BIOLOGICAL VARIATION OF PROCALCITONIN LEVELS IN HEMODIALYSIS PATIENTS WITHOUT INFECTIONS

Shun Kubo[1)], Nobuhiko Joki[1)],Ai Matsukane[1)], Masaki Iwasaki[1)], Toshihide Hayashi[1)], Yuri Tanaka[1)], Yasunori Takahashi[2)], Yoshihiko Imamura[2)], Hiroki Hase[1)].
1)Division of Nephrology, Toho University Ohashi Medical Centre, 2)Dialysis Centre, Nissan Tamagawa Hospital

東邦大学

Introduction

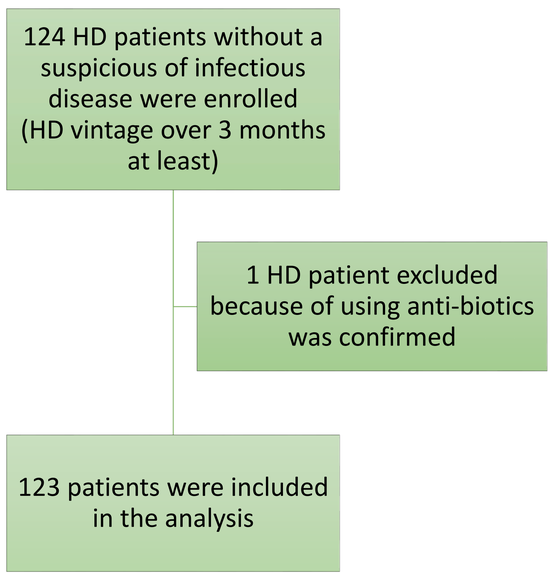
Patients on Hemodialysis (HD) have a greater risk of infection than individuals not on dialysis. Many of hemodialysis patients has been died because of infections indeed. Procalcitonin (PCT) levels have been shown to rise in bacterial infections widely studied in HD patients, but there is no obvious evidence regarding a biological variation in HD patients without infections as well as cut-off level. The aim of this study was to determine the within- and between-person biological variation of PCT in HD patients without infections.

Methods

Design and Methods: We conducted a multicentre prospective cohort study, 123 HD patients without any sign of infectious disease were enrolled. Baseline PCT levels were determined pre- and post-HD, then repeated PCT measurements at pre-HD were performed at 2, 4, 8, 12, 16, 20, and 24 weeks after baseline blood sampling, regardless the presence or absence of infectious disease. Analytical variation (CVa), the within-person biological variation (CVi), between-person biological variation (CVb) and the reference change value (RCV) were calculated from 73 patients without infections and another complication during the observation and/or follow-up period. Statistical analyses were performed using JMP 10.0.3 software (SAS Institute Inc.). Comparison of continuous variables between PCT values pre- and post-dialysis was performed with the Wilcoxon test. RCV was calculated from CVi and CVa values using the formula: $RCV = Z \times 2^{1/2} \times (CVa^2+CVi^2)^{1/2}$, where Z = 2.58 (i.e., the Z-score for 99% confidence with a 2-tailed $P < 0.01$). CVi is the individual biological CV, and CVa is the analytical CV. CVa was calculated from the data of three level samples and controls, they were run in duplicate for 21 days.

The bacterial Definition of bacterial infection

infection was defined as the patients with any combination of signs as follows; 1) body temperature over 38 C, 2) white blood cells >12000/μL or <4000/μL, 3) breathing rate >20/min, 4) heart rate >90 beats/min, 5) prescribing of antibiotics, and 6) physicians judged as infection.



※HD patients with a suspicious of infectious disease who met criteria as follows; 1) body temperature over 38 C, 2) white blood cells >12000/μL or <4000/μL, and 3) breathing rate >20/min were excluded from this study. 124 patients were enrolled, only 1 patient excluded who had bacterial infection and used antibiotics at the point of baseline blood-sampling.

Table 1. Baseline characteristics of 123 hemodialysis patients

Age, years	62.4±13.0
Male, %	77
Smoking,%	49.6
Diabetes, %	32.8
BMI, kg/m^2	21.2 (19.7-24.1)
Duration of hemodialysis, months	87 (7-468)
Primary disease, %	
Diabetic nephropathy	27.9
Glomerulonephritis	33.6
Nephrosclerosis	8.2
PCK	6.6
Others (including unknown)	23.8
Vascular access, %	
AVF	90.2
AVG	9
SFSA	0.8
Cardiac disease, %	26.2
Cerebrovascular disease, %	17.2
Peripheral artery disease, %	13.1
Body temparature, ˚C0.07	36.1 (35.9-36.5)
Systolic BP, mmHg	146(130-165)
Diastolic BP, mmHg	82(72-92.5)
Heart rate, beats/min	77(67-84)
White blood cells, /μL	5500 (4505-6700)
Hemoglobin, g/dL	11.2 (10.4-11.9)
Total protein, g/dL	6.7 (6.4-7.0)
Albumin, g/dL	3.8 (3.6-4.0)
Urea, mg/dL	68 (59.7-77.7)
Creatinine, mg/dL	11.7 (9.72-13.11)
Na, meq/L	140 (138-141)
K, meq/L	5.1 (4.6-5.78)
Calcium, mg/dL	8.7 (8.3-9.0)
Phosphate, mg/dL	5.7 (5.0-6.6)
i-PTH, pg/mL	138 (81.5-251.8)
TSAT, %	24.6 (18.6-32.0)
Ferritin, ng/mL	97.6 (45.0-184)
CRP, mg/dL	0.07 (0.03-0.22)
pre-PCT, ng/mL	0.23 (0.08 - 0.90)
post-PCT, ng/mL	0.16 (0.03 - 1.41)
Dialysis time, hours	4.0±0.22
Kt/V equivalent	1.34 (1.19-1.50)
QB, mL/min	230 (200-250)
Dialysis membrane, %	
PS	73
CTA	2
PES	44
PAN	3
ESA, %	84.4
Vitamin D, %	76.3
Iron, %	28.7
Statin,%	31.1
carnitine,%	18

Results：

The mean age was 62.4 years, 77% male, and 33% diabetes. The mean duration of HD was 87 months.(See detail Table1.) The median value for baseline pre-HD PCT was 0.23[0.08-0.90]ng/mL (Fig1), which is extremely higher than the reference level for the healthy individual. PCT levels decreased significantly in a single session of HD ($p<0.0001$, Fig2), indicating a PCT-removal rate by HD of 46.6±12.16%.Fig1 showed distribution of serum procalcitonin level at baseline, and Fig2 showed PCT-removal rate by a single session of HD, Fig3 showed PCT levels before & after a single session of HD. The median value of the biological variation PCT was 0.24 ng/mL (n=73), there is no statistically significant difference in pre-HD PCT levels at the each time point. CVi was 24.9%,CVb was 54.2%,and RCV was calculated 96.4% (with 99% probability) (Table2).

Fig1.Distribution of serum procalcitonin level at baseline

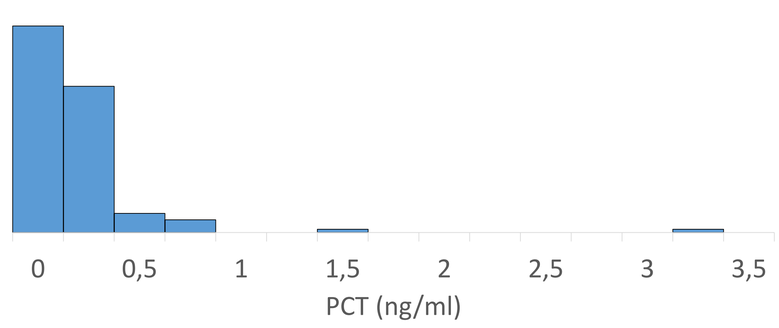


Fig2.PCT-removal rate by a single session of HD

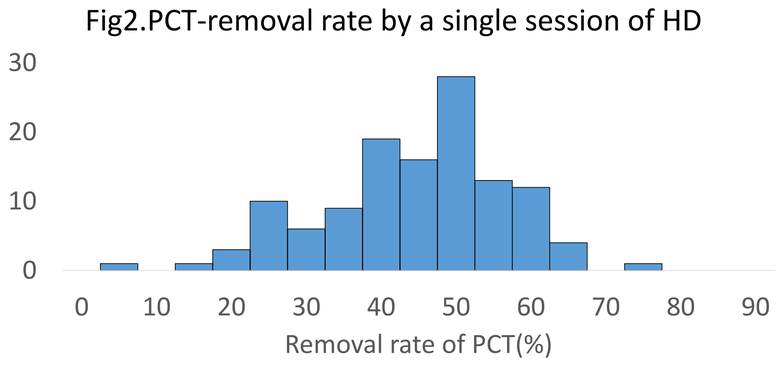


Fig3. PCT levels before & after a single session of HD

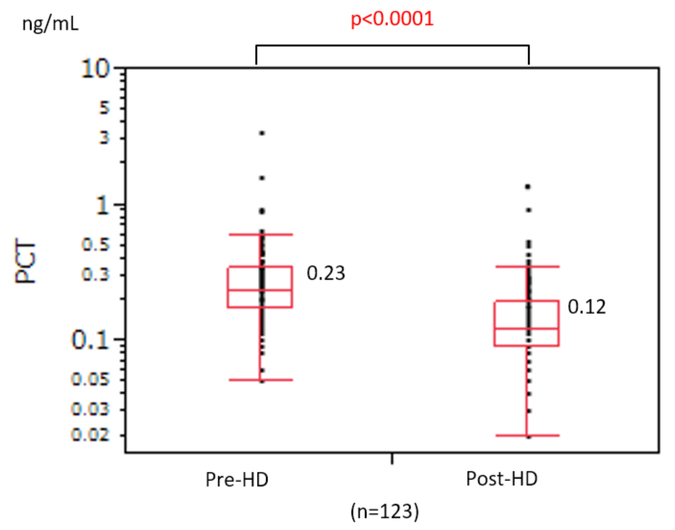


Table2.
Values for Cva, Cvi and CVb, and RCV as measured in this study.

(n=73)

PCT, ng/mL（median）		0.24
CVa,%		8.8
CVi,%		24.9
CVb,%		54.2
RCV,%	with 99% probability	96.4
	with 95% probability	73.2

Conclusions

This study provides four messages as follows: 1) even uninfected, HD patients have higher PCT levels than the general population; 2) PCT levels are influenced by HD therapy; 3) CVb is larger than CVi in HD patients; and 4) based on the RCV result, doubling of the baseline PCT level may suggest the presence of a bacterial infection in patients with HD.
These results imply that a better strategy for determining changes in PCT in patients undergoing HD is to monitor relative changes rather than comparing results to reference intervals. Further study is needed to identify the best cut-off level for diagnosing infectious disease in HD patients by a single point assessment.

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