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Circulating plasma exosomes in obstructive sleep apnoea and reverse dipping blood pressure

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ABSTRACT

Background: Obstructive sleep apnoea (OSA) increases the risk of an abnormal nondipping 24 h blood pressure profile, an independent risk factor for cardiovascular disease (CVD). We examined differential exosomal microRNA (miRNA) expression in untreated OSA patients with normal dipping blood pressure (NDBP) and reverse dipping blood pressure (RDBP), an extreme form of nondipping, to understand the mechanisms underlying nondipping blood pressure in OSA.

Methods: 46 patients (15 RDBP *versus* 31 NDBP) matched for OSA severity (respiratory event index 32.6±22.5 *versus* 32.2±18.1 events·h^{-1}; p=0.9), age (54.8±12.9 *versus* 49±9.9 years; p=0.09) and body mass index (36.2±6.6 *versus* 34.4±6.8 kg·m^{-2}; p=0.4) were included. Plasma exosomes were characterised by flow cytometry and functional *in vitro* reporter assays were conducted on cultured endothelial cells. Exosome miRNA cargo was profiled with microarrays followed by bioinformatics analyses.

Results: Exosomes from RDBP patients increased the permeability of endothelial cell tight junctions and adhesion molecule expression. Principal component analyses of miRNA array data showed strict separation and identification of the two groups. A restricted and validated signature of exosomal miRNAs was identified in the RDBP *versus* NDBP group. Their predicted target genes involved phosphatidylinositol 3-kinase-Akt (p=0.004), Ras (p=3.42E-05), Wnt (p=0.003) and hypoxia inducible factor-1 signalling (p=0.04), inflammatory mediator regulation of transient receptor potential channels (p=0.01), and several cancer-related pathways.

Conclusions: Patients with RDBP have altered miRNA cargoes in circulating exosomes that invoke *in vitro* endothelial dysfunction. A selected number of circulating exosomal miRNAs play an important role in abnormal circadian regulation of blood pressure and may provide prognostic biomarkers of CVD risk in OSA.