Abstract: **P511**

**Deregulations in CD4+ T lymphocytes subsets promote inflammation in atrial fibrillation**

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Background: The precise role of inflammation in the development and perpetuation of atrial fibrillation (AF) is yet to be fully uncovered. T and B lymphocytes, the main cellular effectors of adaptive immunity, have pivotal roles in orchestrating inflammation. Different subsets of lymphocytes either promote or prevent inflammation. We are investigating a unique subset of lymphocytes, the CD4+CD28null T cells that expand in patients with chronic inflammation. These cells secrete high levels of pro-inflammatory cytokines tumour necrosis factor-a (TNF-a) and interferon-g (IFN-g). The response of CD4+CD28null T cells is normally maintained under control by regulatory T cells (Treg), a specialised subset of T lymphocytes with suppressive function that maintain immune homeostasis and prevent pathogenic immune responses. The role of CD4+CD28null and Treg cells has not been investigated in AF.

**Purpose:** We hypothesised that in AF the balance between pro-inflammatory and regulatory T lymphocytes is skewed in favour of inflammatory T cells.

**Methods:** We recruited 65 patients with idiopathic AF who lacked co-morbidities associated with inflammation (coronary artery disease, autoimmune diseases, diabetes, heart failure). Circulating CD4+CD28null T lymphocytes, Tregs and B cells were quantified by flow cytometry in AF patients and healthy controls (n=35). High sensitivity CRP, TNF-a and IFN-g levels were quantified in serum.

**Results:** CD4+CD28null T lymphocytes were significantly increased in the circulation of AF patients compared to controls (p<0.0001). In addition, AF patients had a marked reduction (p=0.0001) in Treg cells. The ratio of CD4+CD28null T lymphocytes to Tregs was significantly increased. In contrast, no alterations were identified in circulating B cell subsets. Levels of hsCRP, TNF-a and IFN-g did not correlate with CD4+CD28null T cell and Treg frequency. Instead, we demonstrate that the expansion of CD4+CD28null T cells is caused by defects in apoptosis pathways and increased activation and proliferation in response to homeostatic cytokines.

**Conclusions:** Our novel findings show that pro-inflammatory CD4+CD28null T cells increase significantly in AF patients, whilst the anti-inflammatory Treg subset is markedly reduced. These novel results suggest an imbalance in the mechanisms that maintain homeostasis in the immune response, which may promote inflammation in patients with AF. An in-depth understanding of the role of various lymphocyte subsets in the inflammatory response in AF may reveal novel therapeutic strategies to re-establish the balance between pro- and anti-inflammatory mechanisms at work in this disease.