WJC-21817

Reviewer #1

Hengelo, 02 October 2015,

Comments on the ESPS Manuscript NO: 21817

Title: Correlation between thoracic aorta 18F-NaF uptake and cardiovascular risk

The authors in a retrospective study evaluated in 78 oncologic patients the correlation between thoracic aorta and in the myocardial tissue of PET/CT 18F-Natrium Fluoride uptake and Cardiovascular Risk. The number of patients in the current study is limited. They found that thoracic aorta and myocardial uptake correlated with CVR.

Dear Reviewer #1

Thank you for reviewing our work. For your convenience, we performed the revision process using the following color code:

Black: Your point or concern.
Blue: Our reply to your point.
Red: Edits to the manuscript that have been performed according to your suggestions.

Larger series is needed to confirm these preliminary findings.
You are right. Obviously, larger series allow more confidence in deriving conclusion from results. This is however a proof-of-concept study, aimed at determining the value of an easily measurable variable (such as is the thoracic aorta uptake) as a surrogate marker for an harder-to-determine parameter (coronary artery uptake). As you correctly pointed out, it serves as a springboard for larger, perspective study, aimed at determining the real value of vascular and plaque NaF uptake in the prediction of development of cardiovascular disease and of cardiovascular events. According to these considerations, the following sentence has been added to the Limitations paragraph in the results section: “Moreover, the strict inclusion criteria limited the size of the population; however, the sample size actually matched the one of several previous studies regarding NaF uptake within plaque and arterial vessels (10,14,18)”.

Page 4: Line 12: "--- in the ---" is mentioned twice, please delete.
Page 8: Line 16: Please consider Mean±Standard Deviation instead of Mean±Standard Seviation
These issues have been addressed. Sorry for the typos.

References in the text should be inserted according to the journal's recommendations.
We edited the reference list, which is now formatted according to the house style.

Reviewer #2

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 PET/TC 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.

Dear Reviewer #2

Thank you for your thorough revision of our work. We are aware of the fact that the present paper is proposed on the wake of several reports linking NaF uptake and ongoing calcification. In this study we focused on finding a way to obtain similar data on the coronary arteries, which by definition cannot be correctly assessed by the limited spatial resolution of commercial PET scanners. These results, whether confirmed by further studies, could allow the utilization of thoracic aorta NaF uptake as a surrogate marker for ongoing coronary atherosclerosis.

In the process of revision, for your convenience, we performed the revision process using the following color code:

Black: Your point or concern.
Blue: Our reply to your point.
Red: Edits to the manuscript that have been performed according to your suggestions.

I think it would be useful to add some data:

Were all images analysed by 2 independent readers?
Please, specify the reproducibility, in particular intra- and interrater agreement and Cohen's K
According to your suggestion, all images were re-analysed by an experienced reader (SM). No significant differences were noted in the TBR values provided by the new analysis. In particular, intra- and inter-rater agreement was excellent, with a Cohen's kappa value of 0.91 and a Pearson's R of 0.95. Accordingly, the following sentence was added to the "statistical analysis" subsection of the Methods:
Intra- and inter-rater agreement were afforded using Cohen's kappa and two-tailed Pearson R for qualitative and quantitative variables, respectively.
And the figures of intra- and inter-rater agreement were included in the results, as follows:
Finally, measurement of TBR was accurate and relatively operator-independent: intra- and inter-rater agreement was excellent (Cohen's kappa value = 0.91; Pearson's R = 0.95).

Please, specify sex and the cardiovascular risk factors in each class of risk in a table
Table 1 has been updated and now includes all the required information.

Please, a hint to the association to individual risk factors (age, male sex, hypertension, hypercholesterolemia, smoking exposure, and diabetes). For example, in the study by

Derlin T (reference n.12) no association was found between diabetes and radiotracer uptake in the common carotid arteries.
We agree that including this information would be of interest to the readers. We therefore analysed the single risk factors: the strongest association with increased fluoride uptake was observed for systolic blood pressure and age; patients with diabetes at the time of PET had significantly increased TBR with respect to non-diabetics. This information was included in the results section (third subsection):
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, $p<0.01$).
Actually, the study by Derlin et al. was focused on measuring the mineral metabolism of plaques that were already visible at the time of scan. Conversely, the present study analysed the entire vessel, regardless of the presence of macroscopic calcification or tracer uptakes areas, as the focus of our paper is to study the earliest phases of vascular calcium deposition and the possible correlation between vascular segments. This could explain the different results that the two analyses yielded in term of diabetes-TBR correlation, which however approached significance in Derlin's paper.

An important limitation is that this study was performed on oncologic patients, thus the results might not be perfectly generalizable to other patients populations.
You are right. Oncologic patients could be not fully representative of the general population, owing to disease- and treatment-related processes. However, as stated in the discussion, ethical concerns prevent radiotracer injection outside of clinical indications. A possible way to bypass this problem in a retrospective study would be to include only patients referred for non-oncological conditions (such as patients candidate to prostheses-replacement surgery); however this would greatly limit the sample size.
On the other hand, evidence for the use of NaF in vascular ailments, whether as a marker of active calcium deposition or of plaque vulnerability, is growing. Actually, the paper by Joshi et al. (ref. #18) highlighted, in cardio-vascular patients, a correlation between NaF uptake and mineral turnover markers within the plaque. An even more recent study by Irkle et al. demonstrated that NaF is selectively and specifically absorbed by calcified regions within the plaque.
In conclusion, there is now strong evidence that what we observe in plaques and in the vascular walls is not mere happenstance and while we should take these results cautiously in the population presented hereby, we have clear evidence on the meaning of plaque NaF uptake.
These considerations were briefly included in the limitations para, that was edited as follows:
Ethical consideration impeded radiotracer injection outside of validated clinical indications; recent studies have yet presented strong evidence that vascular and plaque NaF uptake is linked with active calcification processes (18,30).
The following reference has been included (#30)
Irkle A, Vesey AT, Lewis DY, Skepper JN, Bird JL, Dweck MR, Joshi FR, Gallagher FA, Warburton EA, Bennet MR, Brindle KM, Newby DE, Rudd JH, Davenport AP. Identifying active vascular microcalcification by (18)F-sodium fluoride positron emission tomography. Nat Commun. 2015; 6:7495 [DOI: 10.1038/ncomms8495].