Circadian Leptin Concentration Changes in Critically Ill Heart Failure Patients – Preliminary Results

Running Head: Leptin changes in critically ill

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Summary

Physiologically, leptin concentration is controlled by circadian rhythm. However, in critically ill patients, circadian rhythm is disrupted. Thus we hypothesized that circadian leptin concentration changes are not preserved in critically ill patients. Ten consecutive critically ill heart failure patients with the clinical indication for mechanical ventilation and sedation were included into our study. Plasma leptin concentration was measured every 4 hours during the first day (0-24hrs) and during the third day (48-72hrs) after admission. During the first day, there were significant leptin concentration changes (ANOVA $p<0.05$), characterized by an increase in concentration by 44% (16-58%); $p=0.02$ around noon (10am-2pm) and then a decrease in concentration by 7% (1-27%); $p=0.04$ in the morning (2am-6am). In contrast, there was no significant change in leptin concentration during the third day after admission (ANOVA $p=0.79$). Based on our preliminary results, we concluded that in critically ill heart failure patients, the circadian rhythm of plasma leptin concentration seems to be preserved during the first but not during the third day after admission.

Since its discovery, leptin has emerged as a pleiotropic hormone. Many of the effects of leptin may be important in critically ill patients and introduce a new research possibility. Indeed, in critically ill patients leptin has been shown to have a high degree of efficacy and specificity for the differentiation of sepsis (Yousef et al., 2010). Physiologically, leptin is known to have a circadian rhythm, with the highest concentration during the night and with the lowest concentration during the day (Langendonk et al. 1998). However, in critically ill patients, circadian rhythmicity is impaired (Paul and Lemmer 2007). We hypothesized circadian leptin concentration changes are not preserved in critically ill patients. Accordingly, the aim was to evaluate leptin concentration changes during the first and third day after admission (0-24h and 48-72h).

The subjects were consecutive critically ill patients admitted to an intensive care unit (ICU). Inclusion criteria were clinical indication for mechanical ventilation, sedation and chronic heart failure (NYHA III-IV). There were no exclusion criteria. This study was conducted in accordance with the declaration of Helsinki and approved by the Ethics Committee of the St. Anna University Hospital, Brno, Czech Republic (No.50V/2013-AM). Written informed consent was obtained from all patients or the patients' responsible family member. Plasma leptin concentrations were measured by a commercial ELISA kit (BioVendor, Brno, Czech Republic) with a sensitivity of 0.12 $ng.ml^{-1}$. The intra- and interassay variabilities were less than 5% and less than 10%, respectively. The Shapiro-Wilkov test was used to test data for normality. Friedman's ANOVA was used to test for concentration differences among the time-points. Wilcoxon match pairs test was used to compare every two adjacent time-points. Differences in proportions were tested by two-tailed Fisher exact test. Data are summarized as mean (±SD) or median (IQR); p values <0.05 were considered statistically significant. Statistical analysis was performed using Statistica 12.0 (StatSoft Inc., Prague, Czech Republic).

Ten consecutive chronic heart failure patients with acute decompensation were included. The majority (80%) of the included patients were men (8), the mean age was 69 ± 10 years, BMI 28 ± 6 $kg.m^{-2}$ and left ventricle ejection fraction was 23±13 %. The cause of acute decompensation in three patients (30%) was infection, severe arrhythmia in two patients (20%) and acute coronary syndrome, decompensated hypertension or valvular heart disease in five patients (50%). None of the patients had sepsis at admission or developed sepsis during the first three days. Two patients (20%) were diabetics, 3 patients (30%) had a history of stroke (with no or minimal consequences) and five patients (50%) had chronic renal failure. In the first five included patients, leptin concentration was analyzed every 4 hours during the first day (0-24hrs) after admission. In the second five patients, leptin concentration was analyzed every 4 hours during the first day (0-24hrs) and then also during the third day (48-72hrs) after admission. There was no significant difference in the number of patients being sedated, on mechanical ventilation and on catecholamine support; 9 out of 10 (90%) during the first day vs. 3 out of 5 (60%); p=0.51 during the third day after admission. Leptin concentration changed significantly (ANOVA $p<0.05$) during the first day; there was a significant increase in leptin concentration by 44% (16-58%); p=0.02 around noon (10am-2pm) and significant decrease in leptin concentration by 7% (1-27%); p=0.04 in the morning (2am-6am) (**Figure 1**). In contrast, there were no significant changes (ANOVA p=0.79) in leptin concentration during the third day after admission (**Figure 2**).

In our non-septic critically ill patients, the observed significant leptin concentration changes during the first day are similar to a normal circadian rhythm of leptin (Langendonk et al. 1998). However, no significant leptin concentration changes during the third day in the ICU suggest leptin concentration may no longer have been under the control of circadian rhythm. Altered circadian rhythm of leptin has previously been shown in patients with acute sepsis (Bornstein et al., 1998). Indeed, sepsis is an important factor disrupting circadian

rhythm in critically ill patients (Kamdar et al. 2012). Furthermore, leptin is increased in sepsis and has been shown to strongly correlate with inflammatory mediators (Yousef et al., 2010). Interestingly, similar leptin circadian rhythm alterations as in septic patients (lower leptin concentrations during the night than during the day) (Bornstein et al., 1998) were also observed in our non-septic patients. This may suggest the importance of critical illness itself (irrespective of the cause) in the alterations of circadian leptin rhythm. In our study, leptin circadian rhythm seemed to be preserved on the first, but not on the third day after admission. According to multiple studies, there is no doubt the circadian rhythm is disrupted in ICU patients (Brainard et al. 2015). However, it is not clear when the circadian disturbances first occur in the ICU patients. In our cohort, the preserved circadian rhythmicity of leptin concentration during the first day in the ICU is in agreement with Gehlenbach et al. who showed disturbed sleep rhythm but preserved circadian rhythmicity of melatonin in ventilated and sedated patients on the second day in the ICU (Gehlbach et al. 2012). Contrarily, Olofsson et al. showed abolished melatonin secretion in the ICU patients right from the first day (Olofsson et al. 2004) and Paul et al. showed melatonin and cortisol concentration, heart rate, blood pressure, motor activity and body temperature circadian profiles to be severely disturbed during the first day in the ICU (Paul and Lemmer 2007). Discrepancies in the circadian rhythm disruption timing may be caused by the different measures of circadian rhythmicity used, and by heterogenic patient populations. In the Paul et al. study, most of the included patients were surgical/trauma patients followed by brain injury/hemorrhage patients (Paul and Lemmer 2007), suggesting direct central nervous system injury and increased risk of pain and pain medication use, both of which were shown to severely disturb circadian rhythm (Kamdar et al. 2012). In the study of Olofsson (Olofsson et al. 2004), the majority of patients were treated with sepsis (there was no septic patient in our study cohort), which is also known to be a strong disruptor of circadian rhythm (Kamdar et al. 2012). Contrarily, in

the study of Gehlenbach, most of the included patients were non-surgical and only 23% of the patients were diagnosed with sepsis, which may have contributed to the preserved circadian rhythm of melatonin on the second day after ICU admission (Gehlbach et al. 2012).

Our study had several limitations. This was a pilot study and only chronic heart failure patients were included, which limits the generalizability of our findings. Furthermore, only 10 patients were included, of which only the last 5 were also measured on day 3 after admission. During the first day, all patients were without nutrition, but on the third day enteral feeding (with a fixed dose) was allowed to prevent malnutrition and muscle wasting, which may have interfered with leptin circadian rhythm. However, leptin circadian rhythm has been shown to be preserved also in patients with enteral tube feeding (Simon et al. 1998). Type 2 diabetes mellitus patients and those with obesity were not excluded. Leptin concentration is known to be higher in type 2 diabetes mellitus, however in-vivo regulation of leptin seems to be similar in diabetes mellitus patients as it is in normal individuals (Poretsky et al. 2001). Circadian rhythm of leptin seems to also be preserved in patients with obesity (Langendonk et al. 1998).

We concluded that in non-septic critically ill patients with heart failure, the typical circadian rhythm of plasma leptin concentration seems to be preserved during the first but not during the third day after ICU admission.

Conflict of Interest

There is no conflict of interest

Acknowledgement

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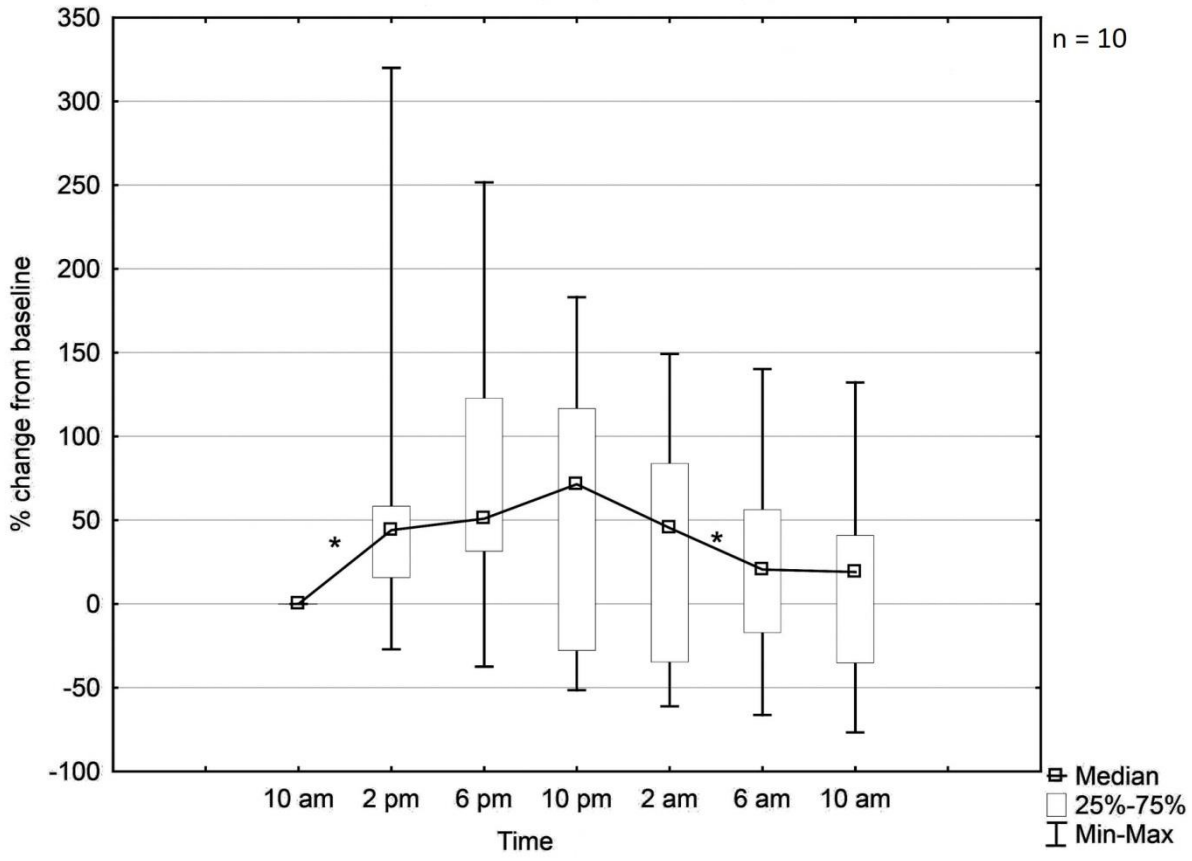

Figure 1. Day 1 leptin concentration changes (n=10). Data are shown as percentage change of leptin concentration from baseline (10am); median (IQR); *p<0.05 vs. next time-point. Friedman's ANOVA p=0.048.

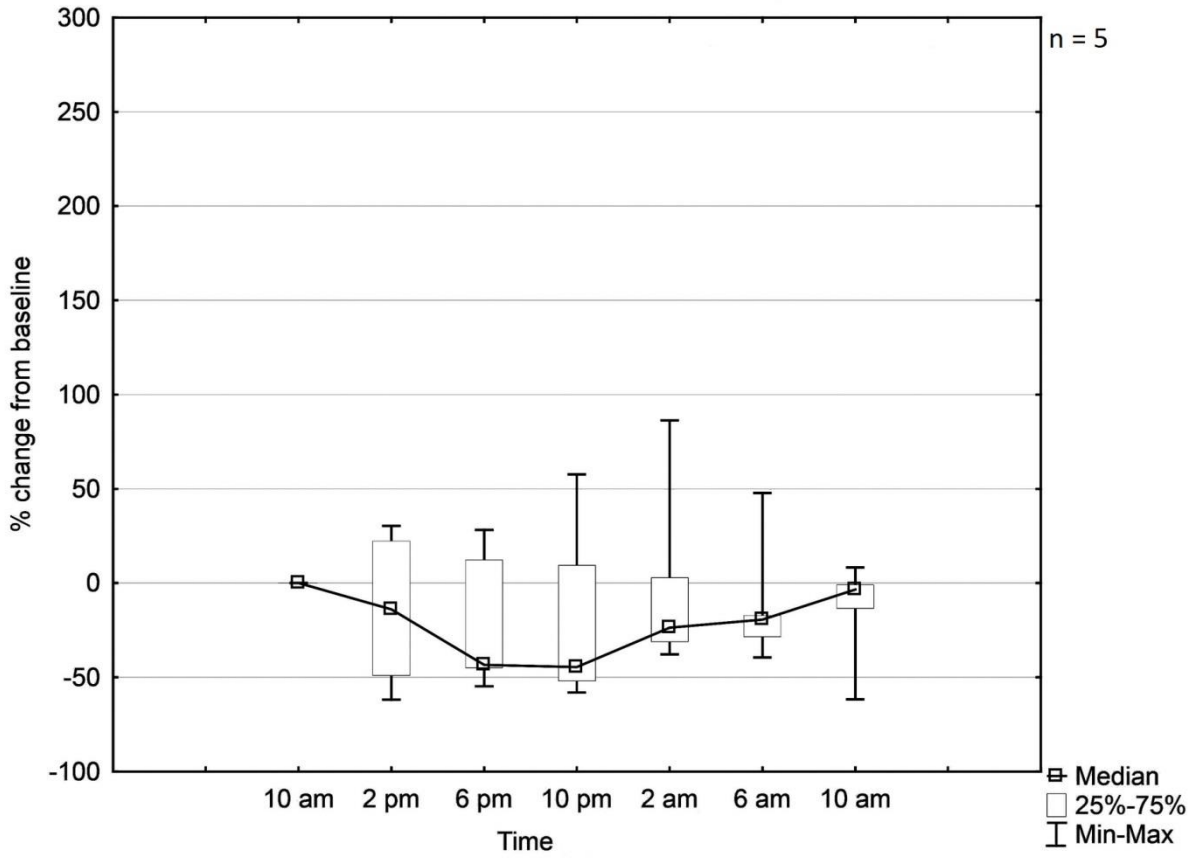

Figure 2. Day 3 leptin concentration changes (n=5). Data are shown as percentage change of leptin concentration from baseline (10am); median (IQR); *p<0.05 vs next time-point. Friedman's ANOVA p=0.787.