

## Association between atrial high rate episode burden and autonomic and vascular function in patients with implanted cardiac device

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**Background:** Patients who experience frequent atrial high rate episodes (AHREs), recorded on implantable cardiac devices, are at an increased risk of stroke and systemic embolism. Increased duration of AHRE is related to higher risk of thromboembolic event. The underlying pathophysiology is unclear; however, autonomic and/or endothelial dysfunction may contribute.

**Purpose:** We tested the hypothesis that patients with high AHRE burden have worse autonomic and vascular function compared to patients with low AHRE burden.

**Design:** We studied 44 patients split in two groups: high AHRE burden (longest AHRE  $\geq 24$  hours; n=22) and low AHRE burden (longest AHRE <24 hours; n=22). Resting time- and frequency-domain measures of HRV were determined to index cardiac autonomic function. High-resolution ultrasound was used to measure brachial artery diameter at rest and during reactive hyperaemia (endothelium-dependent flow mediated dilation (FMD)).

**Results:** FMD was higher in the low AHRE burden group compared to high AHRE group (5.5% [95% confidence interval (CI):3.4–7.6] vs 3.1% [95% CI: 1.9–6.2]; p=0.04) (table 1). Mean heart rate (p<0.001) and AHRE burden (p=0.02) were independent predictors of FMD on multivariate analysis. Time-domain, frequency-domain and non-linear indices of HRV were not significantly different between the groups. A slower heart rate (Spearman's rho 0.369; p=0.01) and high AHRE burden (Spearman's rho -0.315; p=0.04) were independently associated with changes seen on FMD following adjustment for multiple variables (p=0.001 and p=0.03 respectively).

**Conclusion:** Endothelium-dependent FMD is impaired in patients with high AHRE burden, while HRV derived indices of autonomic function were not affected by AHRE burden. Endothelial dysfunction may play an important role in the adverse outcomes seen in patients who experience frequent AHRE.

Table 1 – Differences in autonomic and vascular function in patients with AHREs

	Low AHRE group (n = 22)	High AHRE group (n = 22)	P
Age, years	74.5 [67.5 – 81]	72 [60.8 – 82.8]	0.56
Sex (males/females)	15/7	19/3	0.15
CHA2DS2-VASc score	3 $\pm$ 2	3 $\pm$ 2	0.93
BMI (kg/m <sup>2</sup> )	29.6 [26.9 – 32.9]	27.7 [24.8 – 36.7]	0.70
Heart rate (bpm)	69 [61 – 75]	68 [60 – 80]	0.97
Systolic BP (mm/Hg)	152 $\pm$ 18	135 $\pm$ 17	<b>0.003</b>
Ejection fraction (%)	59 [55 – 62]	55 [40 – 58]	<b>0.009</b>
Baseline diameter (mm)	4.6 [4.3 – 5.0] <sup>a</sup>	4.8 [4.5 – 5.2] <sup>a</sup>	0.36
Absolute FMD change (mm)	0.2 [0.2 – 0.4] <sup>b</sup>	0.1 [0.1 – 0.3] <sup>b</sup>	0.07
FMD (%)	5.5 [3.4 – 7.6] <sup>b</sup>	3.1 [1.9 – 6.2] <sup>b</sup>	<b>0.04</b>
Shear rate stimulus [sec. <sup>-1</sup> ]	5592 [4174 – 9815] <sup>b</sup>	4173 [2458 – 10547] <sup>b</sup>	0.41
SDNN (ms)	41 [28 – 55] <sup>b</sup>	60 [39 – 80] <sup>a</sup>	0.12
rMSSD (ms)	40 [27 – 54] <sup>b</sup>	58 [39 – 77] <sup>a</sup>	0.10
pNN50 (%)	5 [2 – 23] <sup>b</sup>	17 [2 – 60] <sup>b</sup>	0.12
LF (ms <sup>2</sup> )	575 [137 – 1013] <sup>b</sup>	665 [264 – 1593] <sup>a</sup>	0.83
HF (ms <sup>2</sup> )	160 [66 – 687] <sup>b</sup>	112 [42 – 1839] <sup>b</sup>	0.98
LF normalised/HF normalised	0.8 [0.5 – 1.0] <sup>b</sup>	0.9 [0.5 – 1.4] <sup>b</sup>	0.84
SD1 (ms)	29 [19 – 38] <sup>b</sup>	41 [28 – 54] <sup>a</sup>	0.11
SD2 (ms)	49 [31 – 67] <sup>b</sup>	67 [47 – 87] <sup>a</sup>	0.15

Descriptive data are presented as numbers (with percentages). Normally distributed data are expressed as mean [95% confidence intervals (CI)]. Identified by superscript a. Non-normally distributed data are displayed as median [95% CI]. Identified by superscript b. Statistical differences were tested using independent t-test (for parametric data) or Mann-Whitney U test (for non-parametric data). Significance p  $\leq$  0.05