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Endothelial, sympathetic and cardiac function in inherited 6R-L-erythro-5,6,7,8-tetrahydro-L-biopterin deficiency

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Background: 6R-5,6,7,8-tetrahydro-L-biopterin (BH4), synthesised from GTP by the rate-limiting enzyme GTP cyclohydrolase I (GTPCH-1), is a co-factor for nitric oxide and catecholamine synthesis. Acquired BH4 deficiency is involved in the endothelial dysfunction, the sympathetic regulation of vascular tone and may be associated with right ventricular hypertrophy. Lack of specific GTPCH-1 inhibitor, has limited understanding of the role of BH4 in vascular, sympathetic and cardiac function. Genetic deficiency of BH4 due to rare mutations in GTPCH-1 manifests as a movement disorder known as dopa responsive dystonia (DRD). Assessment of autonomic, cardiac and endothelial function in these patients could provide an insight into the neurovascular role of BH4.

Methods: We measured plasma biopterin with HPLC, in 16 DRD patients and 16 age and sex matched controls. Endothelial function was assessed by flow-mediated dilatation (FMD) in presence and absence of NOS inhibitor of monomethyl-L-arginine (L-NMMA) 4 μmol/ml infused intra-arterially.

Sympathetic autonomic function was assessed by means of heart rate and blood pressure response to tilt, mental arithmetic, deep breathing, isometric exercise, and cold pressor stimuli. Plasma noradrenaline (NA) and Adrenaline (A) concentrations were also measured. Cardiac function was assessed by transthoracic echocardiography (TTE).

Results: Plasma biopterin concentration was lower in DRD patients than controls (9.8[1.5] v 5.7[0.5] nmol/L; $P = 0.057$). Despite this difference, FMD response was the same between the two groups (7.7[0.8]% v 7.8[0.9]%; $P = 0.9$). However in DRD patients but not controls, FMD was insensitive to NOS inhibition. TTE and sympathetic responses did not differ in DRD patients and controls despite significantly lower concentrations of A (34.9[5] v 17.8[4] pg/ml; $P = 0.03$) and NA (263[8] v 227[9] pg/ml; $P = 0.006$).

Conclusions: Sympathetic, cardiac function and endothelial function are preserved in patients with GTPCH-1 mutations despite the presence of a neurological phenotype, reduced plasma biopterin, A and NA concentrations. The presence of a non-NO dependent dilator response to flow suggests developmental adaptation involving up-regulation of other dilator systems in the DRD patients

The effect of inhaled air pollutants—sulphur dioxide and carbon particles—on heart rate variability and markers of inflammation and coagulation in human subjects

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Background: Epidemiological studies and animal work suggest that the short-term association between cardiovascular mortality and background levels of air pollutants might be explained either by a systemic inflammatory response or by an effect of pollutants on the cardiac autonomic nervous system. In a controlled human exposure study we have measured the autonomic and inflammatory responses to specific air pollutants in isolation at known concentrations.

Methods: In a random order, double blind, 4 way crossover study, 20 healthy volunteers were exposed for 1 h to medical air (placebo), air containing carbon particles and sulphur dioxide (SO_2), at concentrations shown in epidemiological studies to be associated with increased rates of cardiovascular mortality. Heart rate variability (HRV) was measured before, immediately after and 4 h after exposure during controlled respiration. Blood was taken at the same time points and at 24 h for analysis of high-resolution C-reactive protein (hrCRP) and markers of activation of the coagulation system.

Results: Exposure to SO_2 lead to a decrease in HRV markers of cardiac autonomic control at 4 h. (Table 1). No significant changes were seen in hrCRP, fibrinogen, vWF or d-dimers. No adverse changes were seen in HRV following exposure to air or carbon particles.

Conclusions: The increase in cardiovascular mortality observed when SO_2 concentrations are high may be attributable to a decrease in cardiac vagal control which in subjects with heart disease leads to an increase in susceptibility to lethal ventricular arrhythmia. Exposure to pure carbon particles alone does not cause adverse effects on cardiac autonomic control nor a systemic inflammatory response. Effects previously observed with combustion derived particles are likely to be attributable to some other reactive component such as transition metals found on the particle surface.

Table 1 Percentage change from baseline in heart rate variability markers of cardiac autonomic control at 4 h

	RR INTERVAL	SDNN	RMSSD	HF POWER
AIR	−4.5 (1.4)%	+3.9 (6.0)%	−1.7 (9.6)%	+0.54 (30)%
SULPHUR DIOXIDE	−8.1 (2.0)%*	−11.6 (6.7)%*	−25.0 (7.3)%*	−39.4 (12.1)%*

*$P < 0.05$ changes significantly different from placebo exposure

Quantitative assessment of the accuracy of the Finapres device in the clinical assessment of baroreflex sensitivity

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Baroreflex sensitivity (BRS) was estimated from non-invasive arterial blood pressure (ABP) measurements, collected from the finger using an Ohmeda Finapres 2300 ABP monitor. This was compared to 'gold standard' intra-aortic pressure transducer catheter (IAPTC) ABP data and BRS compared between invasive and non-invasive ABP recordings.

A total of subjects (Male = 38) were recruited from percutaneous transluminal coronary angioplasty (PTCA) patients. Post PTCA, an IAPTC was advanced to the ascending aorta and ECG and ABP data (Invasively from the IAPTC and non-invasively from the finger) recorded.

BRS values were measured using two techniques—spectral and sequence analysis, for both aortic and finger ABP data, using concurrent variation in pulse interval (PI) from ECG data. For both spectral and sequence algorithms, detected sequences were compared to check BRS agreement between invasive and non-invasive measurement sites.

Finapres accurately reported 37.95 ± 20.39% of valid IAPTC sequences, with the remaining Finapres false positives having a mean BRS of 12.4 ± 9.0 ms mm Hg^{-1}. Finapres predicts elevated BRS values versus IAPTC, using both sequence and spectral techniques. Sequence analysis results in an average Finapres BRS of 8.88 ± 5.20 ms $mmHg^{-1}$ versus 6.45 ± 3.75 ms mm Hg^{-1} from IAPTC data (37.76% increase over IAPTC). Spectral estimation increased mean BRS, but reduced error between invasive and non-invasive data. Mean Finapres BRS was 10.63 ± 5.16 ms mm Hg^{-1} versus 9.22 ± 5.03 ms mm Hg^{-1} in IAPTC data (15.27% increase over IAPTC).

Bland–Altman analysis of all IAPTC and Finapres data showed a mean BRS bias of 2.26 ± 4.55 ms mm Hg^{-1} between spectral and sequence estimations of BRS. Likewise, the mean bias between IAPTC and Finapres, for both sequence and spectral analysis, was 1.91 ± 2.8 ms mm Hg^{-1}. BRS comparison of ß-blocker users and non-users showed a small (+6% BRS in non-users) but significant ($P = 0.05$) difference.

Spectral estimation using Finapres data was shown to be more accurate than sequence, but information regarding the location of coherent pressor/depressor reflexes is lost. Clinically, this is less important than BRS, meaning Finapres data can provide accurate, non-invasive BRS estimates that show only a small deviation from IAPTC data.

Effects of spironolactone on blood pressure and heart rate variability in patients with mild-moderate chronic kidney disease

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Background: Premature cardiovascular disease is responsible for over half of all deaths in patients with end-stage chronic kidney disease (CKD), and most will die from heart failure and sudden cardiac death (SCD) [1]. Depressed heart rate variability (HRV) as a marker of impaired cardiac vagal control predicts the incidence of SCD in patients with cardiovascular disease and in CKD [2, 3]. It is postulated that high levels of aldosterone present in progressive CKD may contribute to the high rates of arrhythmic death by causing cardiac hypertrophy and fibrosis and by adversely affecting cardiac, which all patients received sp autonomic control. In a double blind trial we are examining the role of aldosterone inhibition in combination with established ACE inhibitor and/or angiotensin receptor blocker (ARBs) therapy in patients with early non-diabetic CKD. The effects on HRV and blood pressure were studied before and after an active 4-week run in period in ironolactone.

Methods: Around 25 patients with CKD (estimated glomerular filtration rate GFR- 40–80 ml/min) underwent 24-hour ambulatory blood pressure monitoring and Holter electrocardiography before and after 1 month of treatment with spironolactone 25 mg daily. Patients treated with beta-blockers were excluded from analysis. Time domain HRV indices were derived from 24-hour recordings using the Reynolds Pathfinder Software and according to the Task Force guidelines [4].

Results: Chronic therapy with spironolactone significantly reduced mean 24 h ABP with preservation of overall HRV and indices of high frequency HRV after treatment. See Table 1 and graph 1.

Conclusions: In patients with CKD on conventional therapy, the addition of short-term aldosterone blockade with spironolactone significantly improves blood pressure control. Unlike standard antihypertensive therapies [5, 6], with spironolactone HRV measures of cardiac autonomic control are not adversely affected such that vagal control of heart rate and rhythm is preserved.

References

1. Foley RN, Parfrey PS (1998) Cardiovascular disease and mortality in ESRD. J Nephrol 11:239–245
2. Nolan J, Batin PD, Andrews R, Lindsay SJ, Brooksby P, Mullen M, Baig W, Flapan AD, Cowley A, Prescott RJ, Neilson JM, Fox KA (1998) Prospective study of heart rate variability and mortality in chronic heart failure: results of the United Kingdom heart failure evaluation and assessment of risk trial (UK-heart). Circulation 98:1510–1516
3. Robinson TG, Carr SJ (2002) Cardiovascular autonomic dysfunction in uremia. Kidney Int 62:1921–1932
4. Heart rate variability (1996) Standards of measurement, physiological interpretation, and clinical use. Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. Eur Heart J 17:354–381
5. Hamada T, Watanabe M, Kaneda T, Ohtahara A, Kinugawa T, Hisatome I, Fujimoto Y, Yoshida A, Shigemasa C (1998) Evaluation of changes in sympathetic nerve activity and heart rate in essential hypertensive patients induced by amlodipine and nifedipine. J Hypertens 16:111–118
6. Zaliunas R, Brazdzionyte J, Zabiela V, Jurkevicius R (2005) Effects of amlodipine and lacidipine on heart rate variability in hypertensive patients with stable angina pectoris and isolated left ventricular diastolic dysfunction. Int J Cardiol 101:347–353

Table 1 Change from baseline in 24 h BP and HRV indices after 1 month treatment with spironolactone

	Baseline	Month 1
BP mm Hg	128/79	116/72*
MAP mm Hg	95 ± 2	86 ± 2*
RR interval (ms)	790 ± 25	782 ± 28
SDNN (ms)	127 ± 7	136 ± 7
RMSSD (ms)	22 ± 1	21 ± 1
SDANN (ms)	116 ± 8	127 ± 7
SDNNi (ms)	47 ± 2	47 ± 2

Mean ± SEM
*$P = < 0.01$

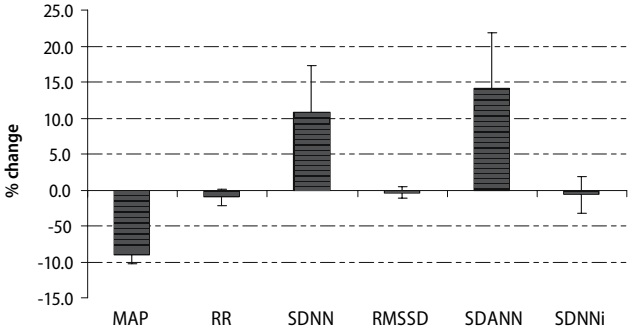

Fig. 1 Changes in blood pressure and time domain parameters of heart rate variability after one month of treatment with spironolactone

An exploratory functional brain imaging study of emotional and autonomic sequelae of spinal cord injury

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Emotional stimuli elicit changes in somatic bodily states, including that expressed in autonomic arousal, which feedback to influence the expression of emotional feelings. In health, emotions are integrated with autonomic bodily responses. In patients with spinal cord injury (SCI) this integration of emotion and bodily arousal is partially disrupted, impairing both efferent generation of sympathetic responses and afferent sensory feedback of visceral state via the spinal cord. To investigate the expression of emotion-related brain activity consequent upon SCI, we used functional magnetic resonance imaging (fMRI) and a basic emotional learning paradigm.

Seven control subjects and seven SCI patients were scanned during an aversive fear-conditioning task. Subjects viewed randomised presentations of four faces bearing angry expression. One of the faces (CS + arm) was associated with delivery of electrical shock to the upper arm on 50 % of trials. A face of the same gender acted as a 'safe' control stimulus (CS-arm).

Electrical stimulation of the arm, which was painful to all subjects, evoked a similar pattern of enhanced brain (dorsal anterior cingulate, right insula and medial temporal lobe) activity in both SCI patients and controls. However, SCI patients differed from controls in conditioning-related brain activity: they showed a significant enhancement of anterior cingulate, periaqueductal grey matter and superior temporal gyrus activity and a relative attenuation of subgenual cingulate, ventromedial prefrontal and posterior cingulate cortex activity to the threat of painful arm stimulation (CS + arm > CS-arm).

These findings provide evidence for differences in emotion-related brain activity in SCI patients. We suggest that the observed functional abnormalities represent impairment in integrating external emotional cues with afferent information concerning emotion generated internal states. Our observations may account for motivational and affective consequences of SCI in some individuals.

Patients with syncope fail to increase postural sway when standing

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We have recently reported that asymptomatic control subjects with poor tolerance to orthostatic stress testing ("false positives") have greater postural movements during normal standing than those with good measured OT [1]. This would enhance venous return and explain why despite poor test results, they do not normally faint. We now describe the spontaneous postural movements in patients who do have posturally-related syncope (PRS) and poor orthostatic tolerance (OT) to determine whether a lack of effective leg movements could contribute to their susceptibility to fainting attacks.

In 13 patients with PRS we assessed OT (by head-upright tilting combined with lower body suction). Postural sway was assessed using a force platform, which determined distance and velocity of movements in anteroposterior and mediolateral directions for 30 s periods after 1 and 5 min of standing. Responses of vascular resistance were assessed as the maximal changes in mean arterial blood pressure/brachial blood velocity. Responses in PRS patients were compared with our published data from control subjects with good and poor OT [1].

In the patients with PRS, the mean time to presyncope was 13.4 ± 1.7 min. This was much less than that in the controls with good OT (36.7 ± 2.1 min, $P < 0.001$), but not very different from that in the controls with poor OT (18.9 ± 1.8 min). Postural sway in the patients was less than that in the healthy non-fainting controls with poor measured OT, and similar to that in controls with good OT. After 5 min of standing the distance and velocity moved in PRS patients was 271.4 ± 18.8 mm and 9.0 ± 0.6 mm/s; in poor OT controls, 374.1 ± 55.1 mm and 12.5 ± 1.9 mm/s (both $P < 0.05$); in good OT controls, 228.8 ± 17.0 mm and 7.6 ± 0.6 mm/s. The vascular resistance responses in patients (+59.2 ± 19.5) were less than that in good OT controls (+152.5 ± 23.9, $P < 0.05$) and not significantly different from that in poor OT controls (+95.3 ± 29.1).

These results suggest that, although PRS patients have reflex vascular responses similar to that in the healthy controls with poor OT, unlike these controls, they fail to compensate for this by increased postural movements and so are prone to frequent syncopal events. We suggest that patients with PRS should be encouraged to increase leg movements when standing in order to prevent syncopal attacks.

1. V. E. Claydon, R Hainsworth (2005) Increased postural sway in control subjects with poor orthostatic tolerance. J Am Coll Cardiol 46:1309–1313

Biofeedback modulation of sympathetic activity as a treatment for epilepsy

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Anti-epileptic drugs are the mainstay in the management of epilepsy. However, despite optimal drug therapy, approximately 30% of patients continue to have seizures. Behavioral interventions including biofeedback have become increasingly popular and they represent an alternative or adjunctive therapeutic option in the management of drug refractory epilepsy.

Biofeedback is a method to control physiological responses, which are usually involuntary. Galvanic Skin Response (GSR) measures small electrical activity on the skin reflecting the subject's emotional and mental state. We demonstrated that modulation of GSR activity using biofeedback has a considerable influence on central arousal systems closely linked to occurrence of epileptic seizures. Increase in peripheral sympathetic arousal (increase in skin conductivity) significantly reduced EEG measurements of cortical arousal, suggesting that an increase in skin conductivity obtained via GSR biofeedback may be associated with reduced frequency of epileptic seizures.

In a preliminary randomised controlled study with 18 medically-refractory patients with epilepsy, we observed a high response rate to GSR biofeedback: 60% of patients showed more than 50% reduction in seizure frequency, compared to no reduction in seizure frequency in controls. Our finding strongly suggested that GSR biofeedback training has the potential to be a potent adjunctive non-pharmacological treatment option.