

ORIGINAL ARTICLE

Cardiovascular

Monthly measurement of high-sensitivity cardiac troponins T and creatine kinase in asymptomatic chronic hemodialysis patients: A one-year prospective study

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Abstract

Background: Cardiology guidelines recommend measuring high-sensitivity cardiac troponin (hs-cTn) for the diagnostic work-up of acute coronary syndromes (ACS). Many hospitals measure hs-cTnT, but preliminary data have shown that hs-cTnT is higher than normal in many hemodialysis patients without evidence of ACS. The purpose of this study was therefore to determine the hs-cTnT levels every month for 1 year in asymptomatic hemodialysis patients, in order to assess their changes over time relative to creatine kinase.

Methods: Forty-four hemodialysis patients (mean age 67 ± 14 years) were included. The predialysis levels of fifth-generation hs-cTnT, CK, and CK-MB were measured every month for 1 year using a Cobas[®] 6000 analyzer (Roche Diagnostics, Switzerland).

Results: Almost 100% of hs-cTnT measurements were higher than normal ($N < 14$ ng/L); the mean \pm SD annual level was 84 ± 59 ng/L, ranging from a minimum of 24 ± 2 to 241 ± 28 ng/L in individual patients. The mean levels of CK and CK-MB were normal. Thirteen myocardial infarctions were analyzed, which were all associated with an initial elevation in hs-cTnT $>45\%$ from the individual baseline value. By comparison, CK and CK-MB only increased in 38% and 31% of these myocardial infarctions, respectively.

Discussion: hs-cTnT is persistently higher than normal in chronic hemodialysis patients. Standard algorithms for diagnosing ACS can obviously not be used and alternative diagnostic strategies need to be developed. According to our data, and given the huge variation in baseline hs-cTnT levels among patients, the use of higher cut-offs as proposed in the literature cannot be recommended. Instead, we consider that hs-cTnT should be checked at regular intervals (e.g., every 3–6 months) in order to establish individual baseline levels for hs-cTnT. This approach, in most instances, not only makes it

possible to more rapidly rule-in but also to rapidly rule-out, cases of ACS in hemodialysis patients who develop cardiac symptoms.

KEYWORDS

biomarkers, creatine kinase, hemodialysis, high-sensitivity cardiac troponin T, myocardial infarction

INTRODUCTION

Patients with end-stage renal disease have a higher mortality rate in comparison with the general population. In chronic hemodialysis patients, mortality related to cardiovascular disease is up to 45%, 10–20 times higher than in the general population.^{1–9} Most of these patients have coronary artery disease, which results in acute myocardial infarction, the leading cause of death and disability among this cohort.^{1–9}

A rapid and accurate diagnosis of acute coronary syndromes (ACS) is therefore critical to the optimum management of these patients. However, this diagnostic process is complicated in this population, because the clinical presentation of ACS is frequently atypical.^{10–13} Patients have a high prevalence of anemia, exercise intolerance, cardiac failure and pre-existing electrocardiographic abnormalities. Moreover, in patients with advanced renal failure or on hemodialysis, chest pain is absent in a third of the cases with myocardial infarction, and 78% of the myocardial infarctions are non-STEMI.¹¹ In these patients, cardiac troponins therefore play a critical role in the detection and diagnosis of myocardial infarction.

The European Society of Cardiology (ESC) guidelines^{14,15} recommend measuring the high-sensitivity cardiac troponins for the diagnostic work-up of ACS. ESC defines biochemical evidence of myocardial ischemia as an increase in high-sensitivity cardiac troponins to at least above the 99th percentile of that in the healthy reference population. The 2015 guidelines also state that many patients with a serum creatinine level of above 221 $\mu\text{mol/L}$ may have elevated troponin levels, and that an assay-specific threshold five times higher than the normal range should therefore be considered in patients with renal dysfunction.¹⁴ However, no clear recommendations are provided for physicians on how to proceed in hemodialysis patients and this remains the case in the 2020 ESC guidelines.¹⁵

In a previous study, we compared the diagnostic accuracy of third-generation cardiac troponin T and I assays in hemodialysis patients.¹⁶ Our results showed that the third-generation cardiac troponin I assay that was used

(cTnI dimension R_xL improved method assay) had a much better specificity than the troponin T assay. Our data actually showed that cardiac troponin T was already higher than normal in 46% of the asymptomatic patients at our center, compared to only 2% for cardiac troponin I.^{16,17} With the introduction in our hospital of the fifth-generation assay for hs-cTnT in 2016, we were surprised to observe that an even greater proportion of the asymptomatic hemodialysis patients at our center showed higher than normal cardiac troponin T levels, introducing additional difficulties in the work-up of ACS.^{18–24}

Taking into consideration the fact that many stable asymptomatic dialysis patients have hs-cTnT levels that are higher than normal, some authors have proposed different clinical approaches in order to adapt the

TABLE 1 Clinical and biological characteristics of the study cohort at inclusion

	n = 44
Age (years)	67.0 \pm 13.8
Sex (F/M)	11/33
Dialysis duration (months)	36.6 \pm 40.6
BMI	26.5 \pm 5.6
Diabetes mellitus	38.6%
Coronary artery disease	37.0%
Peripheral artery disease	47.7%
Cerebro-vascular disease	6.8%
Mean dialysis duration	12 h/week
URR %	72.5 \pm 6.3
Kt/V	1.58 \pm 0.26
Hemoglobin (g/L)	112.9 \pm 13.4
Albumin (g/L)	39.6 \pm 4.2
CRP (mg/L)	12.2 \pm 20
Total cholesterol (mmol/L)	3.80 \pm 1.05
HDL-cholesterol (mmol/L)	1.07 \pm 0.35
Triglycerides (mmol/L)	1.88 \pm 0.94

Abbreviations: BMI, body mass index; CRP, c-reactive protein; URR, urea reduction ratio.

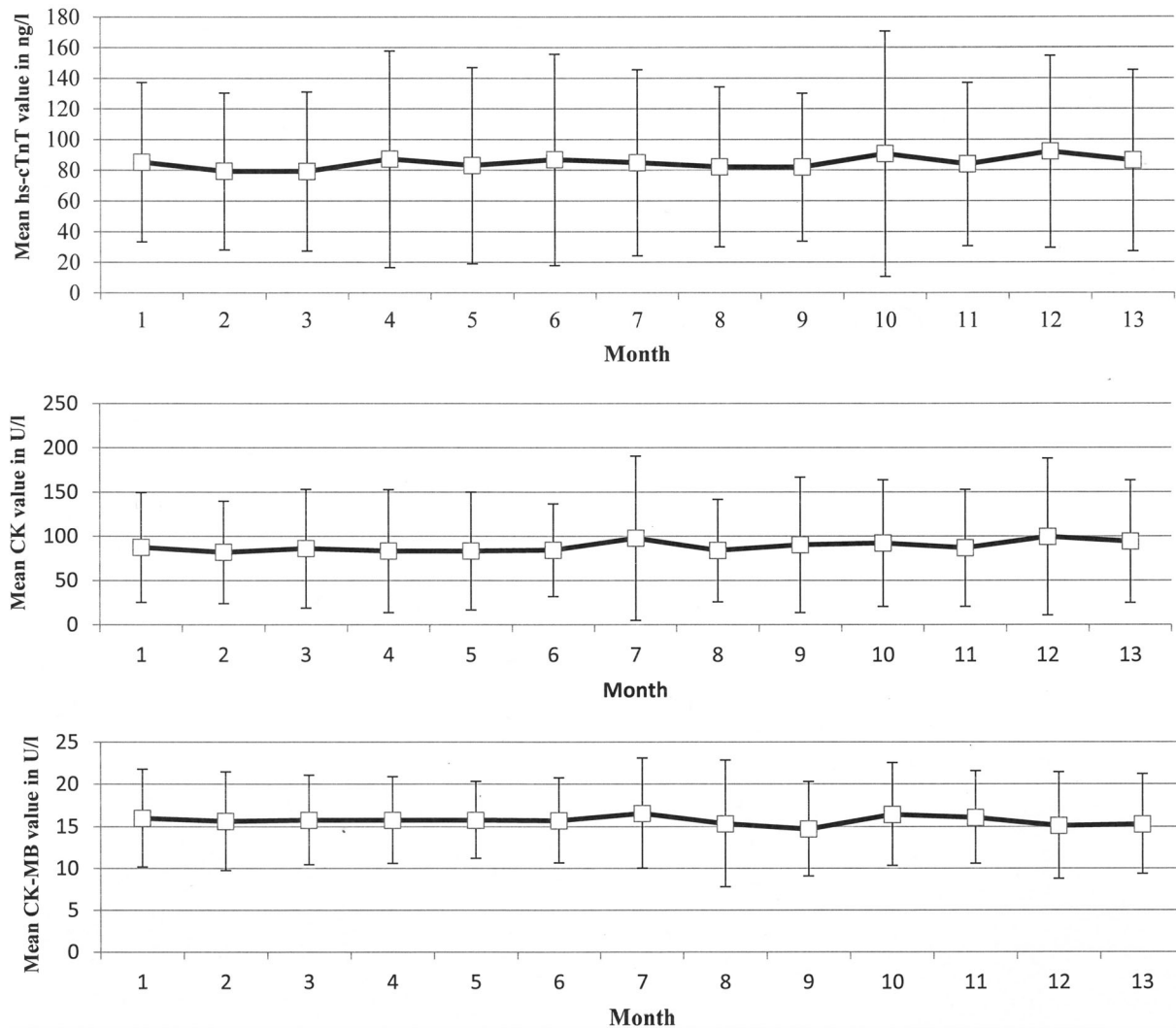


FIGURE 1 Time course of the mean \pm SD levels of hs-cTnT, CK, and CK-MB during the study year. Normal levels are <14 ng/L, <170 U/L, and <25 U/L, respectively

TABLE 2 hs-cTnT, CK, and cK-MB measurements before and after dialysis ($n = 169$). Of the 44 patients, 37 (84%) were on high-flux hemodialysis and 7 on online hemodiafiltration

Parameters	Normal range	Before HD	After HD	% reduction (%)
hs-cTnT	<14 ng/L	84.2 ± 62.6	$72.0 \pm 54.6^*$	-14.50
CK	<170 U/L	98.8 ± 110.3	$92.4 \pm 105.8^*$	-6.40
CK-MB	<25 U/L	16.1 ± 6.1	$15.4 \pm 5.7^*$	-4.90

* $p < 0.001$.

cardiology guidelines for patients with chronic kidney disease or chronic hemodialysis. One of these approaches was to increase the troponin threshold signaling a myocardial infarction, with the proposed threshold ranging from 29.5 ng/L up to 149 ng/L.^{14,24–26} Other authors preferred to consider the dynamic variation of troponin concentrations, with a relative increase from 20% to 33% of the hs-cTnT value in the 3–6 h after presentation to be considered as significant.^{23,25,27–29}

Accordingly, the interpretation of hs-cTnT levels remains difficult in hemodialysis patients with suspected ACS, as discrimination is required between a relevant rise in the hs-cTnT concentration and its background elevation. Thus, the aim of this study was to make monthly measurements over 1 year of hs-cTnT compared with creatine kinase (CK and CK-MB) levels among asymptomatic patients under maintenance hemodialysis, in order to determine the baseline levels, as well as the degree of

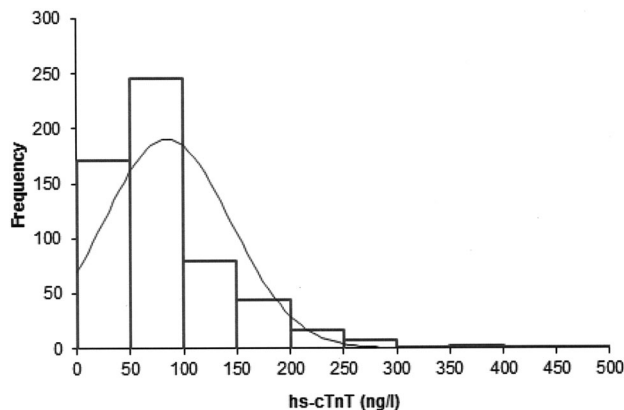


FIGURE 2 Distribution of the predialysis hs-cTnT levels during the study years ($n = 570$, normal level < 14 ng/L)

the long-term variation in these parameters. Our analysis also focused on dynamic changes in hs-cTnT and creatine kinase that occurred during ACS episodes.

PATIENTS AND METHODS

In this prospective cohort study, high-sensitivity troponin T (hs-cTnT), creatine kinase (CK) and creatine kinase MB (CK-MB) were measured monthly over a 1-year period. We included all asymptomatic patients (i.e., without cardiac symptoms) with end-stage renal disease who were undergoing chronic hemodialysis in our dialysis center and could be followed for 1 year from July 2016 to July 2017. Exclusion criteria were ACS or acute myocardial infarction within the previous 4 weeks. Fifty-one patients fulfilled the inclusion criteria, but during the study year two of them underwent kidney transplantation, two went to another dialysis center and three died, so that 44 patients with complete data were included in the final analysis.

Fifth-generation hs-cTnT, CK and enzymatic CK-MB were measured monthly before hemodialysis, at the same time as routine monthly blood analysis, and also every 6 months posthemodialysis. All blood samples were analyzed in the central laboratory at the hospital. The assays were performed with a Cobas® 6000 (e601 + e501) Roche analyzer, using photometry and electrochemiluminescence immunoassay (Roche Diagnostics). The limit of detection for hs-cTnT is 3 ng/L, with a 99th percentile cut-off at 14 ng/L, and a 95% confidence interval between 12.7 and 24.9 ng/L. The limit of detection is 7 U/L (normal value: <170 U/L) for CK and 3 U/L (normal value: <25 U/L) for enzymatic CK-MB.

For patients developing symptoms of ACS, a sudden increase in dyspnea and/or showing a sudden increase in troponin levels, a complete cardiological work-up was

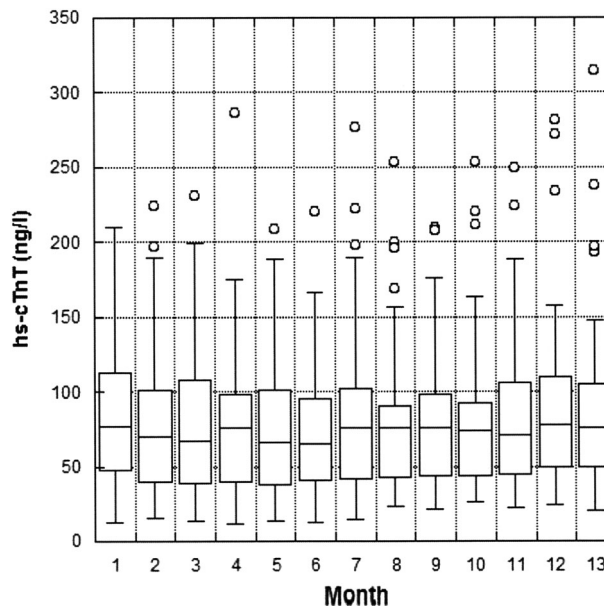


FIGURE 3 Box-and-whisker plot of the hs-cTnT levels during the study year. The boxes indicate the 25th and 75th percentiles and the line inside the boxes is the median value. The lines extending from the top and bottom of each box indicate the minimum and maximum values, except for extreme outliers

performed in order to diagnose or rule out myocardial infarction and to differentiate type 1 from type 2 myocardial infarction.³⁰ This cardiological work-up included an accurate clinical and laboratory evaluation (with serial hs-cTnT determinations and repeated electrocardiograms, as needed), as well as echocardiography and/or coronary angiography, if indicated. To complete our analysis, we identified all the episodes of ACS occurring in the study patients during the study year and in a 3-year follow-up (starting from August 2017), during which hs-cTnT, CK, and CK-MB were no longer measured monthly, but every 3 months.

The study was performed in accordance with the ethical standards of the Declaration of Helsinki and was approved by the ethics committee of our institution (Commission cantonale d'éthique et de recherche sur l'être humain du canton de Vaud; study number 2016-00462). All participants provided informed consent to participate to the study.

The results are reported as mean \pm standard deviation (SD), unless otherwise stated. Groups were compared with the Student's paired t-test and repeat determinations were compared using one-way analysis of variance (ANOVA). A $p < 0.05$ was considered significant.

RESULTS

Forty-four subjects were included in this study. The clinical and biological characteristics of the patients at

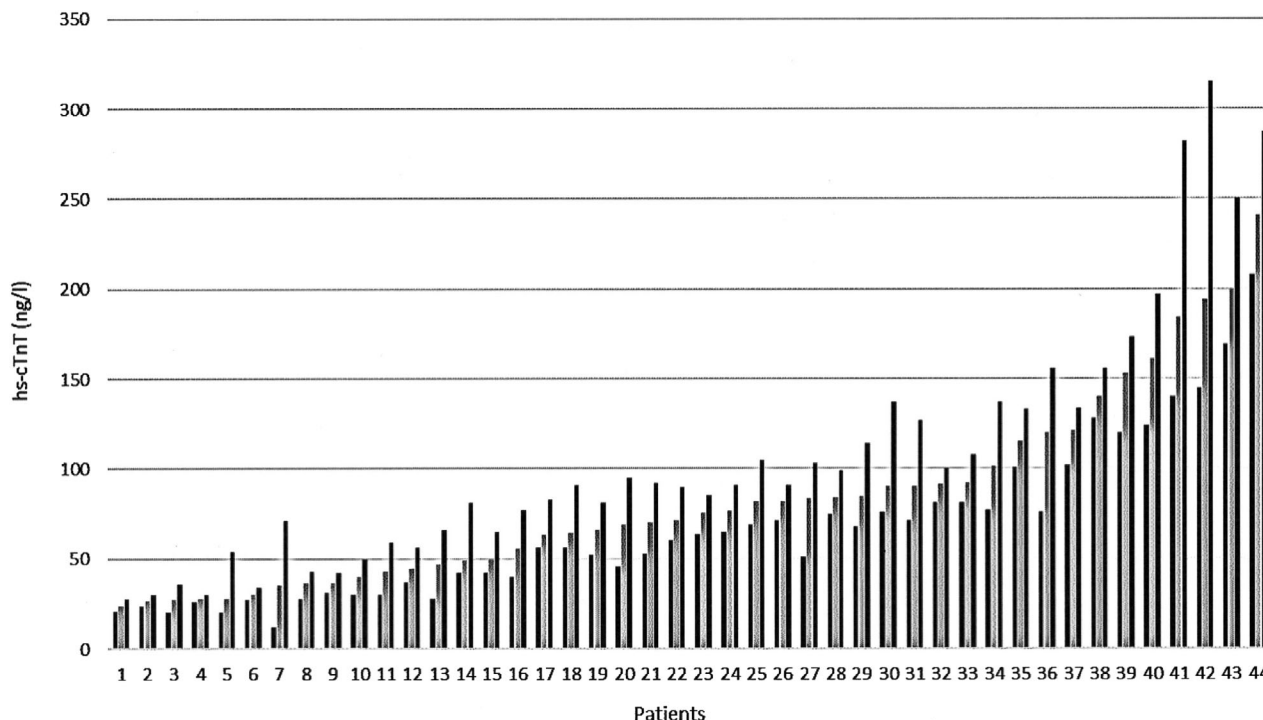


FIGURE 4 Minimum (left), mean (center) and maximum (right) hs-cTnT levels in the 44 patients during the study year

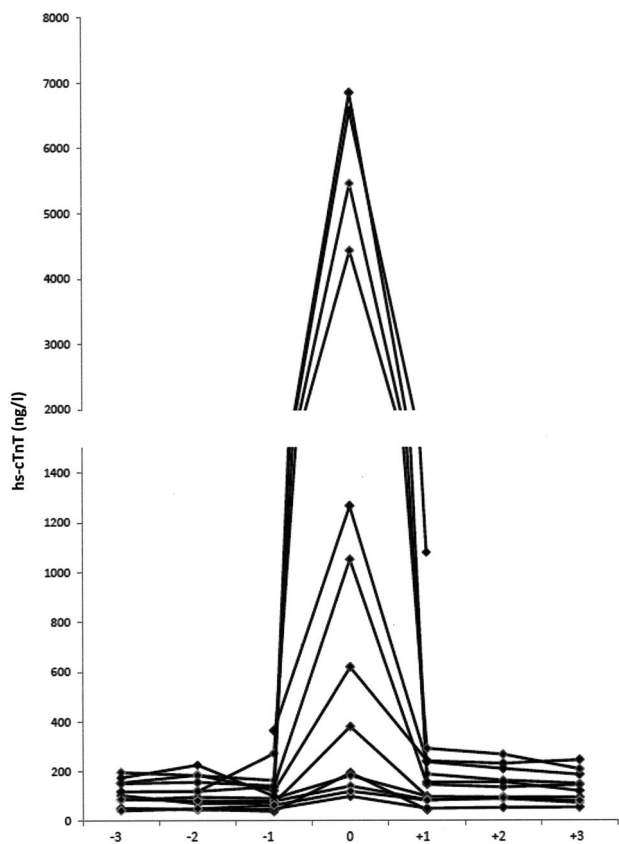


FIGURE 5 Time course of c-TnT before and after the 13 episodes of ACS, with peak values at time 0. *One patient died a few days after the myocardial infarction

inclusion are summarized in Table 1. Briefly, the study cohort included 33 men and 11 women, with a mean age of 67 ± 14 years. They had been under chronic hemodialysis for a mean 37 ± 41 months. Within this cohort, 39% were diabetic and 37% had a history of ischemic heart disease. The patients were dialyzed three times per week using high-flux dialyzers with a surface area ranging from 1.7 to 2.1 m². Thirty-seven patients (84%) were on high-flux hemodialysis and seven on low-volume (n = 3) or high-volume (n = 4) online hemodiafiltration. Mean duration of dialysis was 4 h, and the mean Kt/V at inclusion was 1.58 ± 0.26 .

Figure 1 illustrates the mean time course of hs-cTnT, CK, and CK-MB over the study year. During this period, 570 predialysis blood samples were analyzed. Individual troponin values were higher than normal in 99.5% of measurements, CK values were higher than normal in 8.8% and CK-MB values in 4.2% of the samples. During dialysis, concentrations of both hs-cTnT, CK, and CK-MB diminished significantly, by 14.5%, 6.4%, and 4.9%, respectively (Table 2). The mean hs-cTnT level remained much higher than the 99th percentile ($N < 14$ ng/L) over the entire year, with a mean value of 84 ± 59 ng/L. Mean CK and CK-MB levels were always within normal range and were 88 ± 69 U/L ($N < 170$) and 16 ± 6 U/L ($N < 25$), respectively.

Figure 2 reports the distribution of the 570 predialysis determinations of hs-cTnT and shows that hs-cTnT

values were higher than 100 ng/L in 25% of these measurements. Figure 3 is a box-and-whiskers plot showing the monthly development of hs-cTnT concentrations; there was a slight, but not significant, fluctuation in the monthly hs-cTnT values ($p = \text{ns}$; one-way ANOVA). In individual patients, the mean annual value was always higher than normal and varied between a minimum of 24 ± 2 ng/L and a maximum of 241 ± 28 ng/L. The mean annual levels were lower than 50 ng/L in 34% of patients, between 51 and 100 ng/L in 41%, and higher than 100 ng/L in 25% of patients (14% >150 ng/L). During the study year, monthly hs-cTnT levels in individual patients fluctuated each month, generally in a slow manner. Figure 4 shows the minimum, mean, and maximum hs-cTnT levels observed in our 44 patients during the study year. Variations over time remained within $\pm 25\%$ around the mean annual value in the majority of patients, but this figure was higher in some individuals, particularly in those with mean annual hs-cTnT levels that were higher than 150 ng/L (Figure 4, Patients 40–44).

During the study and follow-up, we identified 13 episodes of Type 1 myocardial infarction (3 STEMI and 10 NSTEMI) in 9 of our 44 patients. All 13 cases underwent coronary angiography, showing significant coronary disease and, of these, 11 had percutaneous angioplasty. In these 13 cases, 100% showed an acute rise in the hs-cTnT concentrations to well above baseline. The CK levels increased in only 5 (38%) of these 13 cases, and CK-MB in only 4 (31%). It should also be noted here that knowledge of baseline hs-cTnT levels has not only been very useful for rapidly ruling in suspected ACS patients, but quite often allowed us—and this is also a very important clinical point—to rapidly rule out myocardial infarction in patients with cardiac symptoms, but in whom hs-cTnT levels had remained unchanged compared to preceding baseline levels.

During these 13 myocardial infarctions, the hs-cTnT level in the first blood samples was always at least >45% higher than the preceding baseline values, and the increase in absolute concentrations varied widely, from 23 to 2534 ng/L. It should be noted, however, that the time lag between symptoms and blood sampling could not be standardized in our patients as our study was not specifically designed to study this point. The percentage reported above thus corresponds rather more to a “real world” figure for a dialysis center. The hs-cTnT peak also varied widely, with an increase in hs-cTnT above baseline ranging from a minimum of 50 ng/L to a maximum of 6410 ng/L. Figure 5 shows the development of peak hs-cTnT values during the 13 myocardial infarctions compared with baseline values over the three previous months. This figure shows that, after the myocardial

infarction, hs-cTnT values returned to a baseline that was slightly higher than the pre-ACS values in a third of the patients.

DISCUSSION

The European Society of Cardiology guidelines recommend measuring high-sensitivity troponins for the diagnostic work-up of ACS.^{14,15} High-sensitivity assays are much more sensitive than those of previous generations, with a 10-fold to 100-fold reduction in the limit of detection, allowing the detection of dynamic changes in cardiac troponins above the 99th percentile level in healthy individuals. The higher sensitivity and diagnostic accuracy of these tests allows the delay in the diagnosis of myocardial infarction to be reduced in patients with normal renal function, with shorter “rule-in” and “rule-out” algorithms, that is, with the use of 0/3 h or even 0/1 h strategies.^{14,15,31} The ECS guidelines suggest that higher assay-specific cut-off levels should be used for both hs-cTnT and hs-cTnI in patients with renal dysfunction.^{14,24} These guidelines refer to the study by Twerenbold et al., conducted on patients with renal dysfunction (eGFR < 60 ml/min/1.73 m²) and including 449 patients with a mean eGFR of 49 ml/min, but with no data or guidelines for patients on maintenance dialysis.²⁴ Other studies have also shown that both hs-cTnT and hs-cTnI progressively increase with decreasing renal function in a relevant proportion of patients.^{32–34} Chuang et al. recently conducted an in-depth review of the three mechanisms for cardiac troponins elevation in CKD patients, including ischemic cardiac injury, non-ischemic cardiac injury, and renal dysfunction.³⁵

Over the past few years, in accordance with the above guidelines, most laboratories around the world have progressively introduced high-sensitivity cardiac troponin assays for the rapid evaluation of ACS. In Switzerland, the majority of hospitals currently use fifth generation hs-cTnT assays (Roche Diagnostics). Since the introduction of hs-cTnT assays in our hospital, we have observed that a majority of stable asymptomatic patients under chronic hemodialysis had hs-cTnT levels above the normal threshold. This was not the case with the third generation cardiac troponin I assay previously used in our institution, based on which only 2% of the hemodialysis patients had cTnI levels higher than the normal range.^{16,17} This is why we decided to monitor hs-cTnT, CK, and CK-MB on a monthly basis for 1 year in all the asymptomatic hemodialysis patients at our center, in order to evaluate their levels, as well as their degree of fluctuation.

The current study shows that almost all patients with end-stage renal disease on chronic hemodialysis

persistently have plasma hs-cTnT levels that are higher or much higher than those in the reference population. This is in agreement with previous studies, which reported higher than normal hs-cTnT levels in 90%–100% of hemodialysis patients.^{20,21,25,28,29,36–38} Also in agreement with earlier studies, our data show that hs-cTnT levels diminish significantly during dialysis, with mean diminution ranging from 10% to 15%.^{38–41} There was high individual variation in the mean annual predialysis hs-cTnT concentrations in our patients, with mean levels ranging from 24 ± 2 ng/L to 241 ± 28 ng/L, that is, 10-fold higher. Conversely, mean creatine kinase (both CK and CK-MB) concentrations remained within normal range during the study year. However, CK and CK-MB also remained within the normal range in over 60% of the 13 myocardial infarctions we analyzed, most of which were NSTEMI. CK and CK-MB are therefore clearly associated with a lack of sensitivity and are no longer a clinically relevant cardiac biomarker in the “troponin era.”^{42,43} Hs-cTnT increased significantly in all our myocardial infarctions and the first determination during the episodes revealed hs-cTnT levels that were at least >45% higher than the preceding baseline values. Therefore, according to our data and our experience, it turns out that the determination of baseline values is quite useful, not only to rapidly rule in an ACS when hs-cTnT values are already significantly higher compared to baseline, but also to rapidly rule out a myocardial infarction when the hs-cTnT levels remain unchanged compared to preceding baseline levels.

The presence of consistently high levels of high-sensitivity troponins seriously complicates the detection of acute myocardial ischemia in hemodialysis patients, as physicians always have to discriminate between a relevant rise in the hs-cTnT concentration and its background elevation. Thus, the question remains of how to interpret hs-cTnT levels and the changes in levels in hemodialysis patients with suspected ACS. Previous authors have already discussed this point and some of them proposed the use of higher cut-off levels in patients with chronic renal failure or on hemodialysis, while others considered that the appropriate approach should rely on the analysis of the dynamic changes in the hs-cTnT levels.

The hs-cTnT thresholds proposed to date in the literature for patients with renal failure or hemodialysis varied widely, from 29.5/51.1 ng/L²⁴ to 70 ng/L,¹⁴ 107.7 ng/L²⁵ up to 149.35 ng/L.²⁶ However, when we consider the data from our cohort of asymptomatic hemodialysis patients, where the mean annual hs-cTnT level was 84 ± 59 ng/L and in whom 25% of the measurements were already higher than 100 ng/L, the proposed cut-offs ranging from 29.5 to 107.7 do not seem to be adapted. Huang et al.

already stated in their work that the 107.7 ng/L cut-off they proposed for hemodialysis patients “was the best cut-off for diagnosis of AMI determined by ROC analysis, however, with a rather low diagnostic accuracy (AUC 0.68, sensitivity of 58% and a specificity of 71%)”.²⁵ The highest threshold of 149.35 ng/L proposed by Yang et al. certainly exhibits a better diagnostic performance, with a sensitivity of 79.2% and a specificity of 81.9% in hemodialysis patients.²⁶ However, two points must be made concerning this threshold. First, it should be noted that 6 out of our 44 patients (13.6%) had mean hs-cTnT levels that were already higher than this cut-off over the course of the entire study year. Second, and more important, if we analyze the 13 episodes of myocardial infarction observed in our cohort, the first hs-cTnT determination was lower than this threshold in 4 out of the 13 patients (31%) and even the hs-cTnT peak level remained lower than 150 ng/L in 3 of them (23%)! Therefore, the use of this threshold carries the risk of delayed diagnosis or underdiagnosis of myocardial infarctions, particularly in those hemodialysis patients with low baseline hs-cTnT levels.

As an alternative to higher thresholds, other authors considered that dynamic changes should be used in hemodialysis patients for the diagnostic work-up of ACS. The relative delta changes proposed to date for two successive blood samples taken at a 3–6 h interval are >20%,^{23,27} >24%,²⁵ >20%–30%²⁸ or 33%.²⁹ Only one author has proposed considering an absolute delta change, as is done in most algorithms put forward for patients with normal renal function, and proposed considering a 32.6 ng/L increase.²⁵ However, if we compare this absolute delta value with the mean annual hs-cTnT levels in our patients, it appears that this value represents an increase of >130% in patients with lower baseline levels (i.e., 24 ng/L), while it represents only a 13.5% increase in those with already very high levels (i.e., 240 ng/L). Therefore, considering the huge differences in mean baseline hs-cTnT levels among hemodialysis patients, it appears that the use of values on absolute change may result in an increased number of false positive and false negative results, depending on the decision threshold that is chosen. It thus turns out that the use of adapted relative delta changes should be considered in hemodialysis patients.^{23,27,29}

In our patients who developed type 1 myocardial infarction,³⁰ the first hs-cTnT determination was always at least 45% higher than previous baseline values. However, it should be noted that, as indicated in the results section, we could not apply a standardized protocol in our patients, as is possible in an emergency department, in particular with reference to the precise timing of blood sampling relative to the onset of cardiac symptoms. It is thus possible that a > 20% increase in two successive

blood samples drawn in the 6–9 h after presentation, as proposed in 2007 by the National Academy of Clinical Biochemistry,²³ is already indicative of ongoing acute myocardial ischemia. Of course, this depends on the time lag between the first symptoms and the time of blood sampling: thus, to also answer this question satisfactorily for hemodialysis patients, further specifically designed studies are required in which the time lag between the onset of cardiac symptoms and the time intervals between blood sampling are precisely known. However, an important point that emerges from our data is that, if baseline values are available for a patient, then in most instances a single blood sample is generally sufficient to either indicate the presence of ongoing acute ischemia (when hs-cTnT is clearly higher than baseline), or its absence (when hs-cTnT is unchanged compared to baseline). In cases of doubt, a second blood sample should be taken 2–4 h after the first. In our experience, the availability of individual baseline hs-cTnT levels can therefore clearly simplify and speed up the diagnostic and therapeutic work-up in most hemodialysis patients who develop cardiac symptoms. Based on this, hs-cTnT values are currently measured every 3 months in all patients at our dialysis center. This protocol involves additional costs, which represent <1% of the annual costs of maintenance hemodialysis in our country. However, considering the high cardiovascular risk and the high inpatient mortality in hemodialysis patients,^{3–12} we consider this extra-cost to be acceptable.

This is the first study in which hs-cTnT levels have been systematically monitored on a monthly basis for 1 year and compared to creatine kinase. Our study also has potential limitations: it represents a single-center study with a relatively limited number of subjects. Furthermore, we used a single laboratory assay (the only one available for hs-cTnT) without a comparison with other hs-cTnI assays. Concerning the myocardial infarction episodes, the number is limited and the timing of blood sampling could not be standardized.

In conclusion, our data show that hs-cTnT is persistently higher than normal in patients on maintenance hemodialysis and that baseline levels vary considerably from one patient to the next, with a 10-fold difference between the lowest and the highest baseline levels. It is clear that the standard algorithms for diagnosing ACS cannot be used and alternative diagnostic strategies need to be developed, but there are currently no firm evidence-based guidelines for dialysis patients. Based on our data and the above discussion, we consider that the use of a higher threshold, as proposed in the literature, cannot be recommended for hemodialysis patients. Instead, we believe that, given the huge differences in mean hs-cTnT levels among HD patients, hs-cTnT should be checked at

regular intervals, in order to establish individual baseline hs-cTnT levels. In our experience, this approach should not only result in faster ruling in, but also, and very importantly from a clinical perspective, allow in many cases rapid ruling out of ACS in hemodialysis patients who develop cardiac symptoms. Further specifically designed studies should therefore address what the minimum relative delta changes in hs-cTnT levels are that should be considered, either in two successive blood samples or in comparison with an individual baseline value, for the diagnostic work-up of ACS in hemodialysis patients.

ACKNOWLEDGMENTS

Preliminary data were presented in abstract form at the 51st Congress of the Swiss Society of Nephrology, Interlaken, Switzerland, December 2019.

CONFLICT OF INTEREST

All authors declare that there is no conflict of interest.

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How to cite this article: Gremaud S, Fellay B, Hemett OM, Magnin J-L, Descombes E. Monthly measurement of high-sensitivity cardiac troponins T and creatine kinase in asymptomatic chronic hemodialysis patients: A one-year prospective study. *Hemodialysis International.* 2022;26:166–75. <https://doi.org/10.1111/hdi.12985>