

Retrospective Study

Correlation between thoracic aorta ¹⁸F-natrium fluoride uptake and cardiovascular risk

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Abstract

AIM: To investigating the relationship between thoracic and cardiac ¹⁸F-Natrium-Fluoride (18F-NaF) uptake, as a marker of ongoing calcification and cardiovascular risk factors.

METHODS: Seventy-eight patients (44 females, mean age 63, range 44-83) underwent whole body 18F-NaF positron emission tomography/computed tomography. Cardiovascular risk (CVR) was used to divide these patients in three categories: Low (LR), medium (MR) and high risk (HR). 18F-NaF uptake was measured by manually drawing volumes of interest on the ascending

aorta, on the aortic arch, on the descending aorta and on the myocardium; average standardized uptake value was normalized for blood-pool, to obtain target-to-background ratio (TBR). Values from the three aortic segments were then averaged to obtain an index of the whole thoracic aorta.

RESULTS: A significant difference in whole thoracic aorta TBR was detected between HR and LR (1.84 ± 0.76 vs 1.07 ± 0.3 , $P < 0.001$), but also between MR and HR-LR (1.4 ± 0.4 , $P < 0.02$ and $P < 0.01$, respectively). Significance of this TBR stratification strongly varied among thoracic aorta subsegments and the lowest P values were reached in the descending aorta ($P < 0.01$). Myocardial uptake provided an effective CVR classes stratification ($P < 0.001$). Correlation between TBR and CVR was appreciable when the whole thoracic aorta was considered ($R = 0.67$), but it peaked when correlating the descending thoracic segment ($R = 0.75$), in comparison with the aortic arch and the ascending segment ($R = 0.55$ and 0.53 , respectively).

CONCLUSION: Fluoride uptake within the thoracic aorta wall effectively depicts patients' risk class and correlates with cardiovascular risk. Descending aorta is the most effective in CVR determination.

Key words: Positron emission tomography/computed tomography; ^{18}F -Natrium fluoride; Plaque imaging; Cardiovascular risk profile; Thoracic aorta

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Core tip: We evaluated, in 78 patients who underwent whole body 18F-Natrium Fluoride (18F-NaF) positron emission tomography/computed tomography, the 18F-NaF uptake in different segments of thoracic aorta and within the myocardium, as a measure of ongoing molecular calcification. In particular, we tested the hypothesis of a correlation between thoracic aorta uptake and cardiovascular risk (CVR). We thus assessed 18F-NaF uptake (TBR) in different CVR groups (high, medium and low) and its correlation with absolute CVR value. TBR stratified the three CVR classes, mostly in the descending aortic segment and in the myocardium. Thoracic aorta uptake correlated with CVR and with myocardial uptake.

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INTRODUCTION

Cardiovascular disease has been representing, for many

decades an ever-ongoing pandemia; acute and chronic cardiovascular ailments, once a hallmark of western population and lifestyle, have seeped through the lower-income population strata^[1]. The assessment of individual cardiovascular risk (CVR) allows the implementation of primary and secondary prevention measures^[2-4], such as lifestyle modifications and the administration of drugs contrasting the development and progression of atherosclerosis^[5].

However, CVR assessment does not provide any information on atherosclerotic plaque biology and progression; it neither can effectively tell whether vascular lesions are stabilized by therapy nor can identify those vascular segments that are at higher risk for occlusion.

To overcome this limitation, non-invasive imaging has been proposed. The most widespread application is coronary calcium scoring (CS), which uses the high attenuation coefficient of calcium to detect calcified plaques within the vascular tree by X-ray computed tomography (CT)^[6]. This technique is able to thoroughly depict the total coronary calcification load, which is an expression of the underlying plaque burden; it is however unclear whether data provided by this type of imaging are able to accurately stratify the actual CVR^[7-9].

Discrepancies between CS and CVR are often related to the relatively low sensitivity of the CT approach, which is unable to detect micro-calcifications^[10] and thus tend to miss the earlier phases of plaque formation, which would probably benefit the most from clinical intervention. In addition, tomo-densitometric approaches are unable to reveal whether the plaque is at risk of rupture.

In order to overcome these limitations, radio-isotope plaque imaging was proposed in relatively recent times^[8,11-14]. In particular, the use of bone-seeking positron-emitting tracer, such as ^{18}F -Natrium Fluoride (18F-NaF) was attempted, given the great similarity in actors participating to bone apposition in the skeleton and plaque calcification in the arterial wall^[15]. These studies confirmed the feasibility of 18F-NaF plaque imaging and the correlation of arterial 18F-NaF uptake with CVR^[8]. Recent evidence points out that this approach is mostly helpful in the earlier phases of calcification, while the plaque is still actively concentrating mineral ions^[16]. Moreover, 18F-NaF plaque imaging has shown potential even in the identification of the vulnerable plaque^[17,18].

These considerations should theoretically bolster the application of 18F-NaF imaging in the coronary district. However, this type of approach is still limited by several positron emission tomography (PET)-related factors, such as the low spatial resolution and the continuous cardiac movement, which prevent an accurate depiction of coronary wall mineral metabolism and causes high variability in the evaluated uptake^[14].

These issues can be overridden in at least two ways. First, there is strong evidence that thoracic aorta calcifications are strongly linked with coronary artery calcifications score^[19,20]; moreover, aortic lesions have been shown to even precede those in the epicardial arteries^[21]. Thus, processes underlying thoracic aorta

mineral turnover could herald or mirror those observed in the coronary tree.

Alternatively, cardiac fluoride deposition could be measured on the entire myocardium, as proposed by Beheshti *et al.*^[22], thus including in the semi-quantitative analysis both the contribution from major vessels and the signal from the microvasculature. This approach could limit the impact of smear artifacts due to cardiac motion and small vessel diameter.

In the present study, we analyze the correlation between clinical CVR score and two indexes of thoracic aorta and global cardiac 18F-NaF uptake, aiming to test the feasibility of their use as surrogate markers of CVR.

MATERIALS AND METHODS

Patients population

The study included 78 patients with either breast or prostate cancer (44 females, mean age 63.3 ± 8.2 range 44-83) undergoing 18F-NaF PET/CT scan for evaluation of presence of bone metastases. Exclusion criteria included history of major cardiac adverse events, vasculitis, autoimmune or systemic inflammatory disease or chemotherapy in the preceding 8 wk, as previously proposed^[8]. Cardiovascular risk stratification was performed according to a simplified version of the Framingham model (including age, diabetes, smoking, systolic blood pressure and body mass index)^[4]. According to the Framingham score, the whole study group was subdivided into three risk categories: High ($> 20\%$), intermediate ($10\%-20\%$) and low ($< 10\%$) risk of cardiovascular events in the next 10 years.

Ongoing or previous treatment with statins was used as a further exclusion criterion to avoid influence of this treatment on the results^[5]. The Internal Review Board evaluated and approved this retrospective study; all patients signed a written informed consent.

18F-NaF PET acquisition and reconstruction

Patients underwent 18F-NaF PET/CT using two 16 slices PET/CT hybrid systems: (1) biograph 16 (Siemens Medical Solutions, Knoxville TN, United States); and (2) discovery LS (GE Medical Systems, Milwaukee, WI, United States). In both cases patients received an intravenous bolus injection of 18F-NaF (4.8-5.2 MBq per kilogram of body weight). PET/CT acquisition started 60-75 min thereafter; in the meantime the patient was hydrated and encouraged to void, as to diminish the unbound tracer fraction. The entire body was scanned from vertex to toes in an "arms down" position; emission scan lasted 120" per bed position. PET raw data were reconstructed by means of ordered subset expectation maximization (OSEM, 3 iterations, 16 subsets) and attenuation correction was performed using CT data. The transaxial field of view and pixel size of the reconstructed PET images were 58.5 cm and 4.57 mm, respectively, with a matrix size of 128×128 mm. As per standard PET/CT imaging protocol, 16-detector row helical CT scan was performed with non-diagnostic current and voltage

settings (120 Kv, 80 mA), with a gantry rotation speed of 0.5 s and table speed of 24 mm per gantry rotation. No contrast medium was injected. The entire CT dataset was fused with the 3-dimensional (3D) PET images using an integrated software interface (Syngo; Siemens Erlangen, Germany) and was used for anatomical localization.

Image analysis

Reconstructed images were anonymized and analyzed offline on a dedicated workstation, running a DICOM image visualizer (Osirix 64-bit, Pixmeo, Geneva, CH). Volume of interest (VOI) were manually drawn on three segments of the thoracic aorta (ascending, arch, descending) using the co-registered CT images as anatomical reference and on the entire myocardium, as proposed by Beheshti *et al.*^[22]. The three aortic segments were averaged to obtain the overall thoracic aorta uptake. See Figure 1 for an example of VOI generation. Average standardized uptake value (SUV) was calculated and then normalized for background activity, obtained as mean SUV of a 10-slice thick VOI drawn on the inferior vena cava. Resulting figure was labeled target-to-background ratio (TBR); myocardial uptake was defined normalized global molecular calcification score (NGMCS), as proposed^[22].

Statistical analysis

All data are reported as mean \pm SD. Differences between groups were tested using one-way analysis of variance, with intergroup comparison afforded using Bonferroni test. Two-tailed Pearson R index was used to test the significance of correlations. Intra- and inter-rater agreement were afforded using Cohen's kappa and two-tailed Pearson R for qualitative and quantitative variables, respectively. Statistical analyses were performed using a software application (SPSS, v. 21.0, IBM, Armonk NY, United States). The statistical review of the manuscript was performed by a biomedical statistician.

RESULTS

Patients population

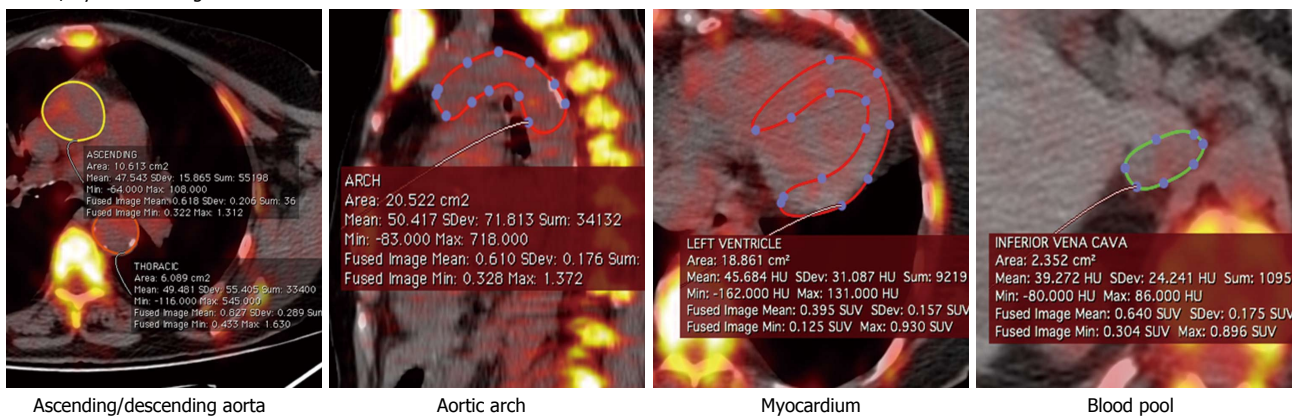
After stratification, 20, 36 and 22 patients belonged to the high, medium and low risk category, respectively. Mean ten-years CV risk was $29\% \pm 2.4\%$ for the high-risk population, 14.3 ± 3 for the medium risk stratum and 6.6 ± 2.3 for the low risk group. The latter patients were also significantly younger with respect to the other two sub-populations (58.3 ± 8.2 vs 65 ± 9.5 - medium risk and 65 ± 9.1 - high risk) (Table 1).

CV risk stratification

TBR effectively stratified the three risk categories, when considering the overall thoracic aorta (1.8 ± 0.75 , 1.4 ± 0.4 and 1.14 ± 0.34 for high, medium and low risk, respectively, $P < 0.05$).

Significance of stratification varied among aortic subsegments, with descending being capable to tell apart the three CVR categories (TBR equal to $1.94 \pm$

Vessel/myocardium segmentation



3D volume reconstruction

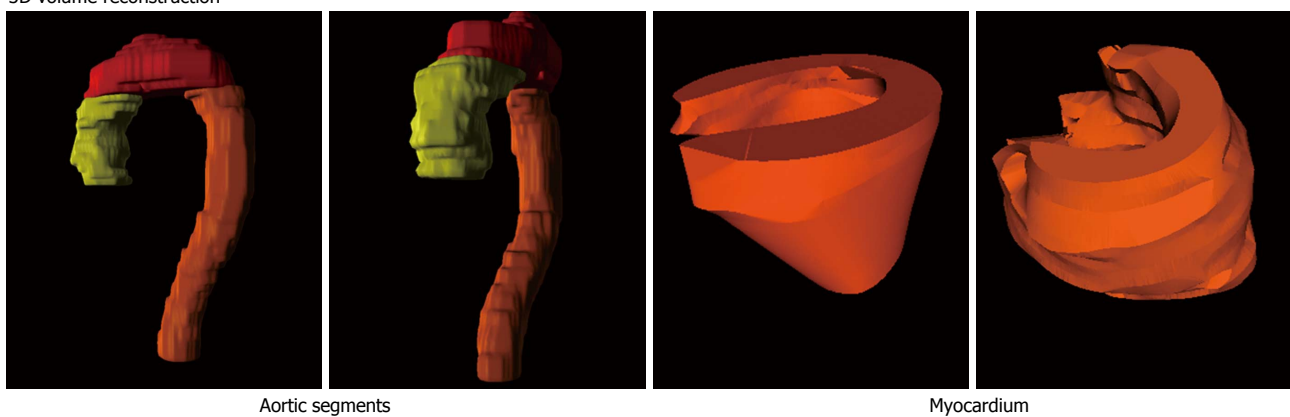


Figure 1 Volume of interest placement and 3-dimensional rendering of the vascular segments and of the myocardium. Volumes of interest were constructed by placing sequential region of interest on the transaxial CT slices, carefully adjusting the edges so as to include the entire vessel/myocardium (top panels). The figure depicts the 3D rendering of the three aortic segments and of the heart (bottom panels). 3D: 3-dimensional; CT: Computed tomography.

Table 1 Patients' characteristics

	Patients number	Mean age	Gender m/f	Systolic bp	Bp treatment (Yes/No)	Smoke	Diabetes	BMI	Mean CVR	Whole thoracic aorta TBR	NGMCS
Low CVR	22	58.3 ± 8.2	7/15	114 ± 5	2/20	1/21	2/22	24 ± 1	6.6% ± 2.3%	1.14 ± 0.34	104 ± 46
Medium CVR	36	65 ± 9.5	10/26	123 ± 6	12/24	14/22	5/31	25 ± 3	14.3% ± 3%	1.4 ± 0.4	62 ± 21
High CVR	20	65 ± 9.1	10/10	128 ± 11	8/12	19/1	15/5	27 ± 2	29% ± 2.4%	1.8 ± 0.75	43 ± 17

CVR: Cardiovascular risk; TBR: Target-to-background ratio; BMI: Body mass index; NGMCS: Normalized global molecular calcification score.

0.8, 1.44 ± 0.45 and 1.14 ± 0.34 , respectively, $P < 0.02$). Conversely, aortic arch and ascending aorta could discriminate high and low risk ($P < 0.01$ and $P < 0.02$) but provided less clear distinction between medium risk and the other two risk categories. Refer to Figure 2 and to Table 2 for the exact figures of TBR and significance.

NGMCS, resulted an effective index of risk assessment: Its values were 104 ± 45.6 , 62 ± 20.8 and 42.7 ± 17.4 in high, medium and low CV risk groups, respectively ($P < 0.001$; Table 2 and Figure 2).

Correlation between aortica 18F-NaF uptake, CV risk and NGMCS

Overall, thoracic aorta TBR showed a significant correlation with CVR ($R = 0.82$, $P < 0.001$). Among segments,

descending aorta displayed the closest correspondence to the clinical risk assessment ($R = 0.79$). Among single risk factors, age and hypertension were tightly associated with aortic TBR ($R = 0.32$, $P < 0.05$; $R = 0.54$, $P < 0.01$, respectively); moreover, patients with diabetes had a significantly higher TBR with respect to non-diabetics (1.7 ± 0.7 and 1.4 ± 0.5 , $P < 0.01$).

Aortic TBR showed a significant correlation with NGMCS as well (whole thoracic aorta vs NGMCS produced an R-index of 0.67). However, this correlation was prevalently observed in descending aorta ($R = 0.72$) (Table 3 and Figure 3).

Finally, measurement of TBR was accurate and relatively operator-independent: Intra- and inter-rater agreement was excellent (Cohen's kappa value = 0.91;

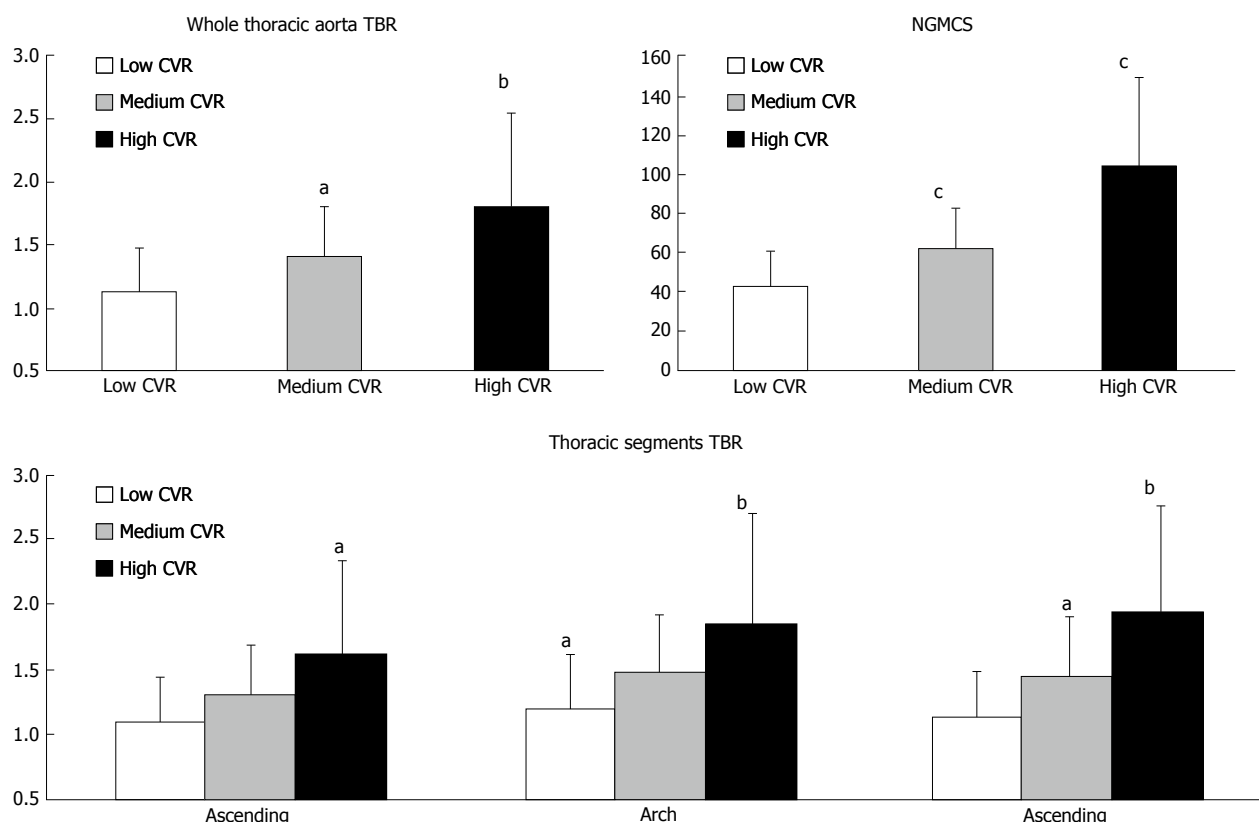


Figure 2 Target-to-background ratio differences in cardiovascular risk classes. The figure highlights the average TBR values for the whole thoracic aorta (top left), the myocardium (top right) and the three different thoracic aorta segments (bottom). ^a $P < 0.05$; ^b $P < 0.01$; ^c $P < 0.001$. TBR: Target-to-background ratio; CVR: Cardiovascular risk; NGMCS: Normalized global molecular calcification score.

Table 2 Target-to-background ratio differences in risk group (P value)

	High	Medium	Low
Thoracic aorta			
High	-	0.031	0.002
Medium	0.031	-	0.023
Low	0.002	0.023	-
Ascending aorta			
High	-	0.085	0.013
Medium	0.085	-	0.056
Low	0.013	0.056	-
Aortic arch			
High	-	0.066	0.007
Medium	0.066	-	0.033
Low	0.007	0.033	-
Descending aorta			
High	-	0.012	0.001
Medium	0.012	-	0.018
Low	0.001	0.018	-
Normalized global molecular calc. Score			
High	-	0.000	0.000
Medium	0.000	-	0.003
Low	0.000	0.003	-

Table 3 Correlation between aortic uptake, cardiovascular risk and normalized global molecular calcification score

Segment TBR	CVR		NGMCS	
	R2	R	R2	R
Ascending	0.52	0.72	0.27	0.52
Arch	0.48	0.70	0.35	0.59
Descending	0.62	0.79	0.52	0.72
All segments	0.67	0.82	0.45	0.67

CVR: Cardiovascular risk; TBR: Target-to-background ratio; NGMCS: Normalized global molecular calcification score.

Pearson's $R = 0.95$).

DISCUSSION

In recent years, non-invasive, functional imaging of the coronary district has received a large attention^[17]. In

particular, the widespread distribution of PET scanner with 3D detection technology has allowed grasping the signal produced by plaque metabolism^[11-14,16]. The scientific background underlying this approach is still relatively young and its applications lie predominantly within the research terrain^[23]. However, a few studies have provided a glimpse of future clinical application: The two main streaks are at present the detection of early (CT-negative) arterial plaque^[16,22,24] and the identification of the vulnerable atherosclerotic lesion^[18,25,26].

Although the issue of organ movement can be solved by gating^[18], the main limiting factor in applying PET imaging on the study of the coronary district is the small size of these vessels^[26], which fall below the resolution capability of most scanner^[27] and can cause underestimation of PET signal due to partial volume

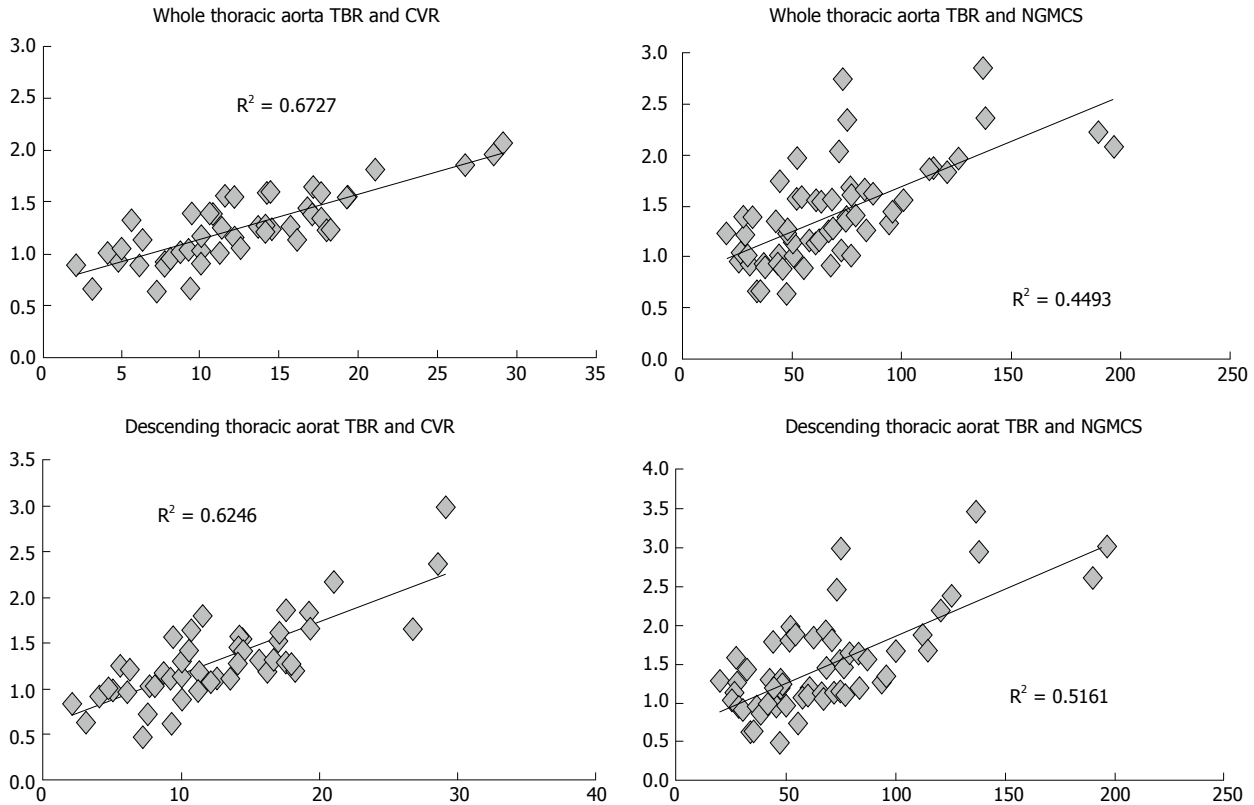


Figure 3 Correlation between fluoride uptake and clinical cardiovascular risk. A strong correlation was noted between thoracic aorta NaF uptake and CVR, but also between aortic and myocardial uptake (top panels). Among the thoracic aorta subsegments, descending aorta provided the strongest correlation (bottom panels). TBR: Target-to-background ratio; CVR: Cardiovascular risk; NGMCS: Normalized global molecular calcification score.

effect.

In this context, the utilization of surrogate measures to estimate the coronary mineral turnover can provide an affordable method to interrogate calcium deposition in this district; our data show a tight correlation between activity of thoracic aorta, activity within the myocardium, depicting the process of arterial calcification as a systemic ailment, rather than a localized phenomenon. The concept of “plaque promoting environment” is further corroborated in the analysis of the whole myocardial volume: The application of the model by Beheshti *et al.*^[22], with subsequent normalization for background activity, provided an excellent stratification among risk classes. The evidence of increased macro and micro-vascular signal from high-risk patients opens new questions, which call for longitudinal studies, aimed to assess whether an increased 18F-NaF activity is the harbinger of future calcifications and/or adverse cardiovascular events.

Correlation between aortic uptake and CV risk was consistent in all three segments but relationship between thoracic and cardiac 18F-NaF accumulation was somewhat less steady and prevailed in the arch and in descending aorta. This is in agreement with our previous observation, which demonstrated that vessel fluoride uptake is “*per se*” a marker of CVR, regardless of the studied segment^[8]. Conversely, intensity of this uptake tends to correlate in vessels that are subject to similar flow conditions. Specifically, these data parallel those reported in the literature for vascular calcification

indicating that vascular regions characterized by vessel branching are more prone to plaque formation, due to the influence of regional flow alterations^[28,29]. These considerations imply that, when using thoracic aorta as a surrogate for coronary artery vascular lesions, the analysis should be focused on the descending segment and on the arch.

This study presents some limitations. It is a retrospective study, performed on patients that were referred for an oncologic condition. Ethical consideration impeded radiotracer injection outside of validated clinical indications; recent studies have yet presented strong evidence that vascular and plaque 18F-NaF uptake is linked with active calcification processes^[18,30]. Moreover, the strict inclusion criteria limited the size of the population; however, the sample size actually matched the one of several previous studies regarding 18F-NaF uptake within plaque and arterial vessels^[10,14,18].

Finally, cardiac volume-of-interest was placed on an ungated PET; however, the large volume of the sampled tissue should have largely limited the influence of motion artifacts.

Altogether, the continuous improvement of PET/CT instrumentation has been opening a whole new perspective on plaque biology. The systematization of this analysis has the potential to allow the quantification of plaque mineral turnover, granting the possibility to stratify the evolutionary pattern of vascular lesions. In the coronary artery setting, where the small vessel size

remains at the boundary of the PET diagnostic capability, the application of an indirect evaluation of active calcification might enable to derive a prognostic index and to measure the effectiveness of plaque treatments.

COMMENTS

Background

18F-Natrium-Fluoride (18F-NaF) is a bone seeking tracer that has been successfully proposed for the imaging of micro-calcification processes within the atherosclerotic plaque. Since coronary arteries are one of the most important targets of this kind of research, but tend to be subject to partial volume effects in images produced by commercial scanners. The authors hypothesized that thoracic aorta could serve as an ersatz, on the bases of the known correlation between thoracic aorta and coronary calcifications.

Research frontiers

The analysis proved that thoracic aorta uptake is related to both the cardiovascular risk profile and the uptake in the whole myocardium (as a measure of the entire calcification activity occurring in the heart micro- and macro-vasculature).

Innovations and breakthroughs

Computational analysis of 18F-NaF uptake within the thoracic aorta vessel walls has the potential to become a robust, independent and non-invasive risk of cardiovascular risk. Differently from clinical scores, which give off a likelihood of acute events, 18F-NaF uptake actually depicts the activity of calcium deposition within arteries, as a marker of plaque growth.

Applications

This research should serve as a base to further perspective studies, used to identify the role of 18F-NaF uptake in predicting future cardiovascular events. This kind of analysis could be automated by applying simple mathematical approaches, so as to become faster and more operator-independent.

Peer-review

The authors present a retrospective analysis of correlation between different segments of thoracic aorta 18F-NaF uptake and cardiovascular risk, as well as to evaluation of correspondence between aortic and myocardial uptake in 78 oncologic patients. The study is interesting, even if there are several reports demonstrating the reliability of 18F-NaF positron emission tomography/computed tomography in imaging plaque inflammation in large arteries and the correlation between radiotracer uptake in atherosclerotic lesions and the presence of cardiovascular risk factors, identifying the patients at risk of future cardiovascular events.

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