Variability of high-sensitivity cardiac troponin T and I in asymptomatic patients receiving hemodialysis

Wanwarang Wongcharoen1, Teetad Chombandit1, Arintaya Phrommintikul1 & Kajohnsak Noppakun2,3

Variation of high-sensitivity cardiac troponin I and T (hs-cTn) during hemodialysis has been observed. Observational studies demonstrated the increased incidence of adverse cardiovascular events after long compared to short interdialytic intervals. Therefore, we aimed to compare variation of hs-cTnI and hs-cTnT before and after hemodialysis and between short and long interdialytic intervals. We enrolled 200 asymptomatic patients receiving regular hemodialysis. The hs-cTnI and hs-cTnT levels were measured before and after hemodialysis on the day after short and long interdialytic intervals. Mean age was 62.3 ± 14.8 years (Male 55.5%). Prevalence of increased hs-cTnI and hs-cTnT was 34.5% and 99.0%, respectively. The median ± interquartile range of hs-cTnT increased significantly after hemodialysis during short and long interdialytic intervals. However, hs-cTnI level did not increase after hemodialysis during short and long intervals. We found that levels of hs-cTnI and T did not differ between short interdialytic and long interdialytic intervals. We demonstrated higher prevalence of elevated hs-cTnT in patients with regular hemodialysis compared to hs-cTnI. The rise of hs-cTnT was observed immediately after hemodialysis but no significant change of hs-cTnI was noted. Accordingly, hs-cTnI may be preferable as a diagnostic marker in patients with suspected acute myocardial infarction than hs-cTnT.

The prevalence of end-stage renal disease (ESRD) and incidence of hemodialysis has distinctly increased during the past two decades1. Coronary artery disease, especially acute coronary syndrome, is a major cause of cardiac hospitalizations and cardiac deaths in hemodialysis population2. According to recent guideline recommendation, high-sensitivity cardiac troponin (hs-cTn) is recommended for the diagnosis of acute myocardial infarction3,4. It is defined as the rise of hs-cTn more than the 99th percentile of the upper reference limit (URL) or a rise of hs-cTn more than 20% if baseline level is elevated4. However, the cutoff level of hs-cTn recommended by international guidelines was derived mostly from patients without chronic kidney disease. Remarkably, it has been well described that the baseline hs-cTn levels in asymptomatic hemodialysis patients were higher than general population5. Recent studies have shown that majority of patients with ESRD with chronic hemodialysis had baseline hs-cTn above the 99th percentile URL6,7. Furthermore, the variation of hs-cTn level before, during, and after hemodialysis has been observed8–10. With this regard, the diagnosis of acute coronary syndrome in patients undergoing regular hemodialysis is challenging.

The hs-cTn I and hs-cTn T are considered the gold-standard biomarkers for detection of myocardial injury4. However, these two biomarkers have different biochemical characteristics and use different cut-off values11. In addition, previous studies have demonstrated the conflicting findings between the results of cTn I and cTn T in some population12,13. Notably, a greater number of patients having an increased cTn T compared to cTn I has been reported in chronic hemodialysis patients1. Currently, the use of conventional cTn has been replaced by hs-cTn due to the much higher sensitivity of the latter1. Nevertheless, the prevalence of elevated hs-cTn I and hs-cTn T levels in hemodialysis patients has rarely been explored. Therefore, we conducted this study to compare the prevalence of increased hs-cTn I and hs-cTn T in hemodialysis patient. The alteration of hs-cTn I and hs-cTn T pre-dialysis and post-hemodialysis in asymptomatic patients was also investigated. Moreover, observational

1Division of Cardiology, Department of Internal Medicine, Faculty of Medicine, Chiang Mai University, Chiang Mai, Thailand. 2Division of Nephrology, Department of Internal Medicine, Faculty of Medicine, Chiang Mai University, Chiang Mai, Thailand. 3Pharmacoepidemiology and Statistics Research Center (PESRC), Faculty of Pharmacy, Chiang Mai University, Chiang Mai, Thailand. 4email: kajohnsak.noppakun@cmu.ac.th
studies have shown that the incidence of adverse cardiovascular events significantly increased during the period after long interdialytic interval compared to short interdialytic interval\textsuperscript{2,14}. Accordingly, we also sought to examine the difference of hs-cTn I and hs-cTn T levels between long and short interdialytic interval.

**Methods**

We enrolled asymptomatic patients diagnosed with ESRD, aged \(> 18\) years, who had undergone regular hemodialysis (two or three times a week) for more than 90 days in the study. We excluded patients who had a recent diagnosis of acute myocardial infarction, heart failure and pulmonary embolism within previous 6 months, had major surgery and trauma within previous 4 weeks, and had coronary and/or valvular intervention within previous 6 months. The hs-cTn I and T levels were measured in all subjects before hemodialysis and after hemodialysis session on the day after short interdialytic interval and the day after long interdialytic interval. With this regard, each patient had four levels of hs-cTn I and four levels of hs-cTn T. The hs-cTn T values were evaluated with electrochemiluminescence immunosay using the Cobas e801 system (Roche Diagnostics). The detection limit of hs-cTn T was 3 ng/L, a cut-off point at 99th percentile was 14 ng/L, and a coefficient of variation of less than 10% was at 13 ng/L. The hs-cTn I values were evaluated with chemiluminescence microparticle immunoassay (CMIA) by using the ARCHITECT i2000SR system (Abbott Diagnostics). The detection limit of hs-cTn I was 3.2 ng/L, a cut-off point at 99th percentile was 26.2 ng/L, and a 10% coefficient of variation was 4.7 ng/L.

We defined the short and long interdialytic intervals as follows. For the patients who have been receiving thrice weekly hemodialysis, the long interdialytic interval was 2-day interval between hemodialysis sessions. The short interdialytic interval was 1-day interval between hemodialysis sessions. For those who have been received twice weekly hemodialysis, the long interdialytic interval was 3-day interval between hemodialysis sessions. The short interdialytic interval was 2-day interval between hemodialysis sessions.

Clinical data were recorded, including age, gender, duration of hemodialysis, medications, echocardiographic results within 1 year, ultrafiltration volume, comorbidity, and blood chemistry. This study was approved by the institutional research board of Faculty of Medicine, Chiang Mai University (Approval No. 112/2563). The study procedure was performed according to the Declaration of Helsinki. Informed consent was obtained from all participants.

**Statistical analysis.** Results are expressed as mean ± SD, unless otherwise specified and compared between group with t-test or paired t-test. Results with non-normal distribution are expressed as median (interquartile range) with non-parametric test. The numerical variables were compared within groups with paired t test or Wilcoxon matched paired sign-rank test. Mann–Whitney U test as appropriate. Proportions were compared by Fisher’s exact test. Univariate and multivariate linear regression analysis was used to examine the association between potential variables and the change of hs-cTn after hemodialysis. \(p\) values < 0.05 was considered statistically significant. Statistical software package IBM SPSS Statistics for Windows, version 23 (IBM Corp., Armonk, NY, USA, https://www.ibm.com/products/spss-statistics) was used for analysis.

**Ethics approval and consent to participate.** The Effect of long and short interdialytic interval of chronic hemodialysis on heart rate variability in patients with end-stage renal disease was approved by the ethics committee of the Faculty of Medicine, Chiang Mai University, approval number 112/2563. The investigations were carried out in accordance with the Declaration of Helsinki, including written informed consent of all participants.

**Results**

Baseline characteristics of the studied population are shown in Table 1. The mean age was 62.3 ± 14.8 years. Male was prevalent in 55.5%. The prevalence of hypertension, diabetes mellitus, and coronary artery disease was 91.0%, 45.0% and 13.0%, respectively. There were 189 (94.5%) patients receiving hemodialysis thrice a week. The rest were hemodialyzed twice a week.

The mean body weight prior to hemodialysis was greater in long interdialytic interval compared to short interdialytic interval (62.8 ± 16.7 kg vs. 62.3 ± 16.8 kg, \(P < 0.001\)). Likewise, the mean net ultrafiltration volume and the mean ultrafiltration rate was significantly greater in long interdialytic interval compared to short interdialytic interval. Table 2 shows hemodialysis parameters between short and long interdialytic intervals.

We demonstrated that 198 (99.0%) patients had an increased level of hs-cTn T above 99th percentile of the URL in both short and long interdialytic intervals. On the other hand, only 64 (32.0%) and 69 (34.5%) patients had increased hs-cTn I during short and long interdialytic intervals, respectively (Fig. 1). The histogram of hs-cTn T and I levels before hemodialysis are presented in Fig. 2. The wider range of hs-cTn T levels among interindividual patients was observed compared to hs-cTn I levels.

Compared pre- and post-hemodialysis, the median level of hs-cTn T increased significantly after hemodialysis, similarly during short interdialytic interval (59.0 ng/L, IQR 35.4–100.4 ng/L vs. 60.5 ng/L, IQR 35.7–98.3 ng/L, \(P < 0.001\)) and during long interdialytic interval (60.6 ng/L, IQR 36.4–101.2 ng/L vs. 61.7 ng/L, IQR 36.9–108.9 ng/L, \(P < 0.001\)). In contrast, the level of hs-cTn I did not increase significantly after hemodialysis during short interdialytic interval (17.1 ng/L, IQR 9.8–34.9 ng/L vs. 16.6 ng/L, IQR 9.5–37.4 ng/L, \(p = 0.59\)) and long interdialytic interval (18.4 ng/L, IQR 9.4–37.0 ng/L vs. 19.4 ng/L, IQR 10.2–33.8 ng/L, \(p = 0.59\)) (Table 3).

We also compared levels of hs-cTn between short interdialysis and long interdialysis intervals. The levels of hs-cTn I and T did not differ between short interdialytic and long interdialytic intervals, either pre-hemodialysis or post-hemodialysis level (Table 3).
We performed the univariate and multivariate linear regression to examine the association of the change of hs-cTn levels after hemodialysis and potential variables including age, medications, hemoglobin (Hb) level, vascular access, underlying coronary artery disease (CAD) and ultrafiltration rate (Table 4).

We found that older age was associated with the greater change of hs-cTn T during short and long interdialytic interval. However, age was not associated with the change of hs-cTn I after hemodialysis. In addition, we demonstrated that ultrafiltration rate was an independent factor to predict the change of hs-cTn I during short and long interdialytic interval and the change of hs-cTn T during long interdialytic interval. Furthermore, the lower Hb level was independently associated with the greater change of hs-cTn I during short interdialytic interval.

There were 127 (63.5%) patients receiving beta-blocker and 63 (31.5%) patients receiving angiotensin converting enzyme inhibitor (ACEI) or angiotensin receptor blocker (ARB). Due to the fact that these medications have been shown to protect myocardial ischemia, we explored the effect of these medications on the change of hs-cTn. We demonstrated that the change of hs-cTn T and I was similar in those receiving beta-blocker and those without beta-blocker therapy. Also, patients with and without ACEI/ARB therapy had the comparable change of hs-cTn T and I.

Table 1. Basic characteristics of the studied population. ACEI = angiotensin converting enzyme inhibitor; ARB = angiotensin receptor blocker.

| Characteristic                  | Value (N = 200) |
|--------------------------------|-----------------|
| Age (year)                     | 62.3 ± 14.8     |
| Male                           | 111 (55.5%)     |
| Smoking status                 | 146 (73.0%)     |
| - No smoking                   | 41 (20.5%)      |
| - Ex-smoker                    | 4 (2.0%)        |
| Frequency of hemodialysis      |                 |
| - Thrice a week                | 189 (94.5%)     |
| - Twice a week                 | 11 (5.5%)       |
| Vascular access                |                 |
| - Arteriovenous fistula        | 139 (69.5%)     |
| - Permanent catheter           | 51 (25.5%)      |
| - Arteriovenous graft          | 8 (4.0%)        |
| Underlying disease             |                 |
| - Hypertension                 | 182 (91.0%)     |
| - Hyperlipidemia               | 107 (53.5%)     |
| - Diabetes mellitus            | 90 (45.0%)      |
| - Coronary artery disease      | 26 (13.0%)      |
| - Atrial fibrillation          | 23 (11.5%)      |
| - Cerebrovascular disease      | 21 (10.5%)      |
| - Peripheral artery disease    | 7 (3.5%)        |
| Medications                    |                 |
| - Calcium channel blocker      | 129 (64.5%)     |
| - Beta-blocker                 | 127 (63.5%)     |
| - Statin                       | 114 (57.0%)     |
| - Diuretics                    | 92 (46.0%)      |
| - Anti-platelets               | 72 (36.0%)      |
| - Alpha adrenergic blocker     | 63 (31.5%)      |
| - ACEI or ARB                  | 51 (25.5%)      |
| - Warfarin                     | 18 (9.0%)       |
| Laboratory                     |                 |
| - Sodium (mmol/L)              | 136.7 ± 3.3     |
| - Potassium (mmol/L)           | 4.4 ± 0.7       |
| - Albumin (g/dl)               | 4.0 ± 0.4       |
| - Hemoglobin (g/dl)            | 10.4 ± 1.4      |

Table 2. Hemodialysis parameters between short and long interdialytic intervals. SBP = systolic blood pressure, DBP = diastolic blood pressure.

| Parameters                        | Short interdialysis interval | Long interdialysis interval | p value |
|-----------------------------------|------------------------------|-----------------------------|---------|
| Body weight (kg)                  |                              |                             |         |
| - Pre-dialysis                    | 62.3 ± 16.8                  | 62.8 ± 16.7                 | <0.001  |
| - Post-dialysis                   | 60.2 ± 16.3                  | 60.5 ± 16.3                 | <0.001  |
| Blood pressure (mmHg)             |                              |                             |         |
| - SBP pre-dialysis                | 143.6 ± 20.0                 | 144.3 ± 20.3                | 0.63    |
| - DBP pre-dialysis                | 76.5 ± 12.1                  | 76.3 ± 12.3                 | 0.84    |
| - SBP post-dialysis               | 137.9 ± 17.1                 | 137.3 ± 16.8                | 0.65    |
| - DBP post-dialysis               | 75.4 ± 11.5                  | 75.7 ± 13.3                 | 0.73    |
| Net filtration volume (ml)        | 2312.5 ± 948.8               | 2623.5 ± 963.1              | <0.001  |
| Ultratilration rate (ml/hour/kg)  | 9.45 ± 3.73                  | 10.70 ± 3.93                | <0.001  |
| Hypotension during hemodialysis (%)| 5 (2.6%)                    | 4 (2.1%)                    | 0.15    |
Figure 1. Individual variation of high-sensitivity cardiac troponin T and high-sensitivity cardiac troponin I pre-hemodialysis and post-hemodialysis during short interdialytic interval. (A) High-sensitivity cardiac troponin T pre-hemodialysis (line indicates cut-off level of 14 ng/L). (B) High-sensitivity cardiac troponin T post-hemodialysis (line indicates cut-off level of 14 ng/L). (C) High-sensitivity cardiac troponin I pre-hemodialysis (line indicates cut-off level of 26.2 ng/L). (D) High-sensitivity cardiac troponin I post-hemodialysis (line indicates cut-off level of 26.2 ng/L).

Figure 2. Histogram of high-sensitivity cardiac troponin T (A) and I (B) levels before hemodialysis.
Table 3. The change of biomarkers before and after hemodialysis in short and long interdialytic intervals. *Compared between pre- and post-hemodialysis, hs-cTn = high-sensitivity cardiac troponin. Data are presented as median level (interquartile range).

| Biomarker | Short interdialysis interval | Long interdialysis interval |
|-----------|-----------------------------|-----------------------------|
|           | Pre-dialysis | Post-dialysis | p value* | Pre-dialysis | Post-dialysis | p value* |
| Hs-cTn (ng/L) | 17.1 (9.8, 34.9) | 16.6 (9.5, 37.4) | 0.59 | 18.4 (9.4, 37.0) | 19.4 (10.2, 33.8) | 0.59 |
| Hs-cTn (pg/L) | 59.0 (35.4, 100.4) | 60.5 (35.7, 98.3) | <0.001 | 60.6 (36.4, 101.2) | 61.7 (36.9, 108.9) | <0.001 |

We examined the effect of different vascular access on the change of hs-cTn. We analyzed the change of hs-cTn after hemodialysis. ACEI/ARB = angiotensin converting enzyme inhibitor/angiotensin receptor blocker, BB = beta-blocker, CAD = coronary artery disease, Hb = Hemoglobin, hs-cTn = high-sensitivity cardiac troponin.

Table 4. Univariate and Multivariate linear regression analysis showing the association of potential variables and the change of hs-cTn after hemodialysis. ACEI/ARB = angiotensin converting enzyme inhibitor/angiotensin receptor blocker, BB = beta-blocker, CAD = coronary artery disease, Hb = Hemoglobin, hs-cTn = high-sensitivity cardiac troponin.

**Discussion**

The elevation of hs-cTn T and I. The hs-cTn level is recommended for the diagnosis of acute myocardial infarction but its cutoff level is derived from epidemiological data in general population without ESRD. Several investigators have shown that patients with regular hemodialysis have elevated hs-cTn levels compared to general population. This could be partly explained by the occurrence of microinfarction, heart failure, degenerative changes or other myocardial pathology in patients with ESRD. Previous study has demonstrated that greater number of patients with regular hemodialysis had an elevated cTn T level compared to Tn I level. In similar, the prevalence of increased hs-cTn T was much higher than hs-cTn I in our studied population. The elevation of troponin levels in dialysis patients could be related to other factors beyond the ischemic cause, such as left ventricular systolic and diastolic dysfunction, left ventricular hypertrophy, myocardial stunning, volume overload, microvascular disease, endothelial dysfunction, and decreased renal clearance.
that showed the increase in cTn T, but not cTn I, in patients after hemodialysis. On the contrary, other two studies showed that hs-cTn I and hs-cTn T decreased slightly after hemodialysis. However, the number of patients in those two studies was small in which only 10 and 20 patients were included.

It is plausible that hs-cTn T may have higher sensitivity to detect minor myocardial injury during hemodialysis compared to hs-cTn I. The hemodialysis has been shown to disrupt myocardial blood flow. In accordance, previous study showed that high ultrafiltration rate was associated with increased hs-cTn levels during hemodialysis. High volume depletion during hemodialysis may cause hemodynamic compromise leading to myocardial ischemia. Nevertheless, our result showed that ultrafiltration rate was associated with the change of both hs-cTn T and I level after hemodialysis. The dissimilar biochemical characteristics between these two biomarkers may also partly explain the different findings. It has been described that hs-cTn I can adsorb onto the dialysis membrane because of its hydrophobicity which may result in the lack of hs-cTn I elevation after hemodialysis.

The change of hs-cTn during short and long interdialytic intervals. Several observational studies have shown that the incidence of adverse cardiovascular events significantly increased during the period after long interdialytic interval compared to that after short interdialytic interval. Numerous factors have been reported to contribute to the major adverse cardiac events during long interdialytic interval compared to short interdialytic interval. Greater degree of hypervolemic status during long interdialytic interval may induce structural and functional disorders in myocardium, leading to the occurrence of myocardial damage. Electrolyte imbalance and the disorder in autonomic nervous system during long interdialytic interval may result in the increased risk of cardiac arrhythmias. In addition, the increase in oxidative stress, inflammation and abnormal calcium or phosphate metabolism during long interdialytic interval, may play some roles in atherosclerosis of coronary artery. Of interest, we did not find any difference in hs-cTn I and T levels between short and long interdialytic interval. Data are presented as median level and interquartile range (IQR).
interdialytic intervals. Our results suggest that myocardial injury may not be a major factor contributing to worse prognosis during long interdialytic interval.

Our study has several limitations. First, the fluid overload and fluid management are significant confounding factors affecting cardiac ischemia via stretching and shrinking cycles. However, we did not assess the fluid status of the patients by any bioimpedance measurements or cardiac biomarkers such as B-type natriuretic peptide (BNP) or N-terminal pro BNP (NTproBNP). We examined only the ultrafiltration volume, the ultrafiltration rate and body weight change which may not be sufficient to evaluate the fluid status of the patients. Second, we did not assess the inflammatory marker in our studied population. This issue should be explored in future studies. Third, we did not include patients with non-dialysis ESRD and those with chronic peritoneal dialysis. Therefore, our findings could not be applied in these population. Future studies are warrant to explore the difference of hs-cTn variability between our studied population and those with peritoneal dialysis and non-dialysis ESRD patients.

Conclusion

We demonstrated the higher prevalence of elevated hs-cTn T in patients with regular hemodialysis compared to hs-cTn I. In addition, the rise of hs-cTn T was observed immediately after hemodialysis but no change of hs-cTn I. In addition, the rise of hs-cTn T was observed immediately after hemodialysis but no change of hs-cTn I. However, from a practical standpoint, hs-cTn I may be more favorable as a diagnostic marker in patients with suspected acute myocardial infarction than hs-cTn T.

Data availability

The informed consent given by effect of long and short interdialytic interval of chronic hemodialysis on heart rate variability in patients with end-stage renal disease study participants does not cover data posting in public databases. However, data are available upon request should be sent to kajohnsak.noppakun@cmu.ac.th and are subject to approval by the Faculty of Medicine, Chiang Mai University Ethics Committee.

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Author contributions
W.W. performed the statistical analyses, evaluated the results and drafted the paper. T.C. recruited patients. A.P. and collected the data and contributed substantially to data preparation and quality assurance. K.N. designed study, participated in the conception and design of the study, revised the paper for important intellectual content. All authors have read and approved the final manuscript.

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Competing interests
The authors declare no competing interests.

Additional information
Correspondence and requests for materials should be addressed to K.N.

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