS. In addition, CRP predicts long-term clinical outcome in patients with AS. These findings suggest that CRP may have a pathogenic role and prognostic impact in asymptomatic patients with AS.

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循環器科，65(3)：298-301，2009

特集 心臓弁膜症の診断と治療―update―（その1）

変性性大動脈弁狭窄症と動脈硬化*

山本一博**
大谷朋仁**

Key Words : aortic stenosis, aging, ethnic difference

はじめに

かつては弁膜症の原因としてリウマチ熱が主流を占めていた．しかしながら，公衆衛生の発達などによりリウマチ熱に基づく弁膜症患者数はわが国では激減し，一時期，循環器疾患における弁膜症の位置づけは低下していた．しかしながら，昨今，これまで弁膜症の範疇で論じられていなかった問題がいくつかクローズアップされており，その中の一つが大動脈弁変性症とこれに基づく大動脈弁狭窄症である．本稿では，この病態に関する現段階での知見について触れる．

疫　学

欧州のデータによると，有意な弁膜症と診断される中でもっとも頻度が高いものが大動脈弁狭窄症であり，全体の30%強を占める．弁置換術などの侵襲的な治療を受けた患者の中に占める大動脈弁狭窄症の割合はさらに増加し40%を超え，現在，成人の弁膜症の中で手術対象となる患者数の第1位は大動脈弁狭窄である[1]．大動脈弁狭窄症の頻度は60歳前後から加齢とともに急激に増加する（図1）[2]．その原因をみると，かつて主流であったリウマチ熱は10%程度で，80%以上の患者が弁変性症に基づいている．65歳以上の高齢者を対象とした疫学調査をみると，大動脈弁変性を29%に，大動脈弁狭窄を2%に認める[3][4]．さらに追跡調査を行うと，大動脈弁に異常を認めない高齢者にも5年間で44%の高率で大動脈弁変性をきたし，1%で大動脈弁狭窄を発症する．大動脈弁変性を認めた症例のうち9%が5年の間に大動脈弁狭窄に移行している．

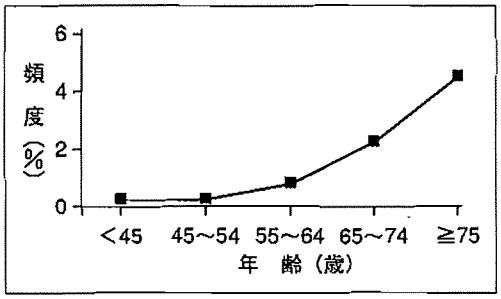

図1　一般住民における中～高度大動脈弁疾患の頻度
加齢とともに，動脈弁疾患患者の頻度は増加する．
（文献[2]より引用）

現在，大動脈弁狭窄症に対する治療方針は，自覚症状の出現などを認めると弁置換術が第一選択となる．この病態が加齢とともに頻度が増加することもあり，高齢化社会の到来とともに弁置換術を受ける患者に占める高齢者の割合は増加している．いったん自覚症状が出現すると薬物療法によるコントロールには限界があるこ

* Degenerative aortic valve disease and atherosclerosis.

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ともあり，最近では80歳以上の患者に対する手術も稀ではなくなってきた．手術成績が向上しているとはいえ手術死亡率は3％程度あり，われわれ循環器内科医としては，いかに手術適応となるレベルの手前で病態の進行をとどめることができるか，ということが大きな課題である．

動脈硬化と大動脈弁変性症

加齢とともに大動脈弁狭窄症は増加するが，ほかの弁狭窄症はそれほど頻度が増加しない．大動脈弁が大動脈に付着しており，大動脈弁狭窄症が弁変性，弁硬化・石灰化を伴うこともあり，この病態を「動脈硬化性大動脈弁硬化」と呼ぶこともあるが，本当に動脈硬化と同一視してよいだろうか？

動脈硬化にも大動脈弁変性にも酸化ストレスが関与していることを裏づけるデータが示されているが，動脈硬化病変ではreactive oxygen species(ROS)産生亢進が主と考えられるデータが多いのに対し，大動脈弁硬化病変ではROSの消去機能が低下していることを示すデータが得られている[5]．また，動脈硬化病変の出現，進行に重要な役割を果たす平滑筋細胞が大動脈弁には存在しない．疫学データをみると，高度大動脈弁狭窄患者で冠動脈疾患を有する割合は50％程度であり，かつ冠動脈疾患を有する患者のほとんどは大動脈弁狭窄を有さないことが示されている．

次に，大動脈弁変性の危険因子について考えてみたい．弁変性を認める患者に付随してみられる因子として，高齢，男性，LP(a)およびLDL高値，高血圧の既往，喫煙があげられている一方で，糖尿病，HDL値，中性脂肪値，冠動脈疾患歴などは無関係であることも明らかとされている[6]．変性が進行すると石灰化をきたし，これが狭窄を招く大きな要因となるが，石灰化と関連する因子は性差(男性)のみで，年齢，高血圧，糖尿病，脂質異常症，喫煙は無関係であった[7]．ただし，これらはcross-sectional studyであり，あくまでも大動脈弁変性や石灰化に付随している因子を指摘しているにすぎず，弁変性の原因を特定することはできない．

そこで，前向き観察研究の結果をみると，年齢，男性，LDL高値が弁変性をきたす危険因子で，高血圧，喫煙，糖尿病，冠動脈疾患，CRPはいずれも無関係であった[4]．さらに，変性症から狭窄症への移行の危険因子は年齢と男性だけであり，脂質異常症も危険因子ではなかった[4]．

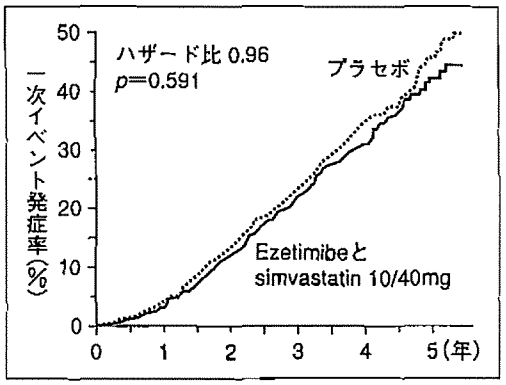

図2　大動脈弁狭窄症に対するコレステロール低下療法の効果(SEAS試験)
一次エンドポイントはASないし動脈硬化に基づくイベント：心血管死，AVR, AS進行による心不全，非致死性心筋梗塞，UAによる入院，PCI, CABG, 非出血性脳卒中．Ezetimibeとsimvastatinを用いたコレステロール低下療法の有効性は認められなかった．
(文献[13]より引用)

狭窄症に移行したあと，その進行に関する因子をみると，年齢や性差さえ関係なく，大動脈弁の病変が進行すればするほど，さらに進行が加速されることを示すデータが得られている[8)-10)]．

これらの結果から判断すると，少なくとも大動脈弁変性と動脈硬化は異なる病態である．

遺伝的要因については，変性性大動脈弁硬化とNOTCH1の変異の関連が指摘されている[11)]．NOTCH1の異常によりHrt抑制ができなくなり，Osteoblastへの分化が促進されると考えられている．

治　療

当初，大動脈弁変性と動脈硬化に共通点が多いと考えられていたこともあり，動脈硬化病変に有効と考えられている薬剤の効果が検討された．もっとも期待されていた薬剤はスタチンであり，いくつかの後ろ向き試験では有効性を示唆するデータが得られている．しかしながら，すでに大動脈弁狭窄に移行してしまっている大

動脈弁変性患者が対象ではあるが，スタチンの効果を前向きに検討したSALTIRE試験[12]，スタチンとezetimibeの併用効果をみたSEAS試験[13]，いずれも有効性は示されなかった(図2)．SEAS試験では，虚血性心疾患イベントは低下させていることから，これらの結果は大動脈弁変性に基づく大動脈弁狭窄病変の進行抑制にはスタチンは無効であることを示すとともに，大動脈弁変性と動脈硬化は異なる病態であることをあらためて裏づけている．ただし，これらは大動脈弁狭窄に移行している患者を対象として得られた結果にすぎず，大動脈弁狭窄を伴っていない弁変性の段階からの治療介入の有効性を否定するデータではない．

アンジオテンシン変換酵素の発現が病変のある大動脈弁でのみ観察され，変性病変のある弁に存在する線維芽細胞のみアンジオテンシン受容体を認めることから，アンジオテンシン変換酵素阻害薬にも有効性が期待されている．これまでは後ろ向き研究の結果しか得られておらず，O'Brienらは有効性を示唆し[14]，Rosenhekらは無効と結論している[15]．しかし，いずれも後ろ向き試験の結果であることから，今後，前向き試験の実施が待たれる．

人種差

循環器疾患の病態には人種差が指摘されているが，大動脈弁変性にも人種差が認められるようである．欧米のデータをみると，African-Americanは弁変性の出現，あるいは弁狭窄への移行リスクが低い[4]．したがって，われわれ日本人において，欧米で得られた結果をそのまま演繹することは許容されない，と考えるべきである．現在，厚生労働科学研究費のもと日本循環器学会の後援を得て，日本人を対象として大動脈弁変成，狭窄の危険因子を明らかとすべく「日本人における動脈硬化性大動脈弁膜疾患の発症・進展予防に関する研究(JASS)」が行われており(http://www.sact.co.jp/jass_top.html)，その結果が待たれる．

おわりに

高齢化社会の到来とともに問題化している疾患の一つが大動脈弁変性とこれに基づく大動脈弁狭窄である．その病態はいまだ解明されておらず，治療手段(進行阻止手段)も明らかではない．これまでの欧米の疫学調査の結果をみると，いったん大動脈弁変性が大動脈弁狭窄に移行すると加速度的に病態が進行し，患者背景因子の影響は少なくなるようである．したがって，内科的に介入しうる病期は大動脈弁狭窄発症前のステージではないかと考えられる．

また，病態に人種差の存在が強く示唆されており，今後，日本人におけるエビデンスが蓄積され，弁置換術を必要とする患者を減少させる指針が導き出されることが望まれる．

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心機能・その他(1)

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平成11年大阪大学医学部卒業．現在大阪大学大学院医学系研究科循環器内科学所属．研究テーマは新しい拡張機能評価法の確立と拡張不全の病態生理解明．特に現在は心臓の硬さの非侵襲的評価法について頭を悩ませています．

Q 拡張機能障害評価において，Forrester分類に代わる新しい分類方法，治療方針について教えてください．

A

diastolic heart failureの認知が広がった現在においても，非侵襲的な拡張機能評価法は確立されておらず，その診断は困難です．そういうこともあり，拡張機能障害に対する分類方法はありません．diastolic heart failureに対する治療のエビデンスも現在のところ少なく，進行中の大規模臨床研究の結果が待たれるところです．

(1)Forrester分類

Forrester分類は，急性心不全の循環動態をSwan-Ganzカテーテルを挿入することで得られる指標から4種類に分類したものである[1]．図1に示すように，縦軸に心係数，横軸に肺動脈楔入圧pulmonary capillary wedge pressure(PCWP)をとり，それぞれ2.2l/min/m^2，18mmHgを境界として分類する．基本的には，Forresterのサブセットの Ⅰ型は，肺うっ血，末梢循環不全を認めず，一般療法のみでよい．Ⅱ型は肺うっ血を伴うが，心拍出量は保たれており，静脈圧を低下させる目的に，血管拡張薬や利尿薬を投与する．Ⅲ型では体液量・血液量が不足しているような状態が考えられ，補液により前負荷を増大させることで対応する．ただし，心収縮機能が著しく低下しているケース，右室梗塞を認めるケースにおいても，このサブセットに入る場合があり，その際には強心薬の投与も併せて考慮する必要がある．Ⅳ型は肺うっ血，末梢循環不全をともに認め，重症心不全を示唆し，強心薬，利尿薬，血管拡張薬などの併用療法が必要で，ときに，大動脈バルーンパンピングなどの補助循環装置を必要とする．

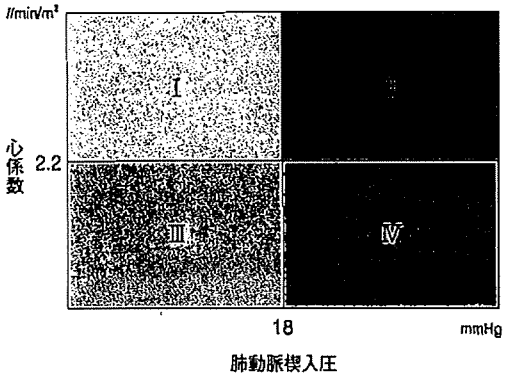

図1 Forrester分類

Forrester分類は拡張機能，収縮機能にかかわ