International Journal of Cardiology 203 (2016) 69–73

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

High evening salivary cortisol is an independent predictor of increased mortality risk in patients with systolic heart failure

Fabian Hammer [a,b,c,*,1], Timo Deutschbein [d,1], Almuth Marx [a], Gülmisal Güder [a,b], Roman Michalski [a,b], Georg Ertl [a,b], Bruno Allolio [a,d], Christiane E. Angermann [a,b], Stefan Störk [a,b,2], Martin Fassnacht [a,d,e,2]

[a] Comprehensive Heart Failure Center, University of Würzburg, Würzburg, Germany
[b] Department of Internal Medicine I, Cardiology, University Hospital Würzburg, Würzburg, Germany
[c] Department of Internal Medicine B, University Medicine Greifswald, Greifswald, Germany
[d] Department of Internal Medicine I, Endocrine and Diabetes Unit, University Hospital Würzburg, Würzburg, Germany
[e] Central Laboratory, Research Unit, University Hospital Würzburg, Würzburg, Germany

ARTICLE INFO

Article history:
Received 1 July 2015
Received in revised form 22 September 2015
Accepted 12 October 2015
Available online 20 October 2015

Keywords:
Cortisol
Glucocorticoids
Mortality
Saliva
Survival
Systolic heart failure

ABSTRACT

Aims: Serum cortisol independently predicts mortality risk in patients with systolic heart failure. Salivary cortisol may provide advantages as it better reflects the biologically active free compound. Furthermore, sampling is non-invasive and may easily be performed in outpatients. We comparatively evaluated associations of morning (MSC) vs. evening salivary cortisol (ESC) and all-cause mortality risk.

Methods and results: MSC (8 am) and ESC (9 pm) were determined in 229 patients with heart failure participating in the Interdisciplinary Network for Heart Failure program (66 ± 13 years; 21% female; 37% New York Heart Association (NYHA) class III/IV, median left ventricular ejection fraction 33%). The association of cortisol with mortality risk was determined by univariate and Cox multivariable regression analyses adjusting for age, sex, NYHA class, and N-terminal pro-hormone B-type natriuretic peptide. Compared to ESC, MSC was significantly higher and exhibited a higher variance: median 0.59 ng/ml (interquartile range 0.41–0.93) vs. 0.25 ng/ml (0.15–0.48), $p < 0.001$. During 18 months of follow-up, 25 (11%) patients died. In univariate and multivariable models mortality risk was not increased in the highest MSC quartile: crude hazard ratio (HR) 1.81 (95% confidence interval 0.79–4.14, $p = 0.160$), adjusted HR 1.26 (0.51–3.13, $p = 0.616$). However, patients in the highest ESC quartile had a significantly increased mortality risk, suggesting that associations of high ESC and increased mortality were independent of disease severity: crude HR 3.33 (1.50–7.42, $p = 0.003$), adjusted HR 2.49 (1.01–6.14, $p = 0.047$). ESC alone proved the best predictor of mortality.

Conclusion: High ESC but not MSC levels independently predict increased mortality risk in heart failure.

1. Introduction

In systolic heart failure, disease progression and outcome are modulated by neuroendocrine activation [1], resulting in elevated adrenal corticosteroid levels including aldosterone [2,3] and cortisol [4,5]. While numerous experimental and clinical studies have established adverse cardiovascular effects of aldosterone in heart failure patients [3,5], the pathophysiological contribution of cortisol is less clear.

Synthesis and secretion of cortisol through the adrenal cortex are regulated by the hypothalamic-pituitary-adrenal (HPA) axis. Under physiological conditions, cortisol exhibits a diurnal pattern with the highest concentrations in the early morning, followed by a decline over the day and a nadir around midnight [6]. Psychological or physical stressors result in increased HPA activity, thereby increasing cortisol levels within the circulation. Chronic hypercortisolism, however, may have deleterious cardiovascular effects, as it becomes obvious in Cushing's syndrome. Due to an autonomous cortisol production, affected patients often develop central obesity, high blood pressure, and diabetes mellitus. Concomitantly, cardiovascular morbidity and mortality are at least 4-fold increased [7,8].

In acute or chronic illness, circulating cortisol concentrations may also be reactively elevated, albeit to a much lesser degree compared to patients with Cushing's syndrome. Irrespective of the underlying disease, hypercortisolemic states have repeatedly been linked to adverse outcome [9–12]. In line, we and others have previously shown that serum cortisol concentrations independently predict cardiovascular events as well as cardiovascular mortality in patients with chronic heart failure [5,13,14].

* Corresponding author at: Department of Internal Medicine B, University Medicine Greifswald, Ferdinand-Sauerbruch-Street, 17475 Greifswald, Germany.
E-mail address: fabian.hammer@uni-greifswald.de (F. Hammer).

[1] Fabian Hammer and Timo Deutschbein contributed equally to this work as first authors.

[2] Stefan Störk and Martin Fassnacht contributed equally to this work as senior authors.

http://dx.doi.org/10.1016/j.ijcard.2015.10.084
0167-5273/

For adequate monitoring of adrenocortical activity, analysis of saliva instead of serum offers several advantages [15,16]. For instance, the vast majority of serum cortisol is bound to cortisol-binding globuline and albumin, while salivary cortisol represents the unbound (i.e., free) hormone which is considered biologically active [17] and may thus be a better representative of the true tissue exposure to the hormone. Moreover, as saliva sampling is stress-free and non-invasive, it can conveniently be performed even by non-professionals (e.g., in an outpatient setting).

So far, however, the potential of salivary cortisol in predicting cardiovascular event rates and mortality risk has not been studied in heart failure populations. Due to its relative robustness to potential stressors, one may hypothesize that evening salivary cortisol (ESC) is a more suitable tool than morning salivary cortisol (MSC) to uncover even a mild degree of impaired HPA function. Consequently, we aimed to investigate the respective associations with a special focus on the differential predictive value of MSC compared to ESC.

2. Methods

2.1. Study design

The present analysis made use of the dataset of the Interdisciplinary Network Heart Failure (INH) program. The INH developed and evaluated a nurse-coordinated disease management program for patients discharged from hospital after an episode of acute cardiac decompensation in a randomized, two-armed, multicenter design. Details of the study have been previously reported [18]. In brief, inclusion criteria comprised age ≥18 years, hospitalization with signs and symptoms of decompensated heart failure, and an ejection fraction ≤40% prior to discharge from hospital. Patients were excluded from the study if logistic or health reasons precluded participation in the telephone-based intervention, or if they had new-onset structural heart disease. For this post-hoc analysis, additional exclusion criteria were intake of more than 5 mg of prednisolone equivalent per day as well as the presence of signs or symptoms suggestive of altered cortisol metabolism (i.e., adrenal insufficiency and/or Cushing's syndrome). Out of a total of 1022 randomized subjects, saliva samples (either for MSC and/or ESC) were available from 229 patients. The trial was approved by the local ethics committees of participating hospitals (http://www.controlled-trials.com, unique identifier: ISRCTN23325295).

2.2. Endpoints

The current analysis of this subset of the INH population studied the following endpoints: time to cardiovascular as well as non-cardiovascular death, all-cause mortality, and all-cause re-hospitalization. Vital status was ascertained 18 months after baseline assessment either by follow-up examination in the INH outpatient clinics or by structured telephone follow-up, which was performed by trained nurses or physicians. Records of general practitioners or cardiologists, hospital discharge letters, reports from patients or relatives, and death certificates were used as source documents to verify hospital readmissions and to determine the date of death in deceased patients.

2.3. Hormone analysis and laboratory measurements

At study start, in-hospital blood samples were collected between 7.30 and 10 am after 10 min of rest. Subsequently, serum aliquots were stored at −80 °C until centralized measurement of cortisol, N-terminal pro-hormone B-type natriuretic peptide (NT-proBNP), and high-sensitivity C-reactive protein (hsCRP) with the Immulite 2000 (Siemens, Erlangen, Germany).

Study participants were also asked to provide two separate saliva samples at 8 am and 9 pm, using a specific collection device (Salivette®, Sarstedt, Nümbrecht, Germany). Patients were instructed to refrain from brushing their teeth, smoking, eating or drinking for a minimum of 30 min prior to sampling. The following day the Salivette® device was centrifuged at 3000 rpm for 5 min. The clear supernatant was then stored in aliquots at −80 °C until biochemical analysis. Salivary cortisol was measured using a commercial immunoassay with luminescence detection (IBL, Hamburg, Germany). The analytical range of this assay was 0.05–40.0 ng/ml, respectively. The intra- and interassay coefficients of variation for two independent standards were ≤14.5%, and ≤7.3%.

2.4. Follow-up

Survival status at 18 months was determined by direct telephone contact with the patients, their family members, or their general practitioners. No patient was lost to follow-up. Patients who were event-free at 18 months were censored at this time point. In case of death the respective cause was categorized as cardiac death (e.g., fatal myocardial infarction, refractory heart arrhythmia, or asystole), non-cardiovascular death (e.g., fatal infection or accident) or non-specified death.

2.5. Data analysis

Variables are given as mean (standard deviation), median (quartiles), and n (percent), as appropriate. Group comparisons were performed using one-way analysis of variance (ANOVA), Kruskal–Wallis tests, and chi-square testing, respectively. Correlation of MSC and ESC was calculated using Spearman's rank correlation coefficient. The association of cortisol with event risk was determined using Cox proportional hazards regression. For these analyses, cortisol was dichotomized using the upper quartile as cutoff (see Table 1). In multivariable models, we corrected for age, sex, New York Heart Association (NYHA) functional class, and NT-proBNP. Statistical analysis was performed with R version 3.1.1.

3. Results

Out of a total of 229 patients, MSC and ESC concentrations were available from 217 and 215 patients, respectively. Their baseline characteristics are shown in Table 1. The combined analysis of both parameters, however, was only feasible in a subgroup of 203 subjects. This discrepancy was due to sampling errors (e.g., inadequate amounts of saliva, incompliance) or analytical problems (e.g., cortisol values below the lower limit of detection).

Concentrations of MSC and ESC were positively correlated ($r = 0.31$, $p < 0.001$). Furthermore, MSC was significantly higher and had a greater variance than ESC: median 0.59 ng/ml (interquartile range 0.41–0.93) vs. 0.25 ng/ml (0.15–0.48), $p < 0.001$ (Fig. 1). Patients with higher ESC had more severe symptoms (as indicated by a higher percentage of subjects in NYHA functional classes III/IV) and more advanced heart failure (as indicated by significantly higher NT-proBNP levels; Table 1).

During the follow-up period of 18 months, 25 (10.9%) patients died: 14 subjects (6.1%) of cardiovascular and 5 subjects (2.2%) of non-cardiovascular causes; in the remaining 6 (2.6%) subjects, the cause of death was not further specified. MSC was not significantly associated with all-cause mortality risk; this was true for both univariate analysis (crude hazard ratio (HR): 1.81 (95% confidence interval) (0.79–4.14, $p = 0.16$)) and multivariable analysis (adjusted HR: 1.26 (0.51–3.13, $p = 0.616$)) (Table 2, Fig. 2A). In contrast, if patients in the highest ESC quartile were compared to those in the lower three ESC quartiles, an increased mortality risk was observed (Table 2, Fig. 2B). The crude HR of 3.33 (1.5–7.42, $p = 0.003$) was not materially affected after adjustment for age, sex, NYHA class, and NT-proBNP: adjusted HR 2.49 (1.01–6.14, $p = 0.047$). Neither ESC nor MSC was associated with all-cause rehospitalization risk in uni- or multivariable analysis (data not shown).

In order to study the combined effect of MSC and ESC (high vs. the other quartiles) on all-cause mortality, patients were divided into 4 subgroups: high ESC/high MSC, high ESC/low MSC, low ESC/high MSC, and low ESC/low MSC. Bivariable Cox regression analysis showed that outcome was only predicted by ESC levels in the highest quartile ($p = 0.017$) but not by MSC ($p = 0.538$). Moreover, neither inclusion of MSC and ESC in a multivariable model nor analysis of a delta SC (MSC-ESC) did improve mortality risk prediction compared to ESC alone (data not shown).

4. Discussion

In this post-hoc analysis of a prospective cohort study, we identified high ESC concentrations as an independent predictor of increased all-cause mortality risk in patients with systolic heart failure. In contrast, MSC was not significantly associated with mortality risk.

It is well known that patients with heart failure have elevated circulating corticosteroids due to neuroendocrine activation [1]. In this context, aldosterone has been shown to augment left ventricular dysfunction through cardiac hypertrophy, fibrosis, and inflammation [19]. Pharmacological blockade of the mineralocorticoid receptor by specific antagonists like spironolactone or eplerenone effectively reduces adverse cardiac remodeling and, most importantly, results in reduced hospitalization and improved survival [20–22]. Accordingly,