Variation of High-Sensitivity Troponin T Results in Patients Undergoing Continuous Renal Replacement Therapy

Vikas Srinivasan Sridhar¹, Michael Chen², Howard Gerson², Elizabeth MacNamara², and Sharon J. Nessim³

Abstract

Background: Cardiac troponins are the preferred biomarker to diagnose myocardial injury. Complicating the interpretation of serial troponins in patients with end-stage renal disease, it has been shown that the hemodialysis procedure results in a small but significant decline in high-sensitivity cardiac troponins (hs-cTnT). This raises the possibility that continuous renal replacement therapy (CRRT) might similarly alter cardiac troponin levels and affect their interpretation when cardiac ischemia is being considered.

Objective: We sought to determine the effect of CRRT on hs-cTnT levels over time in a group of patients without active myocardial injury.

Design: Prospective, observational study

Setting: Single tertiary care hospital, Montreal, Quebec

Patients: Ten critically ill patients with acute kidney injury (AKI) undergoing CRRT. Cardiac ICU (intensive care unit) patients and acute coronary syndrome patients were excluded from the study. The CRRT prescription was at the discretion of the treating intensivist and relatively high doses were used in this study.

Measurements: The hs-cTnT levels were drawn pre-CRRT, within 6 hours of initiation, and approximately every 6 hours thereafter along with routine CRRT blood work.

Methods: Changes in hs-cTnT, creatinine, and albumin levels were recorded over the course of CRRT. Mean change in serum analyte concentration and 95% confidence interval was determined for specified time intervals relative to baseline, with paired t-tests used to determine statistical significance.

Results: Among the 10 patients included in the study, the cause of AKI was primarily acute tubular necrosis from septic shock or hemorrhagic shock. Compared with baseline hs-cTnT levels prior to CRRT initiation, mean hs-cTnT level fell by 42% at 5 to 10 hours post-CRRT initiation, followed by a plateauing of levels for the duration of time on CRRT.

Limitations: Single-center study only applicable to hs-cTnT assay.

Conclusions: This study demonstrates a significant decrease in hs-cTnT within 5 to 10 hours of CRRT initiation. This suggests that interpretation of cardiac troponin changes during CRRT must take into consideration the timing of dialysis initiation relative to the time of sample collection.

Abrégé

Contexte: Les troponines cardiaques constituent le biomarqueur de choix pour diagnostiquer les lésions myocardiques. L’hémodialyse, qui provoque un léger et significatif déclin des troponines cardiaques à haute sensibilité (hs-cTnT), complique leur interprétation chez les patients atteints d’insuffisance rénale terminale. Cette observation suggère que la thérapie de remplacement rénal continue (TRRC) pourrait modifier similaiement les taux de troponines cardiaques et affecter leur interprétation lorsqu’une ischémie cardiaque est examinée.

Objectif: Nous souhaitions évaluer l’effet dans le temps d’une TRRC sur les taux de hs-cTnT chez des patients sans lésions myocardiques actives.

Type d’étude: Une étude observationnelle prospective.

Cadre: Un hôpital de soins tertiaires de Montréal (Québec).

Sujets: Un groupe de dix patients gravement malades, souffrant d’insuffisance rénale aiguë (IRA) et suivant une TRRC. Les patients hospitalisés aux soins intensifs cardiaques ou atteints d’un syndrome coronarien aigu ont été exclus. La prescription
d’une TRRC était laissée à la discrétion du médecin intensiviste traitant et des doses relativement élevées ont été administrées au cours de l’étude.

**Mesures:** Les taux de hs-cTnT ont été mesurés conjointement aux prélèvements sanguins de routine requis pour une TRRC; soit avant son initiation, dans les six heures suivantes, puis aux six heures environ par la suite.

**Méthodologie:** Les variations des taux de hs-cTnT, de créatinine et d’albumine ont été colligées pour la durée de la TRRC. La variation moyenne des concentrations d’analytes sériques par rapport aux valeurs initiales et les intervalles de confiance à 95 % ont été déterminés pour des périodes de temps précises. Des tests t coupés ont été employés pour établir la signification statistique des résultats.

**Résultats:** Chez les patients examinés, l’IRA était principalement due à une nécrose tubulaire aiguë causée par un choc septique ou hémorragique. Le taux moyen de hs-cTnT a chuté de 42 % dans les 5 à 10 heures suivant l’initiation de la TRRC par rapport aux valeurs observées pré-TRRC. Les taux ont ensuite plafonné pour la durée de la TRRC.

**Limites:** Il s’agit d’une étude monocentrique applicable uniquement aux mesures de hs-cTnT.

**Conclusion:** Cette étude démontre une baisse significative des hs-cTnT dans les 5 à 10 heures suivant l’initiation d’une TRRC. Ce résultat suggère que l’interprétation des variations observées dans les taux de troponines cardiaques au cours d’une TRRC devrait tenir compte du moment où l’échantillon est prélevé par rapport à son initiation.

**Keywords**
continuous renal replacement therapy, high-sensitivity troponin T, acute kidney injury

Received October 14, 2018. Accepted for publication December 21, 2018.

**What was known before**
In the hemodialysis (HD) population, it has been shown that high-sensitivity cardiac troponin (hs-cTnT) falls during and shortly after HD, before rising back to baseline levels.

**What this adds**
This study demonstrates a larger drop in high-sensitivity cardiac troponin (hs-cTnT) levels during CRRT, which must be taken into consideration when interpreting cardiac troponin changes in this setting. Further studies are required to see whether these findings extend to different troponin assays and in patients with established myocardial injury.

**Introduction**
Acute kidney injury (AKI) is common among patients admitted to the intensive care unit (ICU), with 57% of such patients meeting the diagnostic criteria for AKI. Among patients admitted to the ICU with AKI, dialysis may be required, and continuous renal replacement therapy (CRRT) is often the modality of choice when hemodynamic instability is an issue. Cardiovascular disease is a significant contributor to AKI-associated mortality. Diagnosing an acute coronary syndrome (ACS) in this setting can be challenging as patients may present with nonspecific symptoms, and as many as 25% of patients can have silent ischemia. Furthermore, critically ill patients are often sedated and intubated. As such, cardiac biomarkers are relied upon to diagnose myocardial injury. In addition, interpretation of cardiac troponins (cTns) can be more difficult in patients with renal disease. For example, patients with chronic kidney disease (CKD) and AKI have been noted to have stable but elevated cTn levels. Such cTn elevations have been demonstrated to have long-term prognostic implications for cardiovascular mortality, but are not necessarily a marker of acute myocardial injury. As such, dynamic changes in cTn remain key to diagnosing an ACS, both in the general population and in patients with AKI and CKD. The impact of renal replacement therapy (RRT) on troponin levels poses another challenge. The molecular weights of cardiac troponin I (cTnI) and cardiac troponin T (cTnT) are 24 kDa and 36 kDa, respectively. The pore size of filters used for CRRT is typically approximately 30 kDa. As such, one would expect relatively little clearance of these molecules. Data in the chronic hemodialysis (HD) population have shown variable results. One study employing non-high-sensitivity cTn demonstrated cTn stability or rise following HD.

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1 Division of Nephrology, Department of Medicine, University of Toronto, ON, Canada
2 Department of Diagnostic Medicine, Sir Mortimer B. Davis Jewish General Hospital, McGill University, Montreal, QC, Canada
3 Division of Nephrology, Sir Mortimer B. Davis Jewish General Hospital, McGill University, Montreal, QC, Canada

**Corresponding Author:**
Vikas Srinivasan Sridhar, Division of Nephrology, Department of Medicine, University of Toronto, Suite 3-805, 190 Elizabeth Street, R. Fraser Elliott Building, Toronto, ON M5G 2C4, Canada.
Email: vikassrinivasan.sridhar@uhn.ca
Another study using high-sensitivity cTnT (hs-cTnT) demonstrated no reduction after conventional HD, but interestingly a significant reduction in serum levels after hemodiafiltration, particularly with a longer duration.\textsuperscript{7} In a study of 10 chronic HD patients, we recently demonstrated that hs-cTnT falls by approximately 11\% during and shortly after HD, before rising back to baseline levels 11 hours later.\textsuperscript{8} The purpose of this study was to describe the influence of CRRT on hs-cTnT levels among patients admitted to the ICU.

Materials and Methods

This was a single-center, prospective observational study conducted at the Jewish General Hospital (Montreal, Quebec, Canada). Patients included were those admitted to the ICU with AKI undergoing CRRT (initiated at the discretion of the attending intensivist). Exclusion criteria included patients with ACS, post-cardiac surgery patients, and those with end-stage renal disease (ESRD). Patient demographics, reason for ICU admission, reason for AKI, and outcome were recorded. All measures of hs-cTnT were blinded to the treating team. Five patients were on continuous veno-venous hemodiafiltration, one patient was on continuous veno-venous hemodialysis, and 4 patients were on continuous veno-venous hemofiltration. The CRRT parameters are included in Table 1. Prismaflex ST150 dialyzers (Baxter Healthcare, Deerfield, Illinois) were used in all patients, and CRRT prescription and dosing was at the discretion of the treating intensivist. The study received ethics approval from the hospital’s research ethics board and was adherent to the Declaration of Helsinki.

Baseline hs-cTnT was measured prior to initiation of CRRT (mean of 3.9 hours prior to initiation with SD of 3.2), within 6 hours of initiation, and subsequently, approximately every 6 hours. The exact frequency of blood collection was at the discretion of ICU nursing staff based on routine clinical care. Given the variable duration on CRRT, patients had varying number of measurements. The hs-cTnT was determined using a fifth-generation hs-cTnT immunoassay with a coefficient of variance <10\% at the 99th percentile (Roche Diagnostics, cat no. 05092744). Creatinine and albumin were also measured with each collection (Roche Diagnostics, cat no. 03263991190 and 11815148216).

To standardize time of collection, analytes were grouped into time intervals: 5 to 10 hours, 11 to 15 hours, 16 to 20 hours, and 21 to 30 hours post-initiation of CRRT. Mean change in analyte concentration and 95\% confidence interval was determined at each time interval relative to baseline. Paired \(t\) tests were used to determine statistical significance of within-patient differences over time (Microsoft Excel).

Results

Ten patients were enrolled in this study (6 males and 4 females) (Table 1). Median age was 59 years (range = 29-86). All patients were admitted to the ICU with shock, with sepsis being the etiology in 80\%. Mean duration of CRRT in this cohort was 51.5 hours with a range of 25 to 72 hours. Mean creatinine prior to CRRT initiation was 454.7 \(\mu\text{mol}/\text{L}\) (SD of 161.3). Five patients died, 1 had sufficient renal recovery to discontinue RRT, and 4 patients were transitioned to intermittent HD post-ICU discharge.

There was a significantly lower mean hs-cTnT during CRRT in each time interval, when compared with levels prior to the start of dialysis (\(P < .05\)) (Figure 1). There was a 42\% decrease in hs-cTnT at 5 to 10 hours post-CRRT initiation, with stable levels thereafter (Figure 1). As expected, creatinine steadily declined after CRRT initiation in all 4 time intervals (\(P < .05\)), while there was no significant change in albumin levels during CRRT. In the 3 patients in whom hs-cTnT was measured after CRRT discontinuation (5-10 hours after last blood work drawn during CRRT), a rise in hs-cTnT was noted (\(P = .057\)).

Discussion

This study has demonstrated significant clearance of hs-cTnT in patients undergoing CRRT. By 5 to 10 hours post-initiation of CRRT, hs-cTnT levels decreased by 42\% from baseline and remained stable thereafter. In patients with available blood work, there appeared to be a rise in hs-cTnT after cessation of CRRT, although this did not reach statistical significance.

Stably elevated troponin levels have been demonstrated in patients with CKD and AKI, likely reflecting subclinical coronary artery disease.\textsuperscript{4} As such, dynamic changes in cTn are important to diagnose ACS. This study, in conjunction with our previous investigation in HD patients, offers some insight into the influence of dialysis on cTn levels. While an 11\% reduction in mean hs-cTnT was demonstrated during HD,\textsuperscript{8} we noted a much larger reduction in CRRT patients. This likely reflects the longer duration of dialysis and possibly the greater convective clearance of larger molecular weight substances such as hs-cTnT (and/or their degradation products, which have been shown to cross-react with the hs-cTnT assay).\textsuperscript{5} This is also consistent with the study by Cardinaels and colleagues\textsuperscript{7} demonstrating greater reduction in serum levels of hs-cTnT with longer duration of hemodiafiltration.

Clinical guidelines currently recommend using a 20\% or more change in cTn levels from baseline to diagnose ACS.\textsuperscript{10} Thus, the greater than 40\% reduction in troponin observed in this study can mask an ACS. Alternatively, a lack of fall in troponin levels upon CRRT initiation should be concerning for myocardial injury. It is important to note that a steady state appears to be reached 5 to 10 hours after CRRT initiation, after which a new baseline hs-cTnT is reached, assuming no further interruptions in CRRT. One might therefore infer that myocardial injury occurring 5 to 10 hours after starting CRRT should manifest as a rise in hs-cTnT above this new baseline.

To our knowledge, this is the first study showing a significant reduction in cTns after CRRT initiation, in keeping with the hs-cTnT studies in HD patients. Nevertheless,
Table 1. Patient Characteristics.

| Patient | Age (y) | Sex | Patient weight (kg) | Cause of renal failure | Reason for ICU admission | Duration of CRRT (h) | Creatinine at CRRT initiation (µmol/L) | Urine output (cc/24 h) | Dialysate rate (cc/kg/h) | Replacement rate (cc/kg/h) | Ultrafiltration (cc/h) | Anticoagulation | Outcome       |
|---------|---------|-----|---------------------|------------------------|--------------------------|----------------------|----------------------------------------|------------------------|------------------------|-------------------------|-------------------------|----------------|--------------|
| 1       | 67      | M   | 85                  | ATN                    | Intra-abdominal sepsis   | 41                    | 410                                    | <200                   | 23.5                   | 23.5                    | 0                       | Heparin (800-1000 U/h) | Renal recovery |
| 2       | 59      | F   | 61.5                | ATN                    | Pneumosepsis with multiorgan dysfunction | 25                    | 228                                    | <200                   | None                   | 32.5                    | 0                       | None           | Died          |
| 3       | 58      | M   | 196                 | ATN                    | Sepsis and hypercapnic respiratory failure | 38                    | 593                                    | <200                   | 10.2                   | None                    | 0                       | Heparin (800-1400 U/h) | IHD           |
| 4       | 49      | F   | 88                  | ATN                    | Post-surgical sepsis and hemorrhage | 66                    | 555                                    | <200                   | 22.7                   | 22.7                    | 0                       | None           | Died          |
| 5       | 68      | M   | 111                 | ATN                    | Post-surgical sepsis     | 56                    | 246                                    | <200                   | 18                     | 18                      | 0                       | None           | IHD           |
| 6       | 86      | M   | 99                  | ATN                    | Ascending cholangitis    | 27                    | 668                                    | <200                   | 15                     | 15                      | 50                      | None           | Died          |
| 7       | 77      | F   | 108.5               | ATN                    | Urosepsis               | 63.5                  | 558                                    | <200                   | None                   | 27.6                    | 25                      | None           | IHD           |
| 8       | 36      | F   | 82.5                | ATN                    | Eclampsia and hemorrhagic shock | 65                    | 401                                    | <200                   | None                   | 24.2                    | 100                     | None           | IHD           |
| 9       | 61      | M   | 82                  | ATN                    | Sepsis                  | 61                    | 288                                    | 450                    | 24.4                   | 24.4                    | 100                     | None           | Died          |
| 10      | 29      | M   | 127                 | ATN                    | Hemophagocytic lymphohistiocytosis and lymphoma | 72                    | 600                                    | <200                   | None                   | 7.9                     | 50                      | None           | Died          |

Note: ICU = intensive care unit; CRRT = continuous renal replacement therapy; ATN = acute tubular necrosis; IHD = intermittent hemodialysis; CKD = chronic kidney disease.

*Pre-filter replacement with 200 cc/h post-filter replacement.
there are several study limitations. First, this was a single-center study with a small sample size and a lack of homogeneity in CRRT prescriptions. Second, only hs-cTnT was studied, so the results cannot be extrapolated to non-high-sensitivity troponin assays or to Troponin I assays. Third, we cannot say with certainty whether the reduction was due to clearance of TnT or of its metabolites which can interfere with the assay. It would be interesting to measure effluent concentrations of hs-cTnT and its metabolites in future studies to explore this further. Fourth, we cannot rule out the possibility of subclinical cardiac ischemia in some patients prior to initiation of CRRT, which could have partly explained the declining hs-cTnT observed after CRRT initiation. Finally, the majority of patients received fairly high doses of CRRT, which likely influenced the magnitude of hs-cTnT removal and must be taken into consideration when anticipating changes in levels. Despite these limitations, our study is novel and sheds light on the highly clinically relevant question of what happens to hs-cTnT levels in patients on CRRT. Further studies are warranted to confirm our findings, and to determine whether this effect is seen with different troponin assays and how this affects post-ACS and post-cardiac surgery patients.

To conclude, hs-cTnT levels decrease within 5 to 10 hours of CRRT initiation. Consequently, interpretation of troponin changes during CRRT must take into consideration the timing of CRRT initiation relative to the timing of sample collection.

Ethics Approval and Consent to Participate

Ethics approval was obtained from the Jewish General Hospital Research Ethics Committee.

Consent for Publication

All authors reviewed the final manuscript and provided consent for publication.

Availability of Data and Materials

Data and materials may be made available upon written request to the corresponding author.

Acknowledgments

The authors thank Dr Joanne M Bargman for her critical review of this article.

Declaration of Conflicting Interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: V.S.S., H.G., M.C., and E.M. have no disclosures to make. S.J.N. has received speaker honoraria from Baxter Healthcare, and consulting fees from Baxter Healthcare, Fresenius, Boehringer Ingelheim, and Otsuka.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

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