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Research Letter
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Cortisol/cortisone levels and quality of life in individuals with pulmonary arterial hypertension

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Abstract

Individuals with pulmonary arterial hypertension experience debilitating symptoms and psychological distress which may influence their cortisol regulation. We describe associations between diurnal salivary cortisol/cortisone levels and quality of life in adults with pulmonary arterial hypertension. Findings suggest potential clinical utility of cortisol/cortisone assessment as applied to a pulmonary arterial hypertension population.

Keywords

pulmonary arterial hypertension, psychological distress, diurnal cortisol, mental health, physical health

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To the Editor,

Pulmonary arterial hypertension (PAH) is an uncommon and unpredictable life-limiting condition.[1] There is currently no cure for PAH, leading to right-sided cardiac failure and eventually, premature death. Many studies have shown PAH patients to experience substantial psychological distress including anxiety, depression and panic.[1–3] There is increased awareness of the need to address psychosocial aspects including well-being in PAH. We previously published a pilot randomised controlled trial demonstrating the effectiveness of mindfulness-based-stress-reduction to improve physical functioning and quality-of-life in people with PAH.[1]

Due to psychological distress, cortisol production may become dysregulated via hypothalamic-pituitary-adrenal axis over activation. This can have a significant impact on bodily systems; prolonged or repeated stressful experiences can lead to accumulated physiological dysregulation and poor health outcomes.[4] Dysregulation of cortisol via flattening of regular diurnal decline has been associated with poorer health outcomes across a range of physical and mental health conditions.[5] Cortisol awakening response (CAR), a sudden rise in cortisol levels approximately 30 min after awakening, is also associated with physical and psychological parameters.[6]

The aim of this current study was to assess levels and patterning of physiological cortisol and cortisone measured from diurnal saliva and to examine associations with psychosocial quality of life (QOL) assessed by questionnaire in adults with PAH.

Participants comprised 19 adult patients (≥16 years old; M_{age} 51.47 years, range 20–88 years; 5 males) recruited from a pulmonary hypertension clinic, with clinical diagnosis of PAH (11 simple Eisenmenger [Ventricular septal defect (VSD) or Atrioventricular septal defect (AVSD)], 2 Double inlet left ventricle with transposed great arteries (DILV/TGA), 1 Pulmonary atresia with ventricular septal

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defect (PA/VSD), 1 Mustard, 2 postoperative repaired Congenital heart disease (CHD), 2 unoperated Atrial septal defect (ASD); 15/19 on disease modifying therapy [phospodiesterase type 5 A inhibitor or Endothelin receptor antagonist (PDE5i/ERA)], Pulmonary artery (PA) mean pressure 67 millimetres of mercury (mmHg)/range = 45-85mmHg), were fluent in English, deemed physically well enough and had consented to take part. Each participant received a saliva sampling pack containing nine Salivettes (Sarstedt, Germany). Saliva was sampled at three intervals during the day: immediately upon awakening, +30 min after awakening and immediately before bed. Cortisone and cortisol levels were analysed using ultra performance liquid chromatography tandem mass spectrometry.

From the three diurnal assessments, four cortisone and four cortisol indices were calculated: area under the curve with respect to ground (AUCg) and increase (AUCi),[7] awakening response (CAR) (+30 min minus awakening) and diurnal slope (bedtime minus awakening). A value with rise of ≥2.49 nmol/L was considered a CAR.[8] For cortisol slope, a more negative value (steeper slope) indicated greater diurnal decline. QOL was assessed using the Short Form Health Survey (SF-36v2), a self-report questionnaire comprising two summary scores, each with four health-related QOL dimensions (Physical Component Score: Physical Functioning, Role Physical, Bodily Pain, General Health; Mental Component Score: Vitality, Social functioning, Role Emotional and Mental Health).[9] For raw scores and normalised scale scores, higher values indicated better health. Cortisol and cortisone indices were initially assessed descriptively; diurnal patterning was analysed using repeated measures ANOVA with Greenhouse-Geisser correction (sphericity not assumed) followed by pairwise comparisons (Bonferroni correction). To examine associations between baseline cortisone/cortisol and QOL scores, correlations were conducted using Spearman's rho (2-tailed) and non-log-transformed values.

As a reference, we compared our data against a salivary cortisone/cortisol range obtained from 119 mixed age and gender non-clinical healthy volunteer adults, with early morning and late evening samples, recruited in a previous study. Reference ranges (2.5–97.5 percentile) were derived for non-Gaussian distributions[10] which revealed an early morning range of 3–20 nmol/L (cortisol) and 12–45 nmol/L (cortisone); and a late evening range of <2 nmol/L (cortisol) and 2–18 nmol/L(cortisone). Cortisol and cortisone values for our PAH sample (Fig. 1) were comparable with this reference range at a level of 88.9% awakening and 83.3% evening (cortisol) and 73.7% awakening and 89.5% evening (cortisone). There were no extreme values indicated and cases falling marginally outside of the comparison range could be explained by requirements of the sampling protocol.

Descriptive analysis of cortisol indices (Fig. 1) showed PAH patients to have a usual CAR pattern and diurnal decline with three exceptions: one with a +30 increase followed by a further increase to evening (A); one with a flat profile across the day (F) and one with a steady decrease across the day (C). For cortisone indices, all patients showed expected diurnal patterning with three exceptions: one with a +30 increase followed by a flat trajectory to evening (A); one that was highest at awakening then declined steeply throughout the day (E); and one which started low and continued to decline across the day (C). CAR was exhibited in 61.1% of the sample. In inferential analysis, cortisol showed significant diurnal change across time points, $F(1,21) = 33.83$; partial $Eta^2 = .67$, $p < .001$. Pairwise comparisons revealed significant differences between awakening to +30 min ($p = .001$), +30 min to evening ($p < .001$), awakening to evening ($p < .001$). Cortisone showed significant diurnal change across time points $F(1,27) = 41.84$; partial $Eta^2 = .70$, $p < .001$. Pairwise comparisons revealed significant differences between awakening to +30 min ($p = .002$), +30 min to evening ($p < .001$) and awakening to evening ($p < .001$). There were detectable associations between age and gender with cortisol/cortisone levels.

A higher level of cortisol at awakening was significantly associated with higher scores on QOL dimensions of Physical Functioning ($r = .59$; $p = .01$), General Health ($r = .65$; $p = .003$) and Vitality ($r = .68$; $p = .002$). Higher cortisol at +30 min was also significantly associated with a better QOL score on Physical Functioning ($r = .51$; $p = .03$) and Vitality ($r = .58$; $p = .012$). Higher evening cortisol was significantly associated with poorer health scores for QOL dimensions of Physical Functioning ($r = -.50$; $p = .03$) and Social Functioning ($r = -.67$; $p = .002$) and the Physical Component Score ($r = -.51$; $p = .028$). No significant correlations were found between AUCg and CAR with QOL scores. A significant association was noted between higher AUCi score and a poorer General Health dimension score ($r = -.49$; $p = .04$). Greater cortisol slope value (flatter slope, less decline from awakening to evening) was also significantly associated with poorer Physical Functioning ($r = -.67$; $p = .002$), lower scores on Role Physical ($r = -.59$; $p = .01$), General Health ($r = -.72$; $p = .001$), Vitality ($r = -.74$; $p = .001$) and Role Emotional ($r = -.55$; $p = .018$) and poorer overall Physical ($r = -.58$; $p = .012$) and Mental Component ($r = -.52$; $p = .027$) scores. The findings indicate that greater AUCi and lesser decline in cortisol level across the day to be associated with poorer quality of life in PAH patients. A higher level of cortisol at awakening and to a lesser extent, at +30 min, appears beneficial for the physical and mental aspects of PAH patients' quality of life. The diurnal slope of cortisol showed the greatest number of effects across five of the eight QOL dimensions and in both physical and mental component scores.

Fewer significant relationships were found between cortisone levels and QOL. However, a higher level of cortisone at awakening was significantly associated with better QOL scores for Physical Functioning ($r = .53$; $p = .02$) and General Health ($r = .56$; $p = .012$) dimensions. A higher level of cortisone at +30 mins was significantly associated with better health scores

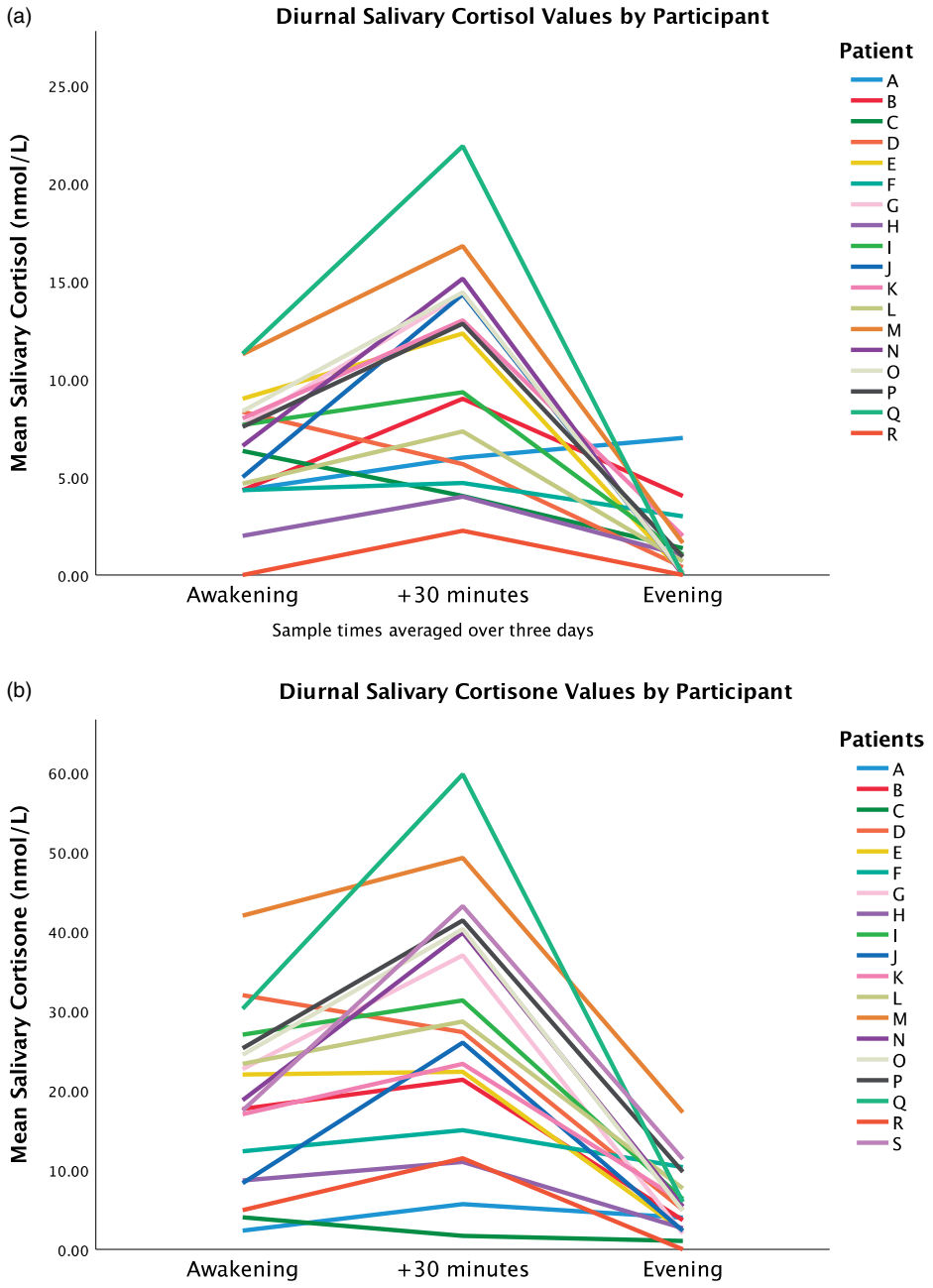

Fig. 1. Cortisol (a) and Cortisone (b) levels by patient participants; measured at awakening, 30 min later and in the evening in people with PAH; displays rise and fall, diurnal rhythm. Data show n = 18 participants (a) and n = 19 (b).

on Physical Functioning ($r = .51$; $p = .026$) and Vitality ($r = .48$; $p = .04$). No significant effects were found for evening cortisone levels with QOL scores. A higher cortisone AUCg was significantly associated with higher scores on Physical Functioning ($r = .50$; $p = .03$) and Vitality ($r = .46$; $p = .048$) dimensions, whereas a higher (flatter) cortisone slope value was associated with poorer Social Functioning ($r = -.66$; $p = .02$). No significant correlations were observed between cortisone AUCi and QOL scores.

Our findings demonstrate ranges and patterning of diurnal cortisol/cortisone in this small sample of PAH patients from a predominantly CHD cohort, to be comparable to that observed in non clinical populations. QOL dimensions as well as overall physical and mental health scores among these PAH patients were below that of general population norms, indicating a below average quality of life. Interestingly, the QOL dimension of Bodily Pain, one aspect of the condition that might frequently be used to evaluate well-being, is the exception to this finding, scores being comparative with population norms. Importantly, despite this comparable range in cortisol/cortisone, indices were significantly associated with both physical and mental QOL in PAH; higher cortisol and cortisone at awakening and +30 min were linked to better QOL across a number of

physical health and vitality scores and higher evening cortisol and flatter diurnal decline of cortisol/cortisone with poorer QOL across a range of physical and mental health scores. The study was designed as an initial pilot and as such has many limitations including the small sample size and lack of a control group, restricting more robust statistical comparisons. Furthermore, methodological limitations include the use of a general health related QOL measure rather than one specific to PAH. Attention to these and other limitations is warranted in future work.

In conclusion, we suggest that cortisol and to a lesser extent cortisone, provide potentially useful clinical indicators of patient well-being in PAH. The current study is only an indication of potential applications but if it were possible to provide more frequent analysis of cortisol levels, even with measurement of a continuous profile, or using sources other than saliva, then we might be able to assess response to medication and provide an objective health related measure of QOL independent of numerical cardio-pulmonary assessments.

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Conflict of interest

The author(s) declare that there is no conflict of interest.

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Contributorship

RT, FQ, JS, VG and JT-C made a substantial contribution to the conceptualisation and design of the work; VG was responsible for data acquisition; FQ and JS for assay analysis; JT-C for data analysis; and RT and JT-C for data interpretation. RT and JT-C drafted the article; all authors revised the article and approved the final version of the manuscript.

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References

1. Tulloh RMR, Garratt V, Tagney J, et al. A pilot randomised controlled trial investigating a mindfulness-based stress reduction (MBSR) intervention in individuals with pulmonary arterial hypertension (PAH): the PATHWAYS study. *Pilot Feasibility Stud* 2018; 4: 78.
2. Lowe B, Grafe K, Ufer C, et al. Anxiety and depression in patients with pulmonary hypertension. *Psychosom Med* 2004; 66: 831–836.
3. Harzheim D, Klose H, Pinado FP, et al. Anxiety and depression disorders in patients with pulmonary arterial hypertension and chronic thromboembolic pulmonary hypertension. *Respir Res* 2013; 14: 104.
4. McEwen BS. Protective and damaging effects of stress mediators. *N Engl J Med* 1998; 338: 171–179.
5. Adam EK, Quinn ME, Tavernier R, et al. Diurnal cortisol slopes and mental and physical health outcomes: a systematic review and meta-analysis. *Psychoneuroendocrinology* 2017; 83: 25–41.
6. Fries E, Dettenborn L and Kirschbaum C. The cortisol awakening response (CAR): facts and future directions. *Int J Psychophysiol* 2009; 72: 67–73.
7. Pruessner JC, Kirschbaum C, Meinlschmid G, et al. Two formulas for computation of the area under the curve represent measures of total hormone concentration versus time-dependent change. *Psychoneuroendocrinology* 2003; 28: 916–931.
8. Stalder T, Kirschbaum C, Kudielka BM, et al. Assessment of the cortisol awakening response: expert consensus guidelines. *Psychoneuroendocrinology* 2016; 63: 414–432.
9. Jenkinson C, Coulter A and Wright L. Short form 36 (SF36) health survey questionnaire: normative data for adults of working age. *BMJ* 1993; 306: 1437–1440.
10. Ceriotti F, Hinzmann R and Panteghini M. Reference intervals: the way forward. *Ann Clin Biochem* 2009; 46: 8–17.