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Intra-day variability of cystatin C, creatinine and estimated GFR in intensive care patients

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ABSTRACT

Background: Markers of renal function are widely used in intensive care and sudden changes are important indicators of acute kidney injury. The problem is to distinguish between disease progression/improvement from the natural variation in the patient. The aim of the present study was thus to study the normal intraday variation in ICU patients.
Methods: We studied the intra-day variation of creatinine, cystatin C and estimated GFR based on these two markers in 28 clinically stable ICU patients.
Results: The median diurnal coefficient of variation sCV) for creatinine was 3.70% (1.92–9.25%) while the median CV for cystatin C was 3.66% (1.36–8.11%). The corresponding CVs for the estimated GFRs were 2.00% (0.89–9.82%) for $eGFR_{creatinine}$ and 4.60% (1.65–10.24%) for $eGFR_{cystc}$.
Conclusions: The $eGFR_{creatinine}$ values in individual patients were clearly higher than the $eGFR_{cystc}$ values. The median CV for creatinine, cystatin C and the eGFR measurements were below 5% which means that 95% of the test results will vary by <10% between sampling times in stable ICU patients. Differences >10% between sampling times are thus likely to be an indication of changes in biomarker levels due to the disease/treatment.

1. Introduction

Most physiologic processes show circadian rhythms, where the body functions are synchronized internally and externally, with the environment. Healthy individuals get environmental time cues from the light-dark cycle. A "biologic clock", located in the suprachiasmic nuclei of the hypothalamus is thought to dictate these near-24-hour rhythms [1,2]. The evaluation of circadian patterns during treatment in intensive care units (ICU) is sparse, but data suggests that these rhythms are disturbed [3–5]

Distorted circadian rhythms may have several physiological effects. It is important to be aware of the total variation for test results and not only the variation for the laboratory method. Without such information it is difficult to determine if a difference between two consecutive laboratory test results reflects natural fluctuations, or if it truly reflects a clinical important change for the patient.

Acute kidney injury (AKI) in the critically ill has been the topic of massive research efforts in the last decade, partly triggered by the proposed consensus definition, in 2004–5, for AKI, using the Risk, Injury, Failure, Loss of kidney function and End-stage kidney disease (RIFLE) criteria [6,7]. Even though the RIFLE criteria have been slightly modified [8], the basis for stratification is still serum creatinine. Serum creatinine is a marker of renal function, although sudden intraindividual changes from baseline are thought to reflect renal injury. Creatinine is an inexpensive test that is widely available in clinical chemistry laboratories, but the assay outcome is hampered by the influence of factors such as age, sex, fluid balance, muscle mass, physical activity, diet, analytical methods and assay standardization [9]. Cystatin C, another marker of renal function, may be a more robust endogenous marker of glomerular filtration rate (GFR) than creatinine, as cystatin C is thought to be produced at a constant rate by all nucleated cells, freely filtered by the glomeruli, minimally bound to proteins, and not reabsorbed to the systemic circulation after filtration [10,11]. Theoretically, cystatin C should not be affected by muscle mass, age, inflammation or fever [12,13]. Since exogenous, gold standard measurements of GFR are comparatively expensive, cumbersome and have long turn-around times, they are unsuitable for ICU care, where rapid decisions and actions are paramount. Thus, clinicians caring for the critically ill will keep using endogenous markers of GFR.

Given that many regulatory hormones, including those that influence renal function, are under the influence of both circadian rhythms and sleep [14], there have been concerns regarding how endogenous GFR markers vary during a 24 h time frame. A previous study on healthy volunteers showed only minor circadian variations of creatinine and cystatin C [15]. The present study sought to examine how GFR markers

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Table 1
Creatinine.

Patient	mean creatinine concentration	CV	mean eGFR	CV
1	34	3.35	155.2	1.38
2	131	5.43	36.4	7.41
3	63	2.88	88.7	3.62
4	52	5.15	102.5	2.33
5	31	3.05	121.6	1.21
6	70	2.00	76.9	2.43
7	143	1.92	37.4	2.31
8	41	2.84	115.5	1.20
9	72	5.42	70.1	6.53
10	52	3.00	114.5	1.25
11	31	6.45	108.4	2.15
12	44	2.89	96.2	0.96
13	28	3.41	133.7	1.38
14	47	3.36	104.6	1.39
15	39	3.26	126.7	1.08
16	54	5.24	63.5	1.84
17	101	7.04	59.3	9.82
18	29	4.88	111.5	1.53
19	61	6.92	107.8	3.30
20	34	2.71	145.8	0.89
21	98	5.12	73.6	7.46
22	39	3.79	100.9	1.31
23	50	2.47	106.3	1.01
24	42	3.78	103.0	1.52
25	37	9.25	114.7	2.92
26	89	3.61	63.7	4.02
27	68	6.20	99.8	2.56
28	68	6.46	95.2	2.44
Median	50	3.70	102.8	2.00

vary in clinically stable ICU patients. Changes greater than the normal variation indicate that it is due to the disease/treatment.

2. Materials and methods

2.1. Patients

This study was approved by the regional ethical review board in Stockholm. Written informed consent was obtained from patients or their next of kin.

28 patients (15 females and 13 males) were included in the study. The inclusion criteria was clinically stable ICU patients treated at the central and/or the neurosurgical intensive care units, Karolinska University Hospital, Stockholm. We lack a consensus definition of "clinical stability" in ICU patients, but Halm and co-workers defined this as normalization of heart rate, systolic blood pressure, respiratory rate, temperature and oxygenation status [16]. Furthermore, we were pragmatic: these patients were expected to stay for >24 h, were not in a septic state and did not require fluid resuscitation. Mean age was 62 years (range 26–82 years) and the study group had a mean weight of 69.5 kg (35–115) and a mean length of 169 cm (145–190). Co-morbidities of the cohort: heart failure in 29%, diabetes 18%, hypertension 39% and unspecified malignancy was 29%. Median length of stay was 25 days and median time to study-inclusion was 16 days. The majority of patients were admitted to ICU due to neurological/neurosurgical problems ($n = 11$), respiratory failure ($n = 9$) or trauma ($n = 4$). Mean SOFA (Sequential Organ Failure Assessment) of 11.2 ($n = 17$).

Blood samples were collected from either an intravascular arterial catheter or a central venous catheter at times = 0, 5, 15, 30, 60, 90, 120, 150, 180, 210, 240, 270 and 300 min after the initial time-zero sample. An additional sample was collected 24 h after the first sample. Sampling was started in the morning between 8:30 and noon in order for the laboratory work to be completed within normal work hours.

Blood samples were collected in Vacutainer tubes (vacutainer BD ref 368498 sst II advanced 3.5 mL). After clotting, the tubes were centrifuged 10 min at 3200 rpm (2000 g) and the serum transferred to new tubes and frozen at —80C.

2.2. Creatinine and cystatin C assays

All samples were analyzed as singletons. We have not excluded any data from any of the included patients.

Serum creatinine and cystatin C were analyzed on a Mindray BS-380 (Shenzhen Mindray Bio-medical Electronics, Shenzhen, China) with enzymatic creatinine reagents (8L24-01) from Abbott Laboratories (Abbott Park, IL, USA) and cystatin C reagents from Gentian (Moss, Norway). The cystatin C method was calibrated with the certified reference material ERM-DA471/IFCC.

The creatinine method was IDMS calibrated and the results were reported using S.I. units (μmol/L). The total coefficient of variation (CV) for the creatinine method was 1.2% at 90 μmol/L and the CV for the cystatin C method was 1.5% at 0.8 mg/L.

$eGFR_{creatinine}$ was calculated using the CKD-EPI equation and $eGFR_{cystc}$ was calculated from serum cystatin C results in mg/L by the formula $130 * (\text{cystatin C}^{-1.069}) * (\text{age}^{-0.117}) - 7$ [17]. eGFR was expressed as mL/min/1.73m^2.

The CV for GFR estimating equations combining standardized cystatin C and creatinine assays was also calculated [18].

2.3. Statistical analysis

Calculation of coefficients of variations was performed with Statistica (StatSoft, Tulsa, OK, USA).

The coefficient of variation (CV) is the standard deviation divided with the mean of all results for each patient. The CV expresses the precision and repeatability of an assay.

3. Results

3.1. Creatinine

The median creatinine concentration in the study cohort was 50 μmol/L (range 28–143 μmol/L) corresponding to a median $eGFR_{creatinine}$ of 102.8 mL/min/1.73m^2 (range 36.4–155.2) (Table 1.).