Sodium [18f]fluoride positron emission tomography for non-invasive identification of micro-calcifications as marker of atherosclerotic plaque vulnerability

Title: Sodium [^{18}F]Fluoride positron emission tomography for non-invasive identification of micro-calcifications as marker of atherosclerotic plaque vulnerability
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Aims: Despite recent medical advances, cardiovascular disease remains the leading cause of death worldwide. Given the high sensitivity and specificity of Na[^{18}F]F and [^{68}Ga]Ga-Pentixafor for cardiovascular calcifications and inflammation respectively and positive emerging data of vitamin K on vascular health, the aim of this thesis was to assess the ability of both tracers to monitor disease progression and therapy with vitamin K.

Materials and methods: Chapter I provided a general introduction. Chapter II identified Na[^{18}F]F PET as the most suitable technique for detecting micro-calcification, after a structured PubMed search. Presenting the pros and cons of available treatments, vitamin K supplementation emerged as a possible safe and cost-effective option to inhibit vascular (micro)-calcification. In Chapter III, a unitary atherosclerotic mouse trial was designed to assess the ability of Na[^{18}F]F PET/CT to monitor therapy and disease progression and of vitamin K to inhibit vascular calcification. In Chapter IV, a prospective double-blind placebo-controlled feasibility study was created to investigate the practicability of the results from the animal study in the human situation, using a hybrid PET/MRI. In Chapter V, the feasibility of monitoring plaque inflammatory status using [^{68}Ga]Ga-Pentixafor was preclinically assessed.

Results and discussion: After selecting Na[^{18}F]F PET as a mean to image vascular (micro-)calcifications and Vitamin K to treat it, the preclinical trial was started. Here mice treated with Warfarin (*i.e.*, a Vitamin K inhibitor) presented spotty calcifications on the CT in the proximal aorta. All the spots corresponded to dense mineralisations on the von Kossa staining. Mice with an advanced atherosclerosis did not develop spotty calcifications, however Na[^{18}F]F uptake was still observed, suggesting the presence of micro-calcifications. After the control, the Vitamin K treated animals had the lowest Na[^{18}F]F uptake, suggestion its protective role. The results of the preclinical study will be tested in the INTRICATE clinical trial, where the primary endpoint is the temporal change of Na[^{18}F]F uptake in human carotid artery atherosclerosis of the treatment arm (*i.e.*, with vitamin K) and the placebo arm. [^{68}Ga]Ga-Pentixafor seems to be able to correctly detect inflammatory changes in the atherosclerotic plaque morphology.

Conclusion: This thesis argues for the practicability of Na[^{18}F]F and [^{68}Ga]Ga-Pentixafor PET to monitor atherosclerotic plaque progression and treatment, while serving as an argument for the increase in the recommended daily dose of vitamin K.