

Background

Radiation-associated aortic valve stenosis is frequently seen as a late sequela after thoracic radiotherapy.¹ Although the clinical relationship between thoracic radiotherapy and valvular dysfunction has been established, the mechanism behind accelerated aortic valve stenosis remains unclear.

We hypothesize that thoracic radiotherapy triggers an increased inflammatory reaction and is related to leaflet fibrosis and calcification of the aortic valve.

Methods

To test this hypothesis, valve specimens from 44 patients were obtained after surgical aortic valve replacement. 28 patients had previously undergone thoracic or mediastinal radiation therapy for breast cancer (n=22) or (non) Hodgkin lymphoma (n=6), respectively. 16 patients who had never undergone thoracic radiotherapy were included as control.

The cellular composition of the valve leaflets was characterized by immunohistochemistry for T-cells (CD3+), B-cells (CD20+) and macrophages (CD68 or CD163+) and analyzed with Image Pro Premier. A color deconvolution algorithm in ImageJ was used to quantify the amount of collagen and mineralization on histological stainings.

Figure 1. Threshold segmentation of calcific nodules using ImageJ.



Results

Mean age at valve replacement was lower in the mediastinal radiation group (61.7±7.3) than in the control (74.1±8.0) and thoracic-radiation group (73.0±7.2yrs, p<0.01). Mean time from radiotherapy to valve replacement was longer after mediastinal radiotherapy (31.5±4.6yrs) than after thoracic radiotherapy (17.9±9.8yrs, p=0.0031).

Characteristics	Thoracic (n=22)	p-value	Control (n=16)	p-value	Mediastinal (n=6)
Age ± SD (yrs)	73.0 ± 7.2	0.671	74.1 ± 8.0	0.003	61.7 ± 7.3
Time between onset oncological treatment and AVR (yrs)	17.9 ± 9.8	0.009	7.6 ± 9.6	<0.001	31.5 ± 4.6
Male gender, n (%)	0 (0)	<0.0001	10 (63)	0.655	3 (50)
Cardiovascular risk factors					
Hypertension, n (%)	13 (59)	0.490	12 (75)	0.023	1 (17)
Dyslipidemia, n (%)	6 (27)	0.730	6 (38)	0.616	1 (17)
Diabetes mellitus, n (%)	7 (32)	0.729	4 (25)	1.000	1 (17)
Tobacco usage, n (%)	1 (5)	1.000	1 (6)	0.481	1 (17)

Table 1. Patient characteristics

Expression of CD68-positive macrophages was significantly lower in the thoracic-radiation group (p=0.0064) when compared to the controls. For CD3, CD20 and CD163, no changes in staining were detected between the groups.

Collagen content was increased in the mediastinal (p<0.001) and the thoracic groups (p=0.014). Aortic valves exposed to mediastinal radiotherapy contain 12±8% calcified tissue, compared to 20±8% after thoracic radiotherapy (p=0.034) and 24±14% in the control group (p=0.07).

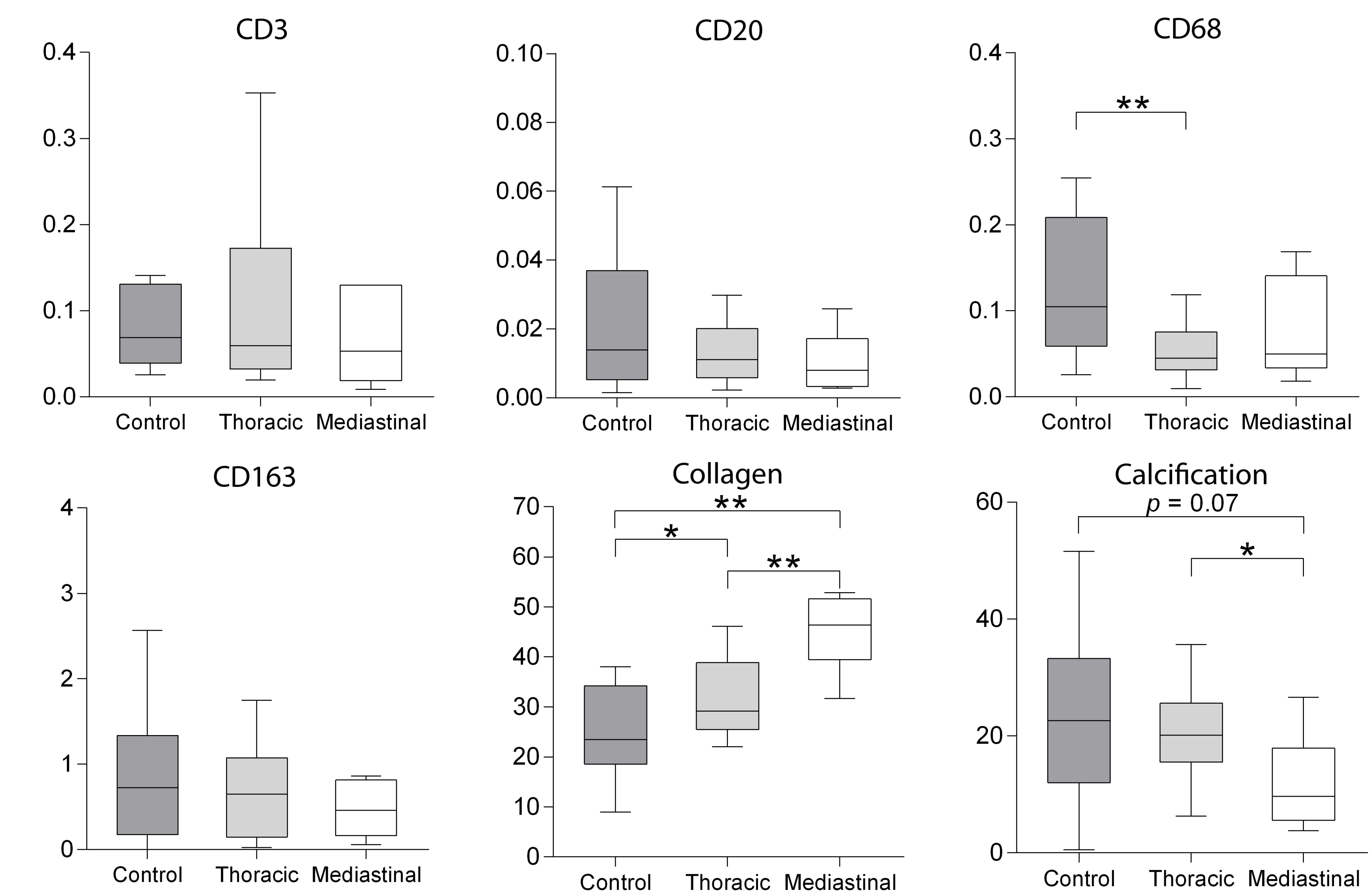


Figure 2. Quantification of immuno(histo)chemical stainings (area %)

Conclusions

The present study is the first to demonstrate the composition of the inflammatory infiltrate and extracellular matrix in the irradiated aortic valve. Thoracic radiotherapy does not result in long-term increases in inflammatory response in human aortic valves. Irradiated aortic valves show the same degree of late T and B lymphocyte infiltration as control valves, while macrophages were found decreased after thoracic radiation.

Furthermore, patients having undergone mediastinal radiotherapy develop aortic valve stenosis earlier in life, but their valves contain more collagen and less calcified tissue than stenotic aortic valves after thoracic radiotherapy.

Reference:

¹Jaworski C, Mariani JA, Wheeler G, Kaye DM. Cardiac Complications of Thoracic Irradiation. J Am Coll Cardiol. 2013 Jun 11;61(23):2319-28