Aortic stenosis, atherosclerosis and skeletal bone Is there a common link with calcification and inflammation?

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Purpose

Aortic stenosis is the most common type of valve disease in the developed world and, in an ageing population, represents an increasing healthcare burden.

The pathophysiology of calcific aortic stenosis appears to share many similarities with atherosclerosis, including lipid deposition, inflammation and calcification. Aortic valve calcification is mediated by many of the processes that drive skeletal bone formation and appears to be accelerated in patients with osteoporosis.

The aims of this study were to assess using PET-CT the relative contributions and inter-relationships of calcification (18F-NaF) and inflammation (18F-FDG) in the aortic valve, regions of thoracic atherosclerosis and the skeletal bone of patients with calcific aortic stenosis.

Methods and Materials

We recruited patients from the out-patient clinic of the Royal Infirmary of Edinburgh, with a full spectrum of calcific aortic valve disease including those with aortic sclerosis.

Combined positron emission and computed tomography (PET CT) scans of the aortic valve, coronary arteries and aorta were performed with a hybrid scanner (Biograph mCT, Siemens Medical Systems, Erlangen, Germany).

PET-CT was performed using 18F-sodium fluoride (18F-NaF; calcification) and 18F-fluorodeoxyglucose (18F-FDG; inflammation) in 101 patients with calcific aortic valve disease (81 aortic stenosis, 20 aortic sclerosis). Tracer activity (tissue-to-background ratio; TBR) and calcium scores were measured in the aortic valve, coronary arteries and aorta.

Results

One hundred and one patients (72±8 years, 69% male) underwent PET imaging of their thorax 66±6 min after injection of 125±10 MBq of 18F-NaF and 94±7 min after administration of 197±12 MBq 18F-FDG on separate days. This cohort comprised 20 patients with aortic sclerosis, and 25 patients with mild, 33 with moderate, and 23 with severe aortic stenosis

Over 90% of the cohort had calcific atheroma, yet correlations between calcium scores were weak or absent (valve vs. aorta r^2=0.090, P=0.002; valve vs. coronaries r^2=0.003; P=0.576) as were associations between calcium scores and bone mineral density (BMD; vs. valve. r^2=0.002; vs. coronaries r^2=0.018; vs. aorta r^2=0.019; P>0.05 for all). 18F-NaF activity in the valve was 28% higher than in the aorta (maximum TBR: 2.66±0.84 vs. 2.11±0.31 respectively, P<0.001) but correlated more strongly with the severity of aortic stenosis (r^2=0.419, P<0.001) than 18F-NaF activity outwith the valve (valve vs. aorta r^2=0.167, P<0.001; valve vs. coronary arteries r^2=0.174, P<0.001; valve vs. bone r^2=0.001, P=806). In contrast 18F-FDG activity was lower in the aortic valve than aortic atheroma (maximum TBR: 1.56±0.21 vs.1.81±0.24 respectively, P<0.001) and was only weakly associated with aortic stenosis severity (r^2=0.105, P<0.001).

Images for this section:

Number	101
Age, y	72±8
Male sex, n (%)	70 (69)
Body mass index, kg/m^2	28±4
Aortic Sclerosis, n (%)	20 (20)
Aortic Stenosis, n (%)	81 (80)
Clinical diagnosis ischemic heart disease, n (%)	36 (36)
Clinical diagnosis cardiovascular disease, n (%)	40 (40)
Smoking n (%)	12 (12)
Diabetes mellitus, n (%)	16 (16)
Hypertension, n (%)	65 (64)
Osteoporosis, n (%)	2 (2)
BMD measurements using CT (mean HU)	155±44
Chronic kidney disease stage 3, n (%)	23 (23)
Chronic kidney disease stage 4, n (%)	1 (1)
Creatinine, mg/dL	1.03±0.31
Urea (BUN), mg/dL	20.6±7.7
Calcium, mg/dL	9.3±0.6
Phosphate, mg/dL	3.6±0.9
Alkaline Phosphatase, U/dL	86±47
Total cholesterol, mg/dL	193±52
LDL cholesterol, mg/dL	106±44
Triglycerides, mg/dL	75±44
Statin therapy, n (%)	58 (57)
ACE inhibitor therapy, n (%)	40 (40)
Peak aortic jet velocity, m/s	3.1±1.1
Peak aortic valve gradient, mm Hg	42.8±28.9
Aortic valve area, cm^2	1.41±0.65
Agatston aortic valve calcium score, AU	1230 (455 to 2448)
Agatston coronary calcium score, AU	490 (104 to 1356)
Agatston aortic calcium score, AU	1186 (267 to 3414)
Calcific coronary atherosclerosis on CT, n (%)	91 (90)
Calcium Score 1–100	13 (13)
Calcium score 101–400	20 (20)
Calcium score 401–1000	24 (24)
Calcium score >1000	33 (33)

Fig. 1: Table 1

	AORTIC VALVE	AORTA	CORONARY ARTERIES	BONE (Method A)	BONE (Method B)
18F-NAF MEAN SUV	1.79 ±0.46	1.49 ±0.27	-	7.52 ±1.63	6.67 ±1.25
18F-NAF MAX SUV	2.59 ±0.85	2.04 ±0.40	1.63 ±0.53	8.28 ±1.76	10.11 ±2.28
18F-NAF MAX TBR	2.68 ±0.84	2.11 ±0.31	1.68 ±0.49	-	-
18F-FDG MAX TBR	1.56 ±0.21	1.81 ±0.24	-	-	-

Fig. 2: Table 2

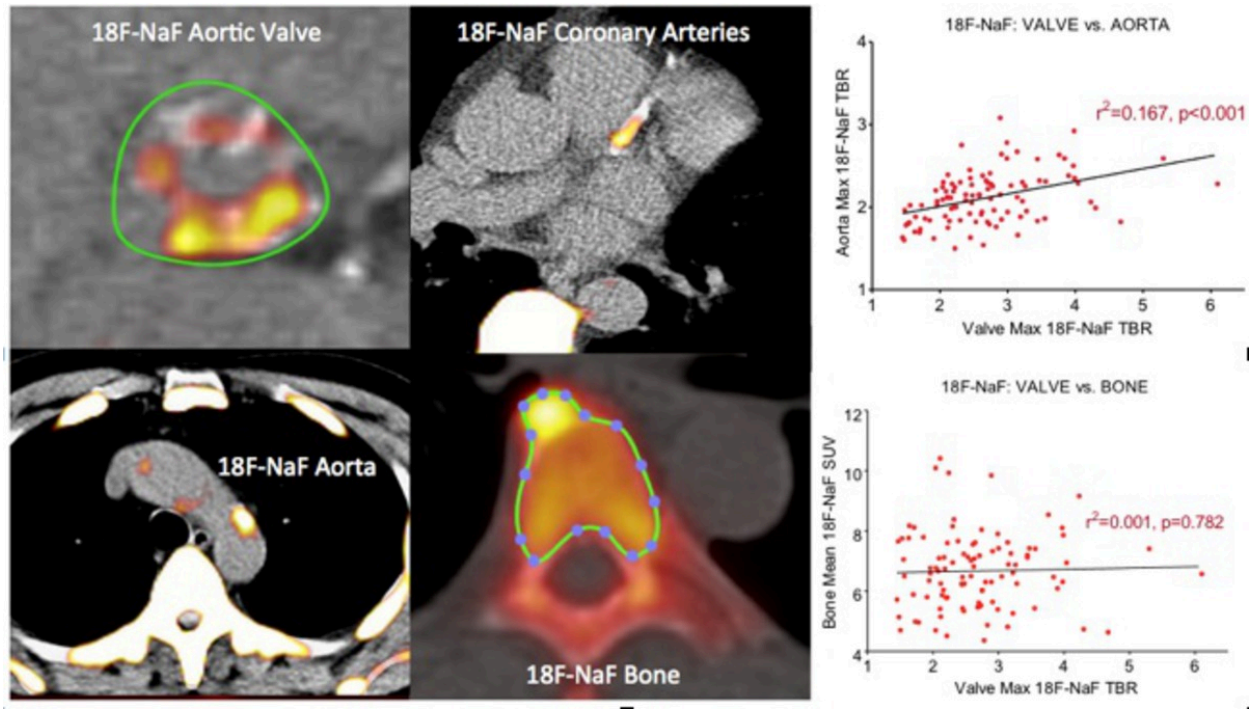

Fig. 3: Fused PET-CT images and correlation graphs

Conclusion

Using PET/CT in patients with calcific aortic valve disease, we have compared calcification and inflammation in the aortic valve with regions of thoracic atheroma and skeletal bone. Whilst coexistent calcific atherosclerosis was observed in the vast majority of our patients, we have demonstrated important differences in the underlying pathophysiology of these two conditions. In particular, active calcification is more pronounced in stenotic aortic valves compared to regions of aortic atheroma, whereas the reverse is true of inflammation. Furthermore we have demonstrated that whilst markers of aortic valve calcification are poorly related to calcific activity in atheroma and bone, they have a strong relationship with the baseline aortic stenosis severity. We conclude that calcification is the predominant pathological process in aortic stenosis and that it is driven largely by local factors specific to the valve.

Aortic stenosis is accompanied by calcific atherosclerosis in over 90% of patients yet it appears to have a distinct pathophysiology underlying its etiology and pathogenesis. In particular we have demonstrated that calcification is accelerated within the valve compared to atheroma and that in contrast to inflammation appears to be largely under the influence of local rather than systemic factors.

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