Histological changes in the aortic valve after balloon dilatation: evidence for a delayed healing process

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Abstract

***Objective*—To investigate whether balloon dilatation of the aortic valve induces long-term macroscopic or histological changes or both to explain the restenosis process.**

***Design*—Prospective study of 39 consecutive patients. Sixteen later (mean (SD) 12 (10) months) required operation. This non-randomised subgroup was compared with 10 patients who had aortic valve replacement without prior dilatation.**

***Setting*—University cardiology and cardiac surgery centre and pathology department.**

***Patients*—16 patients who had aortic valve replacement because of failure of or restenosis after balloon dilatation of the aortic valve. Twelve resected valves were examined.**

***Interventions*—Percutaneous balloon dilatation of the aortic valve (maximal balloon size: trefoil 3 × 12 mm balloon or bifoil 2 × 19 mm balloon) and surgical inspection before excision of the aortic valve leaflets during open-chest aortic valve replacement. Fixation, decalcification, and staining for histology.**

***Main outcome measures*—Presence of long-term pathological changes in the resected valve and their relation to restenosis after balloon dilatation.**

***Results*—Macroscopically the previously dilated valves were indistinguishable from valves from the patients who had valve replacement only. Microscopically, the dilated aortic valves showed areas of young scar tissue that were not seen in a control group of surgically excised stenotic aortic valves. This persistent scarring reaction was seen around small tears or lacerations of the collagenous valve stroma, fractures in calcified areas, and splits in commissures. Young scar tissue without collagenisation was still present 24 months after dilatation.**

***Conclusion*—Organisation and collagenisation of scar tissue develops slowly after balloon dilatation of the aortic valve. This prolonged scarring reaction may explain the late development of restenosis in some patients.**

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Balloon dilatation of the aortic valve has been advocated by several groups as an alternative to aortic valve replacement in patients at high surgical risk or as an intermediate procedure to improve left ventricular function before elective aortic valve replacement.[1–4] Recurrence rates, whether clinically defined or assessed invasively or non-invasively, are high (24–67%).[5–9] This high restenosis rate leads to many subsequent procedures. Two recently published series reported reinterventions in about a quarter of the patients after a mean follow up of six months. A further quarter did not survive this follow up period.[5 7] The immediate effect of balloon dilatation on calcific aortic valves has been extensively studied during in vitro and intraoperative studies.[10 11] Little is known about the effects of balloon dilatation at a microscopic level or the sequence of any histological changes with time.[9 12 13] To examine the frequency and extent of these changes after dilatation we studied 12 previously dilated aortic valves excised during valve replacement and compared the histological findings with those in resected non-dilated aortic valves from patients of a similar age.

Patients and methods

From March 1986 to December 1989, 39 elderly patients underwent percutaneous balloon dilatation of the aortic valve. Sixteen of these patients later underwent aortic valve replacement. Table 1 shows the characteristics of all patients undergoing aortic valve dilatation and of the group who subsequently had aortic valve replacement.

Table 1 Characteristics (mean (SD)) of all patients undergoing balloon dilatation of the aortic valve (BD) and of patients with and without subsequent aortic valve replacement (AVR)

Characteristic	*BD*	*AVR*	*non AVR*
Number	39	16	19
M / F	15/24	6/10	7/12
Mean age (y) (range)	75·1 (58–88)	72·1 (63–85)	77·3 (58–88)
Left ventricular ejection fraction:			
⩾0·55	22	10	12
0·40–0·54	6	2	4
0·20–0·39	5	1	2
⩽0·19	4	1	1
Not-assessed	2	2	0
Aortic valve area before dilatation (cm^2)	0·47 (0·14)	0·51 (0·11)	0·45 (0·15)
Aortic valve area after dilatation (cm^2)	0·75 (0·19)	0·75 (0·15)	0·74 (0·21)
Aortic valve area increase (%)	63·0 (38·0)	52·0 (32·0)	64·0 (33·0)

Table 2 Clinical characteristics and outcome of balloon dilatation of the aortic valve in 16 patients who subsequently had aortic valve replacement

No	Age	Sex	Maximal balloon size (mm)	AVA (cm^2)		% AVA increase	Interval between dilatation and operation (mnth)
				B	A		
1	63	M	20	0·59	0·81	37	13
2	76	M	20	0·53	0·88	66	6
3	74	F	3 × 12	0·34	0·36	6	10
4	65	F	3 × 12	0·49	0·57	16	1
5	75	M	20	0·71	0·96	35	7
6	64	M	3 × 12	0·37	0·64	73	9
7	72	F	19	0·66	AI grade III		6 days
8	74	F	3 × 12	0·46	0·70	52	8
9	85	F	2 × 19	0·57	0·71	30	3
10	73	M	3 × 12	0·59	NA		13
11	64	F	20	0·33	0·80	142	36
12	75	M	20	0·57	0·95	67	24
13	75	F	3 × 12	0·39	0·71	82	27
14	72	F	15	0·62	0·85	37	20
15	71	F	23	0·41	0·71	73	6
16	77	F	3 × 12	0·53	0·78	47	13

A, after; AI, aortic insufficiency; AVA, aortic valve area; B, before dilatation; NA, not assessed.

DILATATION PROCEDURE

All procedures were performed with a percutaneous femoral approach with Schneider-Shiley balloons and introducers (Zurich, Switzerland). After baseline values were recorded the aortic valve area was calculated on line by measuring the mean transvalvar pressure gradient and aortic valve flow. Balloons of increasing size were then introduced to increase the aortic valve area by at least 50% (the maximal balloon diameter in the first 29 patients was trefoil 3 × 12 mm balloon and in the last 10 patients it was bifoil 2 × 19 mm balloon). In the last 22 patients a 100 cm long 16·5 French introducer was used.[14 15] A successful procedure was arbitrarily defined as an increase in aortic valve area of at least 25%, without death or major complications necessitating urgent surgery. Table 1 summarises the haemodynamic data before and after valve dilatation. In five patients the valve area could not be calculated after the procedure (two patients died after the first balloon inflation, two patients had considerable aortic regurgitation after dilatation that precluded calculation of the aortic valve area, while in a fifth patient data were not recorded because of neurological complications). Restenosis was defined as a clinical recurrence of symptoms with either a return of maximal aortic valve flow velocity to predilatation values on Doppler flow measurements or an invasively measured increase in aortic valve area of <25%.

MORTALITY AND PROCEDURAL FAILURE

Four patients died within 28 days after balloon dilatation. Two patients in severe heart failure died during the procedure after the first balloon inflation. In a third patient, also with severe failure, the procedure was successful but he died one week later of progressive heart failure. The fourth patient had signs of aortic base dissection after inflation of a bifoil 2 × 19 mm balloon and died 24 hours later. One patient was operated upon within one week of the procedure because of severe aortic regurgitation (table 2, case 7).

Table 3 Peroperative findings and early postoperative course after inadequate balloon dilatation and subsequent aortic valve replacement

No	Valve anatomy	Commissural fusion	Calcifications	Tearing of leaflets
1	B	No	3+	No
2	B	No	3+	No
3	B	No	3+	No
4	T	No	3+	No
5	B	No	3+	No
6	B	No	2+	No
7	B/T	Yes/No	2+	Yes
8	T	Yes	3+	No
9	T	No	3+	No
10	B	No	3+	No
11	T	No	3+	No
12	T	No	3+	No
13	NA	NA	3+	NA
14	T	No	3+	No
15	T	No	3+	No
16	NA	NA	3+	NA

B, bicuspid aortic valve; +, tricuspid aortic valve; NA, not assessed.

Table 4 Histological findings in 12 excised aortic valves operated after percutaneous balloon dilatation of the aortic valve

Patient	Interval (mnth)	Operative indication	Collagenous stroma	Calcification	Bone formation	Pre-existing pathology		
						Superficial fibrin deposits	Superficial haemorrhages	Young scar in collagenous stroma
2	6	R	++	++	+	++	−	+
3	9	F	++	++	−	−	−	++
4	3 weeks	F	++	++	−	−	−	−
5	6	R	++	++	+	−	+	++
6	9	R	++	++	+	−	+	++
7	6 days	AI	++	++	−	−	−	+++
8	9	R	++	++	+	−	−	++ with sealed commissure
9	2	R	++	++	−	+	+	+
10	13	R/F?	++	++	−	−	+	+ superficial
11	36	R	++	++	−	−	+	−
12	24	R	++	++	−	+	+	++
15	6	R	++	++	−	−	−	++

AI, aortic valve insufficiency; F, dilatation failure; R, restenosis.

The procedure was considered to be unsuccessful in four patients because the valve area had increased by less than 25% after dilatation. Two of these patients subsequently had surgery (table 2, cases 3 and 4). One was operated upon within one month, the other experienced some relief of symptoms and was operated upon 10 months later. Of the other two with failed procedures, one died 19 months after the procedure, while the last patient was in validity class II (New York Heart Association) six months after valve dilatation. Of the remaining 30 patients, 13 had surgery because of clinical restenosis. Table 2 shows the haemodynamic and clinical details of the patients who had surgery.

FOLLOW UP OF NON-SURGICAL PATIENTS

Eight patients died during follow up. Death occurred at a mean (SD) of 15 (5) months after dilatation. Eleven patients were alive after a single dilatation procedure at a mean follow up of 23 (12) months.

SURGICAL PROCEDURE

All 14 patients operated upon in our hospital were treated according to the same standard surgical protocol. After incision of the aortic root we paid special attention to the macroscopic inspection of the previously dilated valve. We specifically looked for laceration of the valve leaflets, fracture of calcific deposits, and rupture of previously fused commissures. The underlying valve anatomy was established as uni, bi or tri cuspid. The amount of calcification was scored as + to +++ indicating minimal, moderate, or extensive involvement. After inspection the valve leaflets from 12 patients were excised and stored for microscopic examination.

HISTOLOGICAL TECHNIQUE

The fragments resected from patients 2 to 12 and 15 were fixed in 10% formalin and decalcified in rapid bone decalcifier (RDO, Dupage Kinetic Laboratories Inc, Plainfield, USA). After a routine paraffin processing cycle 5 μm sections were stained with haematoxylin-eosin and elastic van Gieson stain.

Results

MACROSCOPIC EXAMINATION

Table 3 shows the gross intraoperative anatomical findings in the 16 surgical patients. The aortic valve was bicuspid in six patients and tricuspid in seven patients. In one patient we were uncertain how many cusps were present. In two patients who had surgery in another hospital and one patient who underwent surgical valvuloplasty the aortic valve was not available for analysis (cases 13, 16 and 14). Macroscopic findings attributable to the previous valve dilatation were seen in only one patient (case 7, table 3). In this patient the valve was composed of a posteriorly situated thickened and heavily calcified cusp and of a less calcified anterior cusp (probably a fusion of the left and right coronary cusps). Balloon dilatation had lacerated (7 mm) the right side of the anterior cusp from the aortic wall. Because the posterior cusp was rigid, the radial balloon force was probably exerted more strongly on the more pliable cusp. Fracturing of calcific deposits was not grossly evident in any cases.

Pathology as result of valvuloplasty

Young scar in calcified nodule	*Calcium fragments in scar*	*Iron loaden macrophages*	*Haemorrhages deep in stroma*	*Fibrin deep in stroma*
−	+	−	+	+
−	++ histiocytic infiltrate	−	−	−
−	++	−	+	+
−	++	+	−	−
++	+	−	+	−
++	++	−	−	−
++	++	+	−	+
+	−	−	−	+
+ superficial	+	−	−	−
−	−	−	−	−
+	++	−	−	−
+	++	−	−	−

MICROSCOPIC EXAMINATION

Dilated valves

All the valves (table 4) showed the usual histological features of calcific aortic stenosis.[16] In two patients there was degenerative bone formation in the calcifications. In 11 of the 12 patients young scar tissue (consisting of a rather cell-rich pattern of fibroblasts, capillaries, and an inflammatory infiltrate composed of lymphocytes, plasma cells, and histiocytes) was present. This scar tissue seemed to fill up the small tears and lacerations in the dense collagenous tissue stroma (11 patients) (fig 1A) and the fractures in the calcified nodules (seven patients) (fig 1B). Fragments of calcium embedded in the young scar tissue were seen in 10 patients (fig 1C). In one patient a commissure was re-sealed with recent scar tissue. Haemorrhages and fibrin within the valve stroma were seen in six patients, while superficial fibrin deposits and haemorrhages were seen in all patients. Only one patient showed the basic pathology of calcified aortic stenosis without recent scar tissue. However, this patient was operated upon 36 months after dilatation and by that time the scar tissue may have been completely organised. There was no clear difference in histological appearance between the successfully and the two non-successfully dilated patients, though one of the non-successfully dilated patients (case 3) showed an extensive histiocytic reaction around severely fragmented calcifications as well as young scar tissue in the collagenous valve stroma. The second patient (case 4) only showed scar tissue between fragmented calcifications.

Control valves

We examined a control group of 10 patients undergoing aortic valve replacement because of critical calcific aortic stenosis which was of similar age and sex distribution and gross macroscopic changes as the dilated group. Macroscopically the valves were indistinguishable from those of the dilated group. Histological examination showed superficial fibrin deposits, small haemorrhages, and iron-loaden macrophages in the subendothelium of

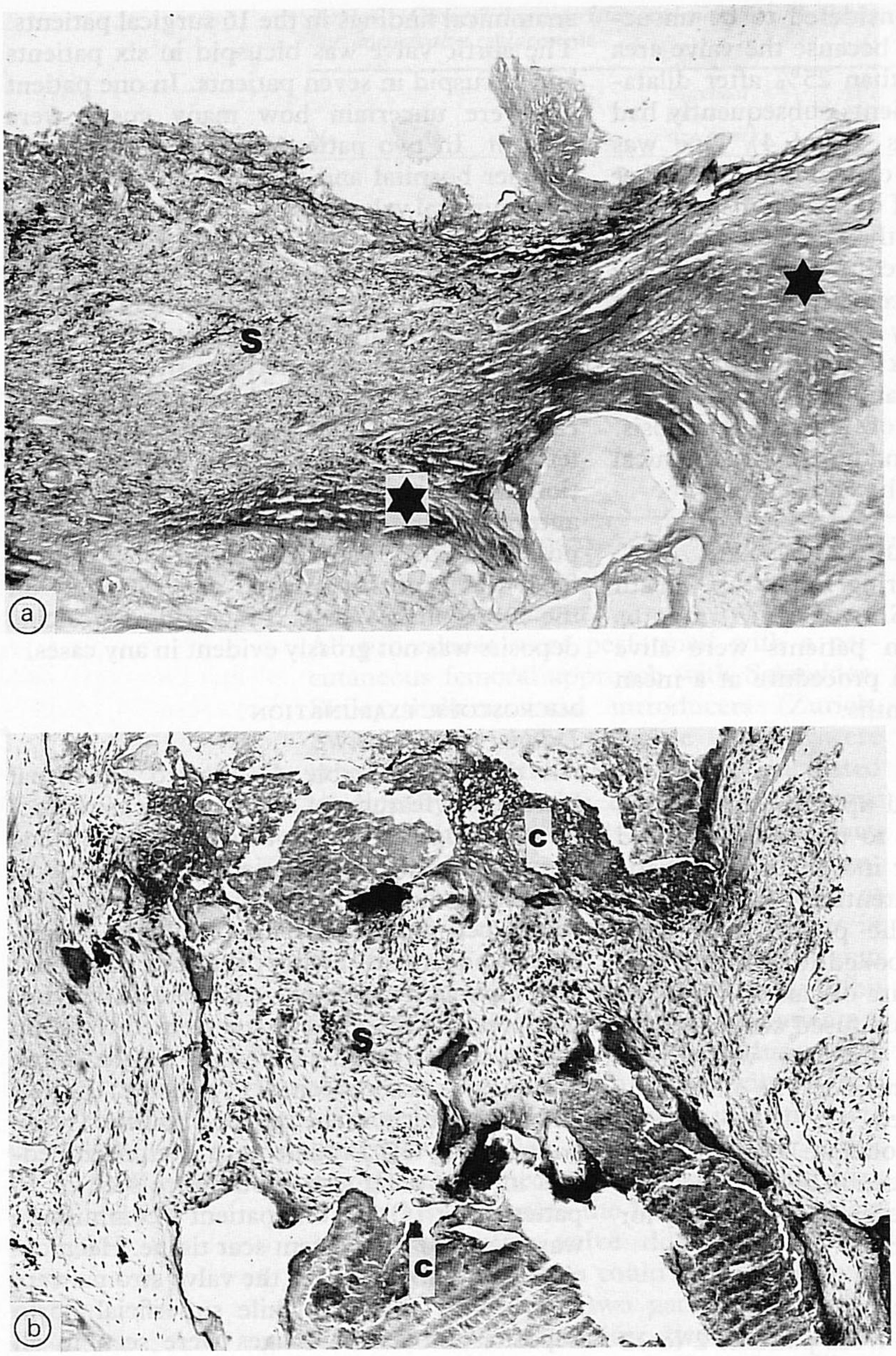

Figure Histological appearance of a segment of aortic valve leaflet after balloon dilatation. (A) Small laceration in the dense collagenous tissue stroma (*), filled with scar tissue (S). (B) Scar tissue (S) filling a fractured calcified nodule (C). (C) Calcium fragments embedded in young scar tissue.

valves from the control group. Although lymphocytes, plasma cells, and capillaries were present in the looser connective tissue stroma surrounding the dense collagenous stroma in some patients, none of the control valves showed the areas of young scar tissue seen in the patients treated with balloon dilatation.

Discussion

Whatever the initial mechanism, the underlying pathology of calcific aortic stenosis in the elderly is severe fibrosis and considerable calcifications of the valve leaflets occasionally associated with commissural fusion. These pathological changes render the valve rigid and immobile.[16]

As evident from our study and other published reports[10–12 17] the mechanisms of successful percutaneous balloon dilatation of the aortic valve are (*a*) cleavage or laceration of the dense collagenous valve stroma, (*b*) fracture and/or fragmentation of calcifications, and (*c*) separation of fused commissures.

It seems that the final outcome of balloon dilatation mainly depends on the severity of the underlying pathological abnormalities in the valve and the extent of the injury created by the balloon. In the two patients who had insufficient dilatation procedures with an increase of the aortic valve area of less than 25% we did indeed see some injury to the valve leaflets, but apparently it was not extensive enough. Commeau *et al* reported a similar finding in an intraoperative study.[9] They noticed that when the valve was extensively calcified there was no grossly obvious effect of dilatation. None the less, in one of our patients severe damage to the valve (a complete tear of a valve leaflet from the aortic wall) caused severe aortic regurgitation.

Injury to the aortic valve seems to be followed by scarring. We and others found that small tears or lacerations in the collagenous valve stroma, fractures in calcifications, and splits between commissures were filled up with young scar tissue.[12 17] Scar formation should be recognised as a possible mechanism for restenosis.[12 13] Indeed, development, organisation, and collagenisation of the young scar tissue in the tears and fractures in the valve will ultimately restore the valve's immobility and lead to restenosis. In addition, it seems from our study that organisation and collagenisation of the scar tissue in these valves takes longer than in other tissues. We saw non-collagenous scar tissue in the valves 24 months after dilatation: normally a scar is completely organised and collagenised within six weeks. The lack of a direct vascular supply to the valve leaflets may explain this prolonged process of repair, which resembles the slowly progressive inflammatory reaction of the chronic endocarditis of rheumatic origin. This observation shows that restenosis can develop slowly so that some patients will have a relatively long-lasting complaint-free period. As a consequence, we think that on the basis of strict indications percutaneous balloon dilatation of the aortic valve still has a place in relieving aortic stenosis in elderly patients with inoperable severe aortic stenosis.

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